difference between the mortality in the treatment (16.7%) and control (10%) arms. In the control group, 2 patients died. There was no significant change in functional class or left ventricular function in this group.

In summary, 24 patients underwent intracoronary stem cell injection with coronary sinus blockage. Four patients died during the 6-month follow-up. Overall EF showed a small but significant improvement of 5.4%. There was a decrease in end-systolic volumes, but no change in end-diastolic volumes. Endomyocardial biopsy done at 3 months showed no significant change in the number of myocytes or capillaries, but the ratio of capillaries to myocytes showed an insignificant increase. There were soft data to suggest cell proliferation (binucleate cells and Ki 67 positivity).

This is the first study of stem cell therapy in dilated nonischemic cardiomyopathy. Over a 6-month period, there was a small albeit significant improvement in ventricular function. Previous clinical studies have also shown a small degree of change in ventricular function of a similar magnitude (1,2). Laboratory experiments in nonischemic dilated cardiomyopathy (3) have previously suggested that benefit from stem cell therapy in this group comes mainly from a decrease in fibrosis and an increase in vascularity, but no evidence has been found supporting transdifferentiation of stem cells to myocytes. Our data also suggest that the benefit of stem cell therapy could be a paracrine effect with changes in vascularity, perhaps stimulation of cell proliferation, or by some still-unexplored mechanism. We did not find any evidence of transdifferentiation.

In this study we wish to highlight a number of issues. It is the first study to show the benefit of stem cells in nonischemic dilated cardiomyopathy, and the first study that uses coronary sinus occlusion to increase cell contact time. It is also the first study in which we have endomyocardial biopsies performed after stem cell therapy.

It provides a stimulus for exploring the benefits of stem cell therapy in nonischemic dilated cardiomyopathy. A double-blind study is being planned to further explore the benefit seen in this preliminary study. The small magnitude of benefit could perhaps be because all patients in this study were in very late stages of their cardiomyopathy, and we probably need to consider stem cell therapy at a much earlier stage. Endomyocardial biopsy, performed for the first time in stem cell therapy, shows no evidence of transdifferentiation of stem cells to myocytes but provides soft data pointing to a possible paracrine effect.

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Are Familial Mediterranean Fever (FMF) Patients at Increased Risk for Atherosclerosis? Impaired Endothelial Function and Increased Intima Media Thickness Are Found in FMF

To the Editor: Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by periodic attacks of fever and serositis caused by mutations in FMF gene (MEFV). Although FMF patients are symptom free between the attacks, subclinical inflammation continues during the attack-free period (1). Patients with inflammatory diseases, such as those with systemic lupus erythematosus and rheumatoid arthritis, are now considered to have an increased risk of atherosclerotic cardiovascular complications. Intima media thickness (IMT) of carotid arteries and endothelial dysfunction are used to define the preclinical atherosclerosis (2). We attempted to determine whether FMF patients have an increased risk of atherosclerosis by assessing endothelium-dependent flow-mediated dilation (FMD) of brachial artery and IMT of carotid arteries. We also investigated the association between these parameters and inflammatory markers.

We studied 43 FMF patients and 29 healthy control subjects. All FMF patients enrolled in the study fulfilled the clinical criteria for FMF (3). Patients with diabetes mellitus, hypertension, atherosclerotic vascular disease, malignancy, amyloidosis, active infectious disease, pregnancy, or other inflammatory diseases were excluded. All subjects had a complete history and physical examination. Clinical and laboratory assessment of FMF patients were performed during an attack-free period. The FMF patients unresponsive to colchicine therapy have been previously defined (4).

Erythrocyte sedimentation rate (ESR) and fibrinogen were measured. Serum glucose and serum lipids were determined by using an autoanalyzer. Serum amyloid A (SAA) was determined by a commercial micro–enzyme-linked immunosorbent assay method, and high-sensitivity C-reactive protein (hs-CRP) was determined by immunonephelometry. Genetic analysis data of FMF patients were obtained from hospital file records.

Endothelial function was assessed by FMD from the brachial artery, and IMT of carotid arteries was measured as previously described (5,6). The maximum IMT (the highest value of the 6

measurements) was used in statistical analysis. The IMT was considered normal when the intima-media complex was ≤0.9 mm according to the current sonographic criteria. Maximum IMT values of 0.9 to 1.3 mm were considered indicative of thickened intima, and the values >1.3 mm indicated an atherosclerotic plaque (6).

