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Patient Care after Percutaneous Coronary Artery Interventions

To the Editor: In their excellent review (1), O'Meara and Dehmer mention that many drugs have been used to inhibit restenosis but that favorable effects were found only in some small studies and no large randomized trial has identified an effective drug. However, a large randomized, well-designed study (2) showed that treatment with probucol substantially reduces luminal narrowing after balloon coronary angioplasty.

In this study of 317 patients, 500 mg of probucol was given twice daily for 4 weeks before and 6 months after angioplasty. The restenosis rate (as defined by quantitative coronary angiography) was 38.9% in the placebo group and 20.7% in the probucol group ($P = 0.003$); the rate of repeated angioplasty was 26.6% in the placebo group and 11.2% in the probucol group ($P = 0.009$). These results are similar to the restenosis rate obtained with coronary artery stenting (3, 4).

Probucol is a cholesterol-lowering drug that has potent antioxidant properties. The mechanism by which probucol reduces the restenosis rate is not entirely clear. Although the drug's antioxidant properties were thought to be important, a different mixture of less potent antioxidants (β-carotene, vitamin C, and vitamin E) did not reduce rates of restenosis or repeated angioplasty in the same study. On the other hand, probucol reduced both low- and high-density lipoprotein cholesterol levels, an effect that may offset its beneficial effect as a lipid-lowering agent.

To date, probucol is the only pharmacologic agent conclusively shown to prevent coronary restenosis after balloon angioplasty.

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References

1. **O'Meara JJ, Dehmer GJ.** Care of the patient and management of complications after percutaneous coronary artery interventions. Ann Intern Med. 1997;127:458-71.
2. **Tardif JC, Côté G, Lespérance J, Bourassa M, Lambert J, Doucet S, et al.** Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. N Engl J Med. 1997;337:365-72.
3. **Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al.** A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994;331:489-95.
4. **Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al.** A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994;331:496-501.

To the Editor: In a review of complications after coronary intervention (1), O'Meara and Dehmer state that the incidence of contrast nephropathy after such intervention is unknown. They also state that renal failure due to this condition is nonoliguric and rarely requires dialysis and that most patients have an uneventful course.

In the past year, we presented results from a cohort study regarding this problem in patients after coronary intervention (2–4). In a derivation set of 1826 consecutive patients, we found the incidence of contrast nephropathy (defined as a transient increase in serum creatinine level >25% above baseline) to be 144.6/1000 cases. The incidence of acute renal failure requiring dialysis was 7.7/1000. The mean in-hospital mortality rate for patients who required dialysis was 35.7%, and the 2-year survival rate was 18.8%. The mortality rate for patients without acute renal failure was 1.1%, and the rate for patients with renal failure who did not require dialysis was 7.1%.

We agree that contrast nephropathy requiring dialysis is rare (incidence < 1%). When it does occur, however, it is associated with high in-hospital mortality rates and poor long-term survival. This example points out the need for *Annals* and other journals to adopt explicit review and search criteria for summary articles so that the published papers include the most comprehensive and contemporary studies available in full-length and abstract form. In this instance, we believe that this additional information aids in the authors' mission to provide the specialist with a firm working knowledge of complications after coronary intervention.

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References

1. **O'Meara JJ, Dehmer GJ.** Care of the patient and management of complications after percutaneous coronary artery interventions. Ann Intern Med. 1997;127:458-71.
2. **McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW.** Acute contrast nephropathy after coronary intervention: incidence, risk factors, and relationship to mortality [Abstract]. J Am Coll Cardiol. 1996; 27(Suppl A):304A-5A.
3. **McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW.** Acute contrast nephropathy after coronary intervention: prediction of dialysis and related mortality in the elderly [Abstract]. Am J Geriatr Cardiol. 1996;5:52.
4. **McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW.** Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med. 1997;103:368-75.

To the Editor: As a general internist practicing hospital-based internal medicine, I found the recent article by O'Meara and Dehmer (1) informative and clinically applicable. As the authors point out, clinicians caring for patients who have recently undergone a percutaneous coronary procedure need to be alert for myriad potential complications. Some of these complications may involve the kidneys and lead to electrolyte derangements and acute renal failure. The authors note that therapy with certain drugs may need to be discontinued before the procedure to minimize the risk for renal injury. Drugs that are known to affect potassium homeostasis and may lead to hyperkalemia include

trimethoprim, heparin, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and β-adrenergic antagonists (2). Patients with underlying chronic renal insufficiency or diabetic nephropathy could experience hyperkalemia if these drugs are used, especially in the setting of dye nephropathy (2).

Another renal complication of percutaneous coronary artery interventions not mentioned by the authors is the cholesterol embolism syndrome, or diffuse atheroembolism. This syndrome, characterized by diffuse embolization of disrupted atherosclerotic plaques, typically occurs after manipulation of the aorta during catheter-based or surgical procedures and may occur in up to 26% of patients undergoing coronary angiography (3–5). Clinical clues to the cholesterol embolism syndrome include fever, livedo reticularis, and blue toes, often with eosinophilia, an elevated erythrocyte sedimentation rate, and hypocomplementemia (3, 5). This syndrome frequently leads to renal failure, usually a few weeks after the predisposing procedure. Thus, clinicians must consider diffuse atheroembolism in patients with worsening renal function after a percutaneous coronary artery procedure.

