

Correspondence



Triggering of Sudden Death from Cardiac Causes by Vigorous Exertion

To the Editor: Albert et al. (Nov. 9 issue)¹ demonstrate an inverse association between the frequency of vigorous exercise at base line and sudden death from cardiac causes during or shortly after single episodes of vigorous exercise over the ensuing 20 years. Although the authors show no association between increasing levels of vigorous exercise and total sudden deaths from cardiac causes, one can calculate from Table 2 of the article that as the frequency of episodes of vigorous exercise at base line increased from less than one to one through four to five or more times per week, the proportion of all sudden deaths that occurred during vigorous exercise increased from 9 percent to 19 percent to 30 percent, and the cumulative risk of sudden death during vigorous exercise over the 20-year period increased from 0.05 percent to 0.11 percent to 0.20 percent. Whereas the overall risk of sudden death during a single episode of vigorous exercise was 1 in 1.51 million, the cumulative risk in the men who exercised five or more times per week was 1 in 500. If the hours of vigorous exercise per year are estimated at 26, 121, and 309 for the three groups and correlated linearly with the 20-year risk of sudden death during exercise, the result is a line with an r of 0.997 and a positive slope, indicating that the cumulative risk of dying suddenly during vigorous exercise over a 20-year period increases by 0.1 percent for every 200 hours of vigorous exercise per year. Thus, the results do not appear to support increasing the frequency of vigorous exercise to protect against sudden death from cardiac causes during vigorous exercise, since the risk associated with achieving protection appears to be greater than the protection conferred.

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1. Albert CM, Mittleman MA, Chae CU, Lee I-M, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med* 2000;343:1355-61.

To the Editor: In their analysis of the data from the Physicians' Health Study, Albert et al. used a nested case-cross-over design¹ to quantify the relative risk of sudden death from cardiac causes during or shortly after vigorous exercise (defined as 30 minutes of 6 MET or more) as compared with the risk during periods of light exertion or none. Their results suggest a relative risk of about 74 for men who engaged in habitual vigorous exercise less than one time per week, a relative risk of about 19 for men who exercised one to four times per week, and a relative risk of about 11 for men who exercised five or more times per week. I used the nested case-cross-over method to see whether an optimal pattern of exercise — one associated with a minimal risk of sudden death from cardiac causes — exists.

The relative risk for this case is essentially a function of the fraction of sudden deaths associated with vigorous exercise (i.e., $F_x/[1-F_x]$) divided by the proportion of time a person exercises (i.e., $P_x/[1-P_x]$).¹ As the proportion of time spent exercising increases, the fraction of deaths related to exercise increases, as shown in Table 2 of the article. These relative changes suggest that an optimal pattern of exercise may exist. Extrapolating from the Physicians' Health Study data and using the case-cross-over methods, I conclude that the optimal frequency of exercise appears to be 30 to 45 minutes per day, seven days per week. In contrast, two hours of exercise per day, seven days per week, increases the minimal risk by 50 percent.

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1. Maclure M. The case-cross-over design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;133:144-53.

To the Editor: The article by Albert et al. reinforces the importance of regular physical exercise and raises new issues with regard to the potential hazards of vigorous exertion. However, we were surprised to find that neither the article nor its accompanying editorial mentioned a previously proposed hypothesis to explain these findings. It is

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well known that potassium is released from exercising muscle because of depolarization of the myocyte membrane. Most of the released potassium is quickly transported back into the myocytes by Na^+/K^+ -ATPase, but with strenuous exercise a fraction enters the systemic circulation, resulting in marked elevations in serum levels of potassium, which can exceed 8 mmol per liter.^{1,2} Physical training attenuates this rise in potassium levels.³ Hence, it has previously been suggested that the rapid change in serum potassium levels in response to vigorous exercise may play a part in sudden death.⁴ Given these data and the consistent findings in the study by Albert et al., we believe that severe hyperkalemia should be considered as a potential contributing factor to at least some of the deaths in their study. If this is indeed the case, then the use of potassium-modulating drugs, particularly beta-blockers, requires scrupulous attention, especially in poorly conditioned patients who are contemplating beginning a regimen of regular vigorous exercise.