The SPSS version 11.0 software (SPSS Inc., Chicago, Illinois) was used for data analysis. Categorical and numeric variables were tested by chi-square or Fisher exact tests and Student *t* test or Mann-Whitney *U* test, respectively. Correlation was tested with Spearman or Pearson correlation coefficients. Analysis of covariance was used to adjust for high-density lipoprotein (HDL) or total cholesterol levels, while checking for the effect of FMF on FMD or maximum IMT. A significance level was set at $p < 0.05$.

General characteristics of the patients with FMF and control subjects were similar. All FMF patients were on colchicine treatment. Five patients (12%) were considered colchicine nonresponders. None of the patients had proteinuria. Data of genetic analysis were available in 28 patients. The most frequent 3 mutations were M694V (53.6%), V726A (14.9%), and M680I (14.9%). Among 28 patients, 9 patients (32%) had homozygote mutations, 13 patients (46%) had compound heterozygote mutations, 2 patients (7%) had heterozygote mutations, and 1 patient (4%) had complex allele with M694V/M694V-E148Q.

Total cholesterol (164 ± 34 mg/dl vs. 188 ± 46 mg/dl, p = 0.02) and HDL cholesterol (49 ± 14 mg/dl vs. 57 ± 14 mg/dl, p = 0.03) were significantly lower, ESR (median: 7 mm/h [range: 2 to 66 mm/h] vs. median: 5 mm/h [range: 1 to 4 mm/h], p = 0.003), fibrinogen (324.64 ± 77.93 mg/dl vs. 283.80 ± 57.10 mg/dl, p = 0.02), and hs-CRP (3 mg/l [0.2 to 30.4 mg/l] vs. 0.7 mg/l [0.2 to 3.6 mg/l], p = 0.001) were significantly higher in the FMF group. Serum amyloid A (21.82 U/l [4.25 to 300 U/l] vs. 10.33 U/l [6.00 to 89.10 U/l], p = 0.004), FMD (5.7 ± 2.4% vs. 10.8 ± 1.9%, p = 0.001), maximum IMT (0.79 ± 0.18 mm vs. 0.61 ± 0.11 mm, p = 0.001), mean IMT (0.62 ± 0.08 mm vs. 0.53 ± 0.07 mm, p = 0.001) of right carotid arteries, and mean IMT (0.61 ± 0.07 mm vs. 0.53 ± 0.07 mm, p = 0.001) of the left carotid arteries were also significantly higher in the FMF group. The FMD impairment was more prominent in M694V homozygote patients compared with those without this mutation (4.3 ± 1.5% vs. 6.5 ± 2.2%, p = 0.005) (Fig. 1). There was a positive correlation between the maximum IMT of carotid arteries and age (r = 0.29; p = 0.014). Atherosclerotic plaques were detected in 2 of the FMF patients and none of the control group. Using covariance analysis, after adjustment by HDL or total cholesterol separately, the presence of FMF was shown to be a significant risk factor for both increased IMT and decreased FMD ($p < 0.001$ for all).

Neither FMD nor maximum IMT of carotid arteries were different between colchicine responder and nonresponder patient groups (p = NS for all). Both FMD of brachial artery and IMT of carotid arteries did not correlate with disease duration, age of symptom onset, duration of colchicine treatment, or current colchicine dosage in FMF patients (p = NS for all).

In this study we found that endothelium-dependent FMD was reduced and IMT of the carotid arteries was increased in FMF patients compared with healthy controls. Acute-phase reactant levels were higher in FMF patients as expected. We suggest that ongoing low-grade inflammation may be the cause of the thickened IMT of the carotid arteries and endothelial dysfunction reflected by reduced FMD in FMF patients.

Langevitz et al. (7) found that ischemic heart disease prevalence was 15.5% in FMF patients, which is lower than expected, but our results suggest that there may still be an increased risk for atherosclerotic vascular complications in FMF patients, as in other inflammatory diseases.

Serum lipid changes in FMF patients resemble those in chronic inflammatory diseases, so we think that these changes may be another feature of the ongoing inflammation (8). Other than the effect of FMF disease itself, a decreased HDL cholesterol level was not found to introduce additional risk for the reduced FMD or thickened maximum IMT of carotid arteries in this study. Although the IMTs of carotid arteries were higher in FMF patients, there were only 2 atherosclerotic plaques detected in FMF patients. These results may be attributable to our relatively young patient population. On the other hand, this is a cross-sectional study with a limited number of subjects; therefore, our results should be assessed cautiously. Our control subjects were enrolled from the hospital staff, which could also be thought to be a potential bias.

