Cardiovascular Autonomic Dysfunction in Familial Mediterranean Fever

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ABSTRACT. ***Objective***. To compare the hemodynamic responses to autonomic challenge evoked by upright tilt table testing in patients with familial Mediterranean fever (FMF).

Methods. Forty consecutive patients with FMF and 25 age and sex matched healthy controls were evaluated using the head-up tilt test (HUTT). The main outcome measures were the values of blood pressure (BP) and heart rate (HR) recorded during recumbence and tilt. The endpoints of vasodepressor and cardioinhibitory reactions, orthostatic tachycardia, and postural tachycardia syndrome were recorded.

Results. Patients with FMF exhibited significantly higher diastolic BP during supine and tilt measurements ($p = 0.003$ and 0.04, respectively). In response to tilt, patients showed significant increases in HR compared to healthy subjects ($p = 0.02$). Pathological endpoints on tilt were observed in the FMF group in 7 patients (17%) and in no controls. FMF severity, genotype, duration of illness, response to therapy, and associated amyloidosis did not correlate with pathological reactions on HUTT.

Conclusion. FMF patients exhibit an abnormal cardiovascular reactivity, which is clinically occult, but can be detected on autonomic challenge. The abnormal autonomic activity in FMF is similar to dysautonomia described in a variety of rheumatic disorders. (J Rheumatol 2002;29:987–9)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER DYSAUTONOMIA TILT TEST

Alterations of autonomic nervous system activity have been evaluated in a variety of rheumatic disorders, including rheumatoid arthritis[1], systemic lupus erythematosus[2], Sjögren's syndrome[3], systemic sclerosis[4], ankylosing spondylitis[5], mixed connective tissue disorder[4], and fibromyalgia[6]. No similar studies have been performed in familial Mediterranean fever (FMF); however, prior work suggested that an inborn error in the metabolism of catecholamines as well as alterations in autonomous nervous activity are implicated in the pathophysiology of FMF[7]. The fast response of blood pressure (BP) and heart rate (HR) to acute stimuli is under autonomic nervous control. Therefore cardiovascular reactivity measurements recorded during a variety of challenges can be used to estimate cardiovascular autonomic activity[1-6]. We assessed the BP and HR responses to postural challenge as an index of cardiovascular autonomic activity in a population with FMF.

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MATERIALS AND METHODS

The study was approved by the institutional committee for human investigation. Written informed consent was obtained from all subjects.

*Patients***.** The study population included 40 consecutive adult patients with FMF from a rheumatology clinic. The entry criteria were as follows: (1) Age between 20 and 60 years; (2) fulfillment of the criteria for the diagnosis of FMF[8]; (3) last attack of FMF remitting at least 7 days prior to tilt test; (4) absence of active comorbidity, excepting amyloidosis; (5) absence of any medications that might affect autonomic nervous system function, including any type of sleeping pills, tranquilizers, or antidepressants, for at least one month prior to the study. The patients' average age was 33.4 years (standard deviation, SD, 10.9) and 64% were male. The subjects had normal findings on physical examination, chest radiography, and electrocardiogram. A comparison group of healthy subjects matched for age and sex distribution was tested along with FMF patients. This group included 25 volunteers who were recruited from the hospital staff. Subjects were eligible if they had no family history of FM, were asymptomatic, did not take medications in the 15 days prior to the study, and had normal findings on physical examination, routine laboratory tests, chest radiography and electrocardiogram. Their average age was 30.1 years (SD 9.2) and 68% were male.

FMF checklist. The subjects' age, ethnic background, family history of FMF, age at disease onset, duration of FMF, frequency of attacks, daily dose of colchicine, response to treatment, presence of associated illnesses, smoking habit, FMF associated DNA mutations[9], and presence of amyloidosis were assessed[10]. Severity of FMF was estimated using the Tel-Hashomer severity score[8].

Protocol of the tilt test and diagnosis of dysautonomia. The protocol was based on the 10 min supine/30 min head-up tilt test (HUTT) as described[11]. The following pathological reactions on HUTT were observed[12,13]: (1) orthostatic hypotension, (2) vasodepressor reaction, (3) cardioinhibitory reaction, and (4) postural tachycardia syndrome. Patients displaying any of these reactions were diagnosed to have dysautonomia[14].