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1. Bystrom S, Sjogaard G. Potassium homeostasis during and following exhaustive submaximal static handgrip contractions. *Acta Physiol Scand* 1991;142:59-66.
2. Medbo JJ, Sejersted OM. Plasma potassium changes with high intensity exercise. *J Physiol* 1990;421:105-22.
3. Kjeldsen K, Norgaard A, Hau C. Exercise-induced hyperkalaemia can be reduced in human subjects by moderate training without change in skeletal muscle Na^+/K^+ -ATPase concentration. *Eur J Clin Invest* 1990;20:642-7.
4. Lindinger MI. Potassium regulation during exercise and recovery in humans: implications for skeletal and cardiac muscle. *J Mol Cell Cardiol* 1995;27:1011-22.

The authors reply:

To the Editor: Dr. Kessler and Dr. Swanson accurately point out that as the absolute amount of time spent in vigorous exertion increased, the absolute number of sudden deaths that occurred in association with exertion also increased during the 12 (not 20) years of our study. Dr. Kessler interprets these data as evidence that the risk of sudden death associated with vigorous exertion is greater than the protection such exertion confers. However, this is not entirely valid, since a relation would be found even if there were no effect of vigorous exertion on the occurrence of sudden death. As one spends more time exercising, the probability that sudden death will occur during exercise would be expected to increase proportionately. Therefore, a simple correlation of the unadjusted data as performed by Dr. Kessler artificially inflates the true risk. The case-crossover method adjusts for this by having patients serve as their own controls and by placing the time each patient spends engaged in vigorous exertion in the denominator of the rate ratio.¹ As displayed in Table 2 of our article, the risk of sudden death during or shortly after vigorous exertion was significantly attenuated with increasing frequency of vigorous exertion. However, it is true that the risk remained significantly elevated in even the most active men. Therefore, this elevation in the transient risk over time could eventually translate into a small increase in the absolute risk of sudden death during exertion in the active men. However, this risk is clearly balanced by the other cardioprotective

benefits of exercise,² including protection against nonsudden death from coronary heart disease,³ stroke,⁴ nonfatal myocardial infarction, and death from all cardiovascular causes.⁵

With respect to Dr. Swanson's calculation of the optimal time to spend engaged in exertion, it is unclear to us how our data and the formula he provides can be used to calculate the optimal time spent exercising. First, the formula eliminates the use of patients as their own controls, which is a major strength of the case-crossover analysis.¹ Second, we did not have direct data on the duration of vigorous exertion and did not provide data on the number of sudden deaths during exertion in those who exercise daily. Therefore, we do not believe our data can be used to support his conclusion. Finally, the hypothesis of Drs. Kochlatyi and Mattana regarding changes in serum potassium levels is interesting and plausible; however, we do not feel that the evidence is strong enough to argue against the use of beta-blockers, which are among the few drugs known to be effective in preventing sudden death.

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1. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;133:144-53.
2. Maron BJ. The paradox of exercise. *N Engl J Med* 2000;343:1409-11.
3. Albert CM, Mittleman MA, Chae CU, Lee I-M, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med* 2000;343:1355-61.
4. Lee I-M, Hennekens CH, Berger K, Buring JE, Manson JE. Exercise and risk of stroke in male physicians. *Stroke* 1999;30:1-6.
5. Chae CU, Albert CM, Lee I-M, Manson JE, Hennekens CH. Relative importance of frequency vs. duration of physical activity in CHD risk reduction in the Physicians' Health Study. *Circulation* 1997;96:Suppl:1-303. abstract.