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References

1. **O'Meara JJ, Dehmer GJ.** Care of the patient and management of complications after percutaneous coronary artery interventions. Ann Intern Med. 1997;127:458-71.
2. **Marinella MA.** Hyperkalemia in elderly patients associated with trimethoprim-sulfamethoxazole. J Geriatr Drug Ther. 1996;11:93-7.
3. **Mayo RR, Swartz RD.** Redefining the incidence of clinically detectable atheroembolism. Am J Med. 1996;100:524-9.
4. **Ramirez G, O'Neill WM, Lambert R, Bloomer HA.** Cholesterol embolization: a complication of angiography. Arch Intern Med. 1978;138:1430-2.
5. **Marinella MA.** Cholesterol crystal embolism [Letter]. Lancet. 1996;348:403-4.

To the Editor: Although O'Meara and Dehmer's discussion of contrast-induced nephropathy was illuminating (1), the authors did not mention another renal complication of these interventions—cholesterol atheroembolic renal disease. This is concerning because the disease is the major consideration in the differential diagnosis of contrast nephropathy and diagnosis of atheroembolic renal disease relies on a high index of suspicion.

Cholesterol atheroembolic renal disease results when cholesterol crystals separate from atheromatous plaques; lodge in small renal arteries; and cause ischemia, renal failure, and perivascular inflammation. Embolization results from mechanical disruption of atheromatous plaque during angiographic procedure or, rarely, results spontaneously (2). It is also helpful to note the differences between contrast nephropathy and atheroembolic renal disease. The former presents with renal failure soon after exposure to contrast (24 to 48 hours) and reaches a nadir in 3 to 4 days. Complete renal recovery occurs within a few days. The onset of atheroembolic renal disease may be delayed for several days or weeks after the inciting event, progression of renal failure is often slow, and recovery of renal function is less likely (3). Finally, atheroembolic renal disease may present with other features, such as flank pain, hematuria, eosinophilia, livedo reticularis, changes in the lower extremities, and retinal plaque (4).

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References

1. **O'Meara JJ, Dehmer GJ.** Care of the patient and management of complications after percutaneous coronary artery interventions. Ann Intern Med. 1997;127:458-71.
2. **Colt HG, Begg RJ, Saporito JJ, Cooper WM, Shapiro AP.** Cholesterol emboli after cardiac catheterization. Eight cases and review of the literature. Medicine (Baltimore). 1988;67:389-400.
3. **Fine MJ, Kapoor W, Falanga V.** Cholesterol crystal embolization. A review of 221 cases in the English literature. Angiology. 1987;38:769-84.
4. **Tunick PA, Perez JL, Kronzon I.** Protruding atheromas in the thoracic aorta and systemic embolization. Ann Intern Med. 1991;115:423-7.

In response: Dr. Rashdan cites the results of a recent trial in which probucol was used to limit restenosis after angioplasty (1). This report was published on 7 August 1997, well after our manuscript had been accepted and typeset for publication. We did not include the abstract form of this study because the number of probucol recipients reported in the abstract was small ($n = 91$) and the reduction in restenosis (35.2% in the placebo group and 22.6% in the probucol group; $P = 0.055$) was of borderline significance (2). Experience with restenosis trials has repeatedly shown that drugs, thought to be beneficial in small studies, often have no effect when examined in large trials. In this case, however, the full-length paper reported on 180 probucol recipients and showed significant results. The value of an abstract is sometimes hard to judge. Data presented in some abstracts are excellent and result in major publications; others, however, do not survive the peer review process or are substantially different when published in full-length form. For this reason, some journals do not allow the citation of abstracts and others only allow the citation of abstracts less than 2 years old.

The letter from Drs. McCullough and O'Neill requires two comments. First, these authors express concern about what constitutes an appropriate literature search for a review article. At the time we wrote our paper, their study of contrast nephropathy after coronary interventions had been published twice in abstract form. Cardiology abstracts are not listed in any of the major computerized databases, including MEDLINE. The only way to search abstracts is by manually reviewing abstract booklets or finding them in the reference list of a published paper. In the abstracts for the 1996 meeting of the American College of Cardiology, the study by McCullough and colleagues is presented in a section titled "Age, Lipids, Clots and Dysrhythmias," an odd place for an abstract related to contrast nephropathy (3). Moreover, the abstract is not indexed under the key words *angioplasty*, *angiography*, or *contrast media* but is listed only under *renal function*. This abstract was not included because, honestly, we just missed it. Had we not, we would have included it because the retrospective analysis is the only information we are aware of specifically related to contrast nephropathy after coronary interventions.