The MEFV mutations were found to be associated with the severity of inflammatory diseases. Homozygote M694V mutation is associated with a more severe disease course and risk for developing amyloidosis in FMF. The carrier rate of MEFV mutations reaches about 20% to 30% of the population in certain ethnic groups. Ongoing low-grade inflammation was shown not only in FMF patients but also in carriers of MEFV mutations (1). Further assessment of the effect of these mutations on the atherosclerotic process will provide more a accurate risk stratification for those who have these mutations. The role of impaired endothelial function and IMT of carotid arteries in detecting amyloidosis should also be evaluated in patients with FMF. Further investigations in larger samples are needed to establish the relationship between FMF and atherosclerosis.

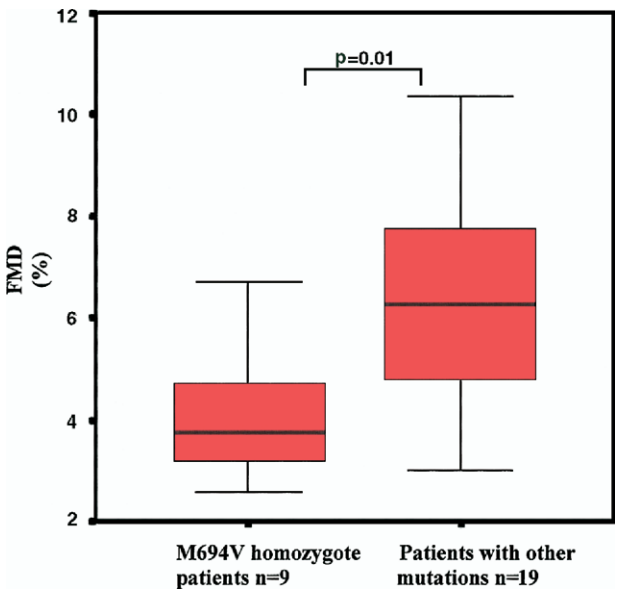

Figure 1. Comparison of flow-mediated dilation (FMD) between M694V homozygote FMF patients and FMF patients with other mutations. FMF = familial Mediterranean fever.

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Letters to the Editor

Physiologic Timing for Objective Checking of Instantaneous Maximal Aortic Stenotic Area

Feuchtner et al. (1) recently proposed a new and successful method for imaging and evaluating aortic valve area (AVA) in aortic stenosis (AS) using a 16-row multislice computed tomography MSCT scanner. The investigators reasonably indicated that MSCT was not a primary diagnosis imaging technique, recalling the feasibility and cost-effectiveness of the usual echo-Doppler techniques in clinical practice. I agree with these general considerations and appreciated the study. Some comments are needed about the methodology they used to acquire images.

On the one hand, an obvious discrepancy exists between the described method in their study, assuming an approximate value of 50 ms for isovolumetric contraction (IC), and the diagram shown in their Figure 1 (top row). This 50-ms time interval is stated to be subtracted from the duration of the cardiac cycle for the reconstruction of the first image. Everyone may agree with the 50-ms approximation for IC. Figure 1, however, shows that the so-called IC starts with QRS of the electrocardiogram (ECG) and covers the full duration of the QRS complex. This illustration raises a didactical issue: the total QRS duration normally ranges about 120 ms and, thus; widely exceeds 50 ms. The QRS onset is the initial marker of the pre-ejection period, of which IC is only a component, succeeding to the electromechanical delay, and ending with the opening of the aortic valve, marker of ejection onset. The IC has a physiologic interest because it corresponds to the rapid rise of left ventricular pressure, which requires mitral valve closure and lags behind QRS onset.

In brief, if only 50 ms were subtracted, the latest part of pre-ejection, which is precisely IC, would be integrated into the duration of the cardiac cycle. This may be of limited consequence on final imaging measurements, but, regretably, it makes Figure 1 erroneous and confuses the reader.

On the other hand, MSCT enables one to directly image *instantaneous* AVA, which varies along systole. The assumption that maximal AVA coincides with the maximal pressure drop has been substantiated by studies using the continuity equation over systole (2). No significant difference was reported either between timings of maximal Doppler jet flow AVA and maximal pressure gradient (3). Rather than studying reconstructed images generated during the entire mid-late systole every 50 ms in order to identify the phase of maximal AVA (1), a less empiric way of selecting maximal AVA would consist of triggering the image at peak velocity of the stenotic jet recorded by continuous-wave Doppler. Peak velocity has a reproducible timing (3). The reliable ultrasound assessment of AVA it provides could easily be applied to other imaging modalities. Advantages of this specific timing are 3-fold: 1) it relies on a physiologic substrate; 2) it enables comparison between laboratories; and 3) it facilitates follow-up of patients by relying on an objective landmark.

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