Prevention of Hip Fracture with Use of a Hip Protector

To the Editor: Kannus et al. (Nov. 23 issue)¹ report that the use of external hip protectors reduces the risk of hip fracture in elderly people by 60 percent. We believe that there is uncertainty about the magnitude of the effect because the analysis was not performed on an intention-to-treat basis. The authors excluded 298 subjects who declined to participate after randomization, 68 percent of whom had been assigned to the hip-protector group. An additional 657 subjects dropped out after the study had begun. Some of those who dropped out were replaced by subjects from the waiting list (95 percent of those who dropped out in the hip-protector group were replaced, as compared with only 38 percent in the control group). The rate of "refusal to continue" was also higher in the hip-protector group.

The authors report the rate of falls among subjects in the hip-protector group, but not among those in the control group. If the rate of falls in the intervention group was

lower than that in the control group, it might suggest the use of some cointervention.

The subjects were assigned to study groups by block randomization, according to treatment units, but the data were analyzed as if randomization had been done at the level of individual subjects. This aspect of the analysis of previously published trials of hip protectors has been criticized.² Also, the number of blocks is unclear from the report because the total number of treatment units within the 22 community-based health care centers is not stated.

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1. Kannus P, Parkkari J, Niemi S, et al. Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 2000;343:1506-13.
2. Parker MJ, Gillespie LD, Gillespie WJ. Hip protectors for preventing hip fractures in the elderly (Cochrane Review). *Cochrane Database Syst Rev* 2000;4:CD001255 (software).

To the Editor: Kannus et al. state that subjects with a history of fractures were included in their study, but they do not say how many of these patients had a previous hip fracture or any previous surgery for such a fracture. Periprosthetic hip fractures, if they occurred, would bias the study, as would the mere presence of a prosthetic device, because it might protect against falls.

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To the Editor: Kannus et al. document the effectiveness of hip protectors in preventing hip fractures. However, in their study, compliance was problematic: 31 percent of the subjects refused to wear the protector at all, and many of the fractures in the hip-protector group occurred when the protector was not being worn. Subjects may not wear hip protectors for many reasons, among them discomfort (e.g., the protector is too tight, too warm, or too unpleasant to wear), appearance (e.g., the bulkiness of the protector makes the subject appear chubby), and practicality (e.g., the protector interferes with the ability to use the toilet). These obstacles can be addressed through modifications in design. However, noncompliance with the use of hip protectors is more complex.

The cost of hip protectors in the United States must often be borne by the subjects themselves. Because older people are largely uneducated about the value of hip protectors, they may not be willing to pay for them. Subjects who are knowledgeable about their risk of hip fracture are more likely to purchase and use a protector. Also, allowing subjects to wear a protector only when they engage in activities that increase their risk of fracture (e.g., going outdoors on windy or wintry days or days when their balance seems especially poor), rather than insisting on daily use, improves compliance. In addition, a fear of falling associated with restricted mobility motivates many people to try protectors. Finally, the attitudes of health care providers

toward hip protectors are important. If health care providers are not convinced of the benefits of hip protectors, then their patients will not be convinced either.

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To the Editor: A possible reason for the underuse of hip protectors may be uncertainty as to who should prescribe these devices; in particular, there may be a reluctance among orthopedic surgeons to address issues of preventive care. We recently conducted a survey of all orthopedic surgeons in the Republic of Ireland, in which we asked about the treatment of a hypothetical patient presenting with a hip fracture and a history of a previous osteoporotic fracture.¹ A total of 89 of 133 surgeons replied — a response rate of 67 percent. Only one of these surgeons would recommend a hip protector for such a high-risk patient.

Surgeons in the United States seem similarly reluctant to recommend hip protectors. In correspondence with a hip-protector manufacturer in the United States, we were told that the company has not sold a hip protector to an orthopedic surgeon in the past five years. Hip protectors have been purchased by physical therapists, occupational therapists, and geriatric and family physicians. Given the data we now have on the benefits of hip protectors, guidelines are needed from the professional associations in order to prevent patients who might benefit from this device from slipping through the cracks between generalist and specialist care.

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1. Sheehan J, Mohamed F, Reilly M, Perry IJ. Secondary prevention following fractured neck of femur: a survey of orthopaedic surgeons practice. *Ir Med J* 2000;93:105-7.