Second, what are the important points of this abstract, and how do they differ from our paper? McCullough and O'Neill's observations reaffirm almost everything we said in our paper. Contrast nephropathy rarely requires dialysis (0.8% of cases in McCullough and colleagues' data set) and is independently related to baseline creatinine level, diabetes, and the amount of contrast used. Our results differ on the long-term outlook for patients. McCullough and O'Neill state that the in-hospital mortality rate for patients requiring dialysis is 36%, with a 2-year survival rate of only 19%. These sobering statistics differ from our own experience and published data on contrast nephropathy occurring in situations other than coronary interventions. This difference may exist because of other comorbid conditions, such as acute myocardial infarction, but McCullough and colleagues' abstract provides no such data that might allow for risk adjustments. This lack of information highlights some of the difficulties encountered in the evaluation of abstracts. McCullough and associates' perspective is important, and we are sorry we failed to include it. Readers should note that the full-length report of McCullough and colleagues' work was recently published (4).

Dr. Marinella lists several drugs that contribute to hyperkalemia, especially in the setting of contrast nephropathy. All of these drugs are important, and we thank him. Both Dr. Marinella and Dr. Nzerue comment that we neglected to mention cholesterol embolization. In our experience, this is a serious but uncommon event. As Dr. Nzerue notes, there are differences between contrast nephropathy and cholesterol atheroembolism.

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References

1. **Tardif JC, Côté G, Lespérance J, Bourassa M, Lambert J, Doucet S, et al.** Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. N Engl J Med. 1997;337:365-72.
2. **Tardif JC, Côté G, Lespérance J, Bourassa M, Bilodeau J, Doucet S, et al.** Prevention of restenosis by pre and post-PTCA probucol therapy. A

randomized clinical trial [Abstract]. Circulation. 1996;94(Suppl I):I-91.
3. **McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW.** Acute contrast nephropathy after coronary intervention: incidence, risk factors, and relationship to mortality [Abstract]. J Am Coll Cardiol. 1996; 27(Suppl A):304A-5A.
4. **McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW.** Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med. 1997;103:368-75.

Catheter-Related Bacteremia in Patients Undergoing Hemodialysis

To the Editor: In the article on the advisability of maintaining an infected catheter in patients who are undergoing hemodialysis and have catheter-related bacteremia (1), Marr and colleagues report that only 12 catheters (19%) in 62 episodes of bacteremia were salvaged successfully. This contrasts with our experience, previously published (2) and later re-evaluated (3), showing high success rates in treating catheter-related bacteremia without catheter removal. During a 41-month period, 37 of 185 patients with a central venous catheter implanted for hemodialysis had a total of 42 episodes of catheter-related bacteremia. This represents 1.3 episodes per 1000 days of catheterization. According to strict inclusion criteria, 40 of 42 episodes were successfully treated and showed no septic complications during extended follow-up (mean, 20.5 months [range, 2 to 44 months]).

We believe that some points in the authors' evaluation of conservative management of catheter-related bacteremia need to be clarified. First, the authors did not discuss results of catheter-tip culture in withdrawn catheters. In our patients, bacteremia was confirmed by quantitative blood culture (4), and removed catheters were microbiologically assessed to confirm catheter colonization or cure. Second, when Marr and colleagues attempted catheter salvage, they administered only antibiotics to treat bacteremia; they did not sterilize the catheter. Patients having hemodialysis are given low doses of antibiotics because of renal failure. In this situation, the catheter is briefly in contact with the frequently given antibiotic only once a week. We used the antibiotic-lock technique to achieve high concentrations of antibiotics within the catheter during the interdialysis period.

Conservative management of catheter-related bacteremia in patients who need permanent vascular access is a strategy that implies considerable benefits. To evaluate the advisability of this strategy, each case must be strictly defined. Attempts should be made to sterilize the catheter while bacteremia is being treated.

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References

1. **Marr KA, Sexton DJ, Conlon PJ, Corey GR, Schwab SJ, Kirkland KB.** Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. Ann Intern Med. 1997;127:275-80.
2. **Capdevila JA, Segarra A, Planes AM, Ramirez-Arellano M, Pahissa A, Piera L, et al.** Successful treatment of haemodialysis catheter-related sepsis without catheter removal. Nephrol Dial Transplant. 1993;8:231-4.
3. **Capdevila JA, Segarra A, Planes AM, Gasser I, Gavaldà J, Pahissa A.** Long term follow-up of patients with catheter related sepsis (CRS) treated without catheter removal [Abstract]. In: Program and Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco. Washington, DC: American Society for Microbiology: 1995.
4. **Capdevila JA, Planes AM, Palomar M, Gasser I, Almirante B, Pahissa A, et al.** Usefulness of quantitative blood culture for diagnosis of catheter related sepsis. Eur J Clin Microbiol. 1992;11:403-7.

In response: All of the patients in our study met the clinical case definition of catheter-related bloodstream infection suggested by the Centers for Disease Control and Prevention: isolation of the same microorganism from blood cultures obtained by venipuncture and drawn from the catheter in a patient with signs of sepsis and no source of bloodstream infection