Statistical analysis. Comparisons between groups were based on Student's unpaired t tests. A value of 2 tailed $p \leq 0.05$ was accepted as statistically significant.

RESULTS

The estimated average age of onset of FMF was 15.8 years (SD 10.2), and the average duration of FMF at the time of the study was 17.6 years (SD 9.7). During the year prior to HUTT, the frequency of FMF attacks was one per month or less in 42% of patients, and greater than one per month in 58% of patients. According to the Tel-Hashomer severity score, 16 patients had mild disease, 19 patients had moderate disease severity, and 5 patients had severe disease. In 31 patients, the average daily dose of colchicine administered at the time of the study was 1.5 mg (SD 0.6). Six patients who were recently diagnosed were not receiving colchicine. In 59% of FMF patients, one or more of the family members were diagnosed with FMF. Genetic studies were performed in 15 patients: 5 patients were homozygous for the M694V mutation, 10 were heterozygous for M694V, M690I, V726A, M680I, and E148Q. The presence of amyloidosis was judged likely in 5 patients, based on the presence of persistent proteinuria, normal urinary sediment, and absence of monoclonal protein in plasma and urine[10]. One of these had amyloid deposits in the appendectomy specimen. On direct questioning, neither patients with nor those without presumed amyloidosis reported fainting, orthostatic symptoms, erectile disorder, or decreased sweating.

Table 1 shows the BP and HR group averages and SD in patients with FMF and healthy subjects. Patients exhibited significantly higher diastolic BP measurements during both recumbence ($p = 0.0003$) and head-up tilt ($p = 0.04$). In response to tilt, patients showed significant increases in HR compared to healthy subjects ($p = 0.02$). Pathological reactions on HUTT were observed in the FMF group in 7 patients (17%) and in no controls. Among patients, 4 exhibited the postural tachycardia syndrome, 4 had vasodepressor or cardioinhibitory reactions, and one had orthostatic hypotension. Pathological reactions on HUTT were not significantly associated with patients' age, ethnic group, family history of FMF, age at onset of FMF, duration of FMF, frequency of attacks, daily dose of colchicine, response to treatment, FMF severity score, or presence of associated illnesses or FMF associated DNA mutations.

Table 1. Blood pressure (BP) and heart rate (HR) responses to head up tilt testing. Values are mean (SD).

Measurements	FMF, n = 40	Healthy Controls, n = 25	p*
Last supine			
Systolic BP	118.5 (17.8)	117.0 (8.71)	NS
Diastolic BP	79.4 (11.7)	69.2 (7.26)	0.0003
HR	69.8 (10.2)	68.75 (9.5)	NS
At termination of tilt			
Systolic BP	109.3 (16.5)	109.4 (8.3)	NS
Diastolic BP	78.6 (13.7)	72.6 (6.6)	0.04
HR	84.1 (13.7)	76.8 (10.1)	0.02

* Student's unpaired t test.

DISCUSSION

In our study, HR and BP response to postural challenge differed in patients with FMF compared to healthy individuals (Table 1). Recognized pathological reactions to tilt[12,13] were only observed in the FMF group (17%). In addition, HR increases were more prominent in the FMF group. This abnormal cardiovascular reactivity in FMF is consistent with dysautonomia[1-6,14].

Dysautonomia has been described in a variety of inflammatory rheumatic diseases and has been attributed to vasculitic neuropathy, amyloid neuropathy, inflammatory cytokines, baroreflex deconditioning following prolonged bed rest, or adverse effects of antirheumatic medications[1,2,15]. As our patients were fully ambulatory, it is improbable that baroreflex deconditioning had a role in causing dysautonomia. The association between clinical amyloidosis and abnormal cardiovascular reactivity was not significant, and could therefore not clarify the role of amyloidosis in the pathogenesis of dysautonomia in FMF. There was no correlation with colchicine usage. Our analysis of data could not suggest a pathogenic mechanism for the subtle dysautonomia of FMF.

Patients with familial Mediterranean fever exhibit abnormal cardiovascular reactivity that is clinically occult and can be detected on autonomic challenge. The abnormal cardiovascular autonomic activity in FMF is similar to dysautonomia described in a variety of rheumatic disorders.

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