Dr. Kannus replies:

To the Editor: Cameron and colleagues discuss problems that are difficult to avoid in studies that cannot use double blinding. We used an intention-to-treat analysis for all the subjects who did not refuse to participate by comparing the hip-protector group to the control group, irrespective of the use of the device. According to the standards of investigation involving human subjects, we could not follow the persons who initially declined to participate. The dropout rate was similar in the two groups (49 percent in the hip-protector group and 45 percent in the control group), although the reasons for dropping out differed somewhat between the groups. The difference between the groups in terms of “refusal to continue” might be related in part to the protector, but since the subjects did not have to specify the reasons for their withdrawal of consent, this matter could not be analyzed further. During the trial, somewhat less attention was paid to recruiting new subjects for the control group, because there were 981 subjects in this group at base line (the sample size required according to the cal-

cultation of statistical power was 820 persons). The rate of fall-induced fractures other than hip and pelvis fractures was similar in the two groups, providing evidence that the rate of falling must have been similar in these groups and that no cointervention (attention effect) occurred in the hip-protector group.

Concerning Haranath's comments: 82 subjects in the hip-protector group (12.6 percent) and 125 subjects in the control group (10.9 percent) had a history of hip fracture when they entered the study. All were treated surgically, but fewer than 50 percent had a prosthesis. During the trial, only two periprosthetic hip fractures occurred, so these could not have biased the study. A prosthetic device is not necessarily protective against falling and fracture.

My colleagues and I agree with Tideiksaar that compliance by users is a problem with hip protectors, but we believe that, with proper education, compliance can become as good as that in our study (69 percent of subjects initially accepted the hip protectors, and 74 percent of falls in the hip-protector group occurred while the subject was wearing the protector). Design modifications to provide even greater comfort are welcome, but should not be made at the cost of reduced safety.

We agree with Sheehan and Perry that surgeons should be more aware of hip protectors. However, if general guidelines on hip protection are promulgated, they must be evidence based and protector specific; the results achieved with one protector in preventing fractures cannot be generalized to other hip-protection systems.¹ Each hip protector has to be studied individually, beginning with the biomechanical antifracture efficacy in vitro and in actual falls, continuing with compliance by users, and ending with a user-control comparison in a randomized study.

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1. Kannus P, Parkkari J, Poutala J. Comparison of force attenuation properties of four different hip protectors under simulated falling conditions in the elderly: an in vitro biomechanical study. *Bone* 1999;25:229-35.

Myocarditis

To the Editor: A large variety of infectious agents are associated with acute and chronic myocarditis, as discussed by Feldman and McNamara (Nov. 9 issue).¹ In areas infested with vector ticks of Lyme borreliosis, infection with *Borrelia burgdorferi* may also be involved in myocarditis, pericarditis, and cardiac-rhythm disorders.²

The seminal description of a patient with dilated cardiomyopathy and culture of an endomyocardial-biopsy specimen that was positive for *B. burgdorferi* was published in the *Journal*.³ Specific histologic staining may also confirm the diagnosis of Lyme borreliosis in acute myocarditis; however, as with other causes of myocarditis, even negative results cannot rule out the infection. To support the diagnosis in patients with positive serologic findings, use of antimyosin scintigraphy, echocardiography, and magnetic resonance imaging can be helpful.⁴

Treatment with appropriate antibiotics may lead to improvement of ventricular function in myocarditis and even cardiomyopathy due to Lyme borreliosis.^{3,5} Thus, in areas

where the disease is endemic, Lyme borreliosis should be considered in the differential diagnosis of perimyocarditis.

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1. Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388-98.
2. Steere AC. Lyme disease. *N Engl J Med* 1989;321:586-96.
3. Stanek G, Klein J, Bittner R, Glogar D. Isolation of *Borrelia burgdorferi* from the myocardium of a patient with longstanding cardiomyopathy. *N Engl J Med* 1990;322:249-52.
4. Bergler-Klein J, Sochor H, Stanek G, Globits S, Ullrich R, Glogar D. Indium 111-monoclonal antimyosin antibody and magnetic resonance imaging in the diagnosis of acute Lyme myopericarditis. *Arch Intern Med* 1993;153:2696-700.
5. Gasser R, Fruhwald F, Schumacher M, et al. Reversal of *Borrelia burgdorferi* associated dilated cardiomyopathy by antibiotic treatment? *Cardiovasc Drugs Ther* 1996;10:351-60.

To the Editor: Feldman and McNamara mention thyrotoxicosis as an immune-mediated cause of myocarditis. I wonder how they come to this view.

As far as I know, there are only rare case reports of cardiomyopathy associated with Graves' disease.¹ Despite the fact that thyrotropin-receptor messenger RNA has been found by several investigators to be expressed in the myocardium,^{1,3} the authors of a recent report on a series from the Mayo Clinic⁴ concluded on the basis of endomyocardial-biopsy findings that "among patients with Graves' disease, most cases of low-output cardiac dysfunction appear to be due to causes other than an active autoimmune inflammatory process."

Are there other data of which I am unaware? The clinical ramification of this issue seems important: should a patient with Graves' disease and concomitant low-output cardiac dysfunction be evaluated for myocarditis, or is this unnecessary because of a "well-known" relation?

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1. Koshiyama H, Sellitti DF, Akamizu T, et al. Cardiomyopathy associated with Graves' disease. *Clin Endocrinol (Oxf)* 1996;45:111-6.
2. Drvota V, Janson A, Norman C, et al. Evidence for the presence of functional thyrotropin receptor in cardiac muscle. *Biochem Biophys Res Commun* 1995;211:426-31.
3. Sellitti DF, Hill R, Doi SQ, et al. Differential expression of thyrotropin receptor mRNA in the porcine heart. *Thyroid* 1997;7:641-6.
4. Fatourechi V, Edwards WD. Graves' disease and low-output cardiac dysfunction: implications for autoimmune disease in endomyocardial biopsy tissue from eleven patients. *Thyroid* 2000;10:601-5.

To the Editor: The important review article on myocarditis by Feldman and McNamara is very carefully written and clearly documented. However, Table 1, entitled Causes of Myocarditis, mislabels actinomycetes as a fungus. Actinomycetes are anaerobic, non-spore-forming, gram-positive bacilli.¹ In addition, since the authors separate bacterial from spirochetal causes of myocarditis, why does *Treponema pallidum* remain in the first group?

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1. Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 3rd ed. St. Louis: Mosby, 1998.

The authors reply:

To the Editor: Drs. Bergler-Klein and Stanek raise important points regarding the importance of considering Lyme borreliosis as a possible cause of myocarditis in areas infected with vector ticks. However, we would argue that antimyosin scintigraphy does not have sufficient sensitivity and specificity to be useful in the diagnosis and that serologic analysis is far more useful.

Our inclusion of thyrotoxicosis as an immune-mediated cause of myocarditis is based on rare case reports in which thyroiditis was associated with myocarditis in a patient with severe lupus,¹ a patient with both giant-cell thyroiditis and myocarditis,² and a woman during the postpartum period.³ Although the recent report from the Mayo Clinic⁴ suggests that autoimmune myocardial disease in patients with thyroiditis is a rare finding, the possibility of its presence should not be overlooked in patients who have relevant symptoms.

It is correct that actinomyces are gram-positive bacteria, not fungi.

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1. Macro M, Le Gangneux E, Gallet E, Maragnes P, Galateau F, Loyau G. Severe lupus with infectious thyroiditis and lethal cardiomyopathy. *Clin Exp Rheumatol* 1995;13:99-102.
2. Benisch BM, Josephson M. Subacute (giant cell) thyroiditis and giant cell myocarditis in patient with carcinoma of lung. *Chest* 1973;64:764-5.
3. Yagoro A, Tada H, Hidaka Y, et al. Postpartum onset of acute heart failure possibly due to postpartum autoimmune myocarditis: a report of three cases. *J Intern Med* 1999;245:199-203.
4. Fatourechhi V, Edwards WD. Graves' disease and low-output cardiac dys-

function: implications for autoimmune disease in endomyocardial biopsy tissue from eleven patients. *Thyroid* 2000;10:601-5.

Case 30-2000: Churg–Strauss Syndrome

To the Editor: Dr. Arm's discussion (Sept. 28 issue)¹ of a case of the Churg–Strauss syndrome in a man who was receiving multiple asthma medications, including montelukast (Singulair, Merck), did not include important medical history. Information received through our pharmacovigilance program indicates that, before treatment with montelukast was started, the patient had recurrent bilateral pulmonary infiltrates and an ill-defined episode of asthma, diarrhea, weight loss, anemia, and pleural effusion, which responded rapidly to treatment with high doses of corticosteroids. All this suggests that the patient had a forme fruste of the Churg–Strauss syndrome before the initiation of montelukast.

Elements of the Churg–Strauss syndrome (Table 1), in addition to asthma, were observed before the initiation of montelukast treatment in 14 of the first 16 reports to Merck of the Churg–Strauss syndrome in association with montelukast use. As in the case discussed by Arm, this sequence appears to rule out montelukast as a primary cause of the Churg–Strauss syndrome in these cases. Corticosteroids were withdrawn or reduced before the diagnosis in 15 of the 16 reports. As suggested by Wechsler et al.,² a reduction in corticosteroids, which might be facilitated by the use of a leukotriene modifier, may play a decisive part in the appearance of the Churg–Strauss syndrome.

The patient described in the Case Records was also included (as Case 2) in a report by Wechsler et al.³

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TABLE 1. PRIOR MANIFESTATIONS OF THE CHURG–STRAUSS SYNDROME IN PATIENTS WHO WERE GIVEN A DIAGNOSIS OF THE SYNDROME AFTER THERAPY WITH MONTELUKAST.

PATIENT No.	DURATION OF ASTHMA	MARKED EOSINOPHILIA	PULMONARY INFILTRATES	VASCULITIS
	yr			
1	10	Peripheral blood		Cardiac and neurologic involvement
2	1.3			
3	7	Peripheral blood		
4	16	Peripheral blood		
5	16	Peripheral blood	+	Cardiac involvement (Churg–Strauss syndrome diagnosed)
6	27	Peripheral blood	+	
7	4	Peripheral blood		Neurologic and skin involvement
8	0.2			
9	6		+	Neurologic and skin involvement
10	15	Peripheral blood		
11	22	Peripheral blood		Joint involvement
12	1.5		+	
13	3	—*		
14	24	Peripheral blood		
15	6	Peripheral blood		
16	2	—*		Skin involvement (Churg–Strauss syndrome diagnosed)

*This patient had eosinophilic infiltration of nonpulmonary tissue.

1. Case Records of the Massachusetts General Hospital (Case 30-2000). *N Engl J Med* 2000;343:953-61.
2. Wechsler ME, Pauwels R, Drazen JM. Leukotriene modifiers and Churg-Strauss syndrome: adverse effect or response to corticosteroid withdrawal? *Drug Saf* 1999;21:241-51.
3. Wechsler ME, Finn D, Gunawardena D, et al. Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. *Chest* 2000;117:708-13.

Dr. Arm replies:

To the Editor: I am grateful to Gruer and colleagues for their comments on this case. The additional history they provide was not available to me at the time of the case presentation. The apparent association of the introduction of a new asthma therapy with the onset of the Churg-Strauss syndrome has been observed for medications other than leukotriene-modifying drugs, such as inhaled corticosteroids.¹ Wechsler has suggested that this apparent association may be due to the withdrawal of corticosteroids or may reflect the natural history of a disease in which new therapy has been introduced in the presence of worsening asthma.² The pathobiology and epidemiology of the Churg-Strauss syndrome are poorly understood, making it difficult to comment on the possible role of certain asthma therapies in facilitating the onset or progression of the syndrome in a subgroup of patients. The Churg-Strauss syndrome is a rare disease, and modern asthma therapy, including low-to-moderate doses of inhaled corticosteroids and leukotriene-modifying drugs, provides effective and safe treatment in the majority of patients. When oral corticosteroids are withdrawn, patients should be carefully monitored for evidence of systemic disease.

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1. Wechsler ME, Finn D, Gunawardena D, et al. Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. *Chest* 2000;117:708-13.
2. Le Gall C, Pham S, Vignes S, et al. Inhaled corticosteroids and Churg-Strauss syndrome: a report of five cases. *Eur Respir J* 2000;15:978-81.

Biventricular Cardiac Thrombosis during Interleukin-2 Infusion

To the Editor: We report on the phenomenon of intracardiac thrombosis with features of Löffler's syndrome observed in conjunction with interleukin-2 therapy.

Patient 1, a 26-year-old woman with stage IV Hodgkin's disease, began to receive a continuous infusion of recombinant human interleukin-2 (aldesleukin; Proleukin, Chiron) in an experimental outpatient protocol; the initial dose was 75,000 IU per kilogram of body weight per day and was increased weekly, as tolerated, to a maximum of 150,000 IU per kilogram per day. The patient had a corresponding increase in eosinophils in peripheral blood to a maximum of 11,400 cells per cubic millimeter.

On day 27 of therapy, she presented with a two-day history of increasing fatigue. Her heart rate was 120 beats per minute, her blood pressure was 79/50 mm Hg, her respiratory rate was 16 per minute, and her temperature was 97.7°F. The oxygen saturation while the patient was breath-

ing room air was 95 percent. The patient had normal findings on cardiac auscultation, clear lungs, an enlarged, tender liver that was palpable 10 cm below the right costal margin, no ascites, and no pedal edema. Laboratory evaluation revealed leukocytosis (white-cell count, 15,900 per cubic millimeter) with eosinophilia (33 percent; absolute count, 5300 per cubic millimeter), a hematocrit of 27 percent, and a platelet count of 17,000 per cubic millimeter.

Interleukin-2 treatment was discontinued, but the patient's condition deteriorated. Surface echocardiography showed bilateral intraventricular masses. The patient died on day 29. An autopsy showed biventricular thrombi, normal coronary arteries, and prominent eosinophilic infiltration of the endomyocardium (Fig. 1).

Subsequent patients were monitored by surface echocardiography during the study. Patient 2 (the 11th patient treated and the 2nd with findings), a 33-year-old woman with stage IV Hodgkin's disease, was treated with a continuous infusion of interleukin-2 at 75,000 to 234,000 IU per kilogram per day, and had a maximal eosinophil count of 5000 per cubic millimeter. An asymptomatic change in cardiac function developed during a three-week period of exposure to interleukin-2 (week 6 to week 8), with gradual thickening of the apical left ventricular and right ventricular walls, which was interpreted as early thrombus formation, focal abnormalities of apical motion, and a reduction in the ejection fraction from 55 percent to 40 percent, without elevations in creatine kinase. Treatment with interleukin-2 was discontinued. Prompt normalization of the ejection fraction was followed later by spontaneous resolution of thrombus and wall-motion abnormalities.

Interleukin-2 therapy is associated with increased peripheral eosinophilia; the eosinophil count may exceed 5000 to 10,000 per cubic millimeter.¹ In turn, hypereosinophilia has been associated with cardiac fibrosis, ventricular thrombosis, and death in diverse disorders collectively known as Löffler's syndrome (as well as eosinophilic endomyocardial disease and tropical endomyocardial fibrosis),² but these findings have not been associated with interleukin-2 therapy.³ Released eosinophil cationic proteins have been proposed as the mechanism of damage to the endocardium that initiates thrombus development.⁴ Typically, symptomatic cardiac disease occurs after periods of hypereosinophilia lasting several months to years.² Hence, death due to thrombosis in Patient 1 was unusually rapid for any cause.

This catastrophic event prompted us to perform prospective serial echocardiography on subsequent patients receiving prolonged infusion of interleukin-2. We observed early signs of thrombosis in 1 additional (asymptomatic) patient among the next 10 (Patient 2), for an incidence of 1 in 10, or 10 percent (95 percent confidence interval, 0.5 percent to 45 percent; the index case is not included in the statistical analysis). The signs fully reversed after the withdrawal of interleukin-2. The reversal of thrombus and improved cardiac function in Patient 2 are in accord with prior reports on the reversal of eosinophilia in Löffler's syndrome from other causes.⁵

The long history of clinical applications of interleukin-2, and the lack of clinical recognition of an association with intracardiac thrombosis with features of Löffler's syndrome,³ both strongly support the safety of interleukin-2 as it is currently used. For newer regimens employing longer, uninterrupted schedules of infusion, however, this report may serve to create awareness of a potentially impor-

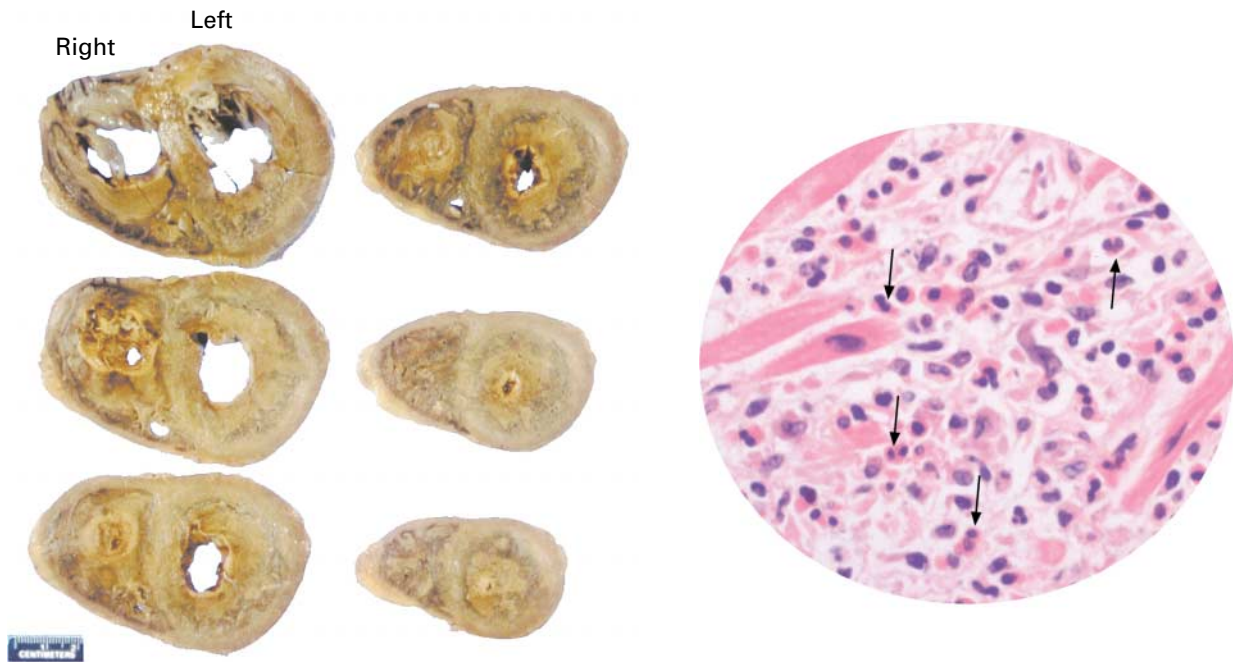


Figure 1. Pathological Evaluation of the Heart of Patient 1.

Serial sections are shown. Approaching the apex, there is a progressive occlusion of the right and left ventricular chambers by thrombi. Microscopical evaluation of a section stained with hematoxylin and eosin (inset, $\times 1000$) of subendocardial ventricular tissue revealed eosinophilic infiltration. Eosinophils (arrows) were abundant in the vessels, in the paravascular myocardial tissue, and in the thrombus (not shown), which had various levels of organization.

tant alternative in the differential diagnosis of symptoms that occur during interleukin-2 therapy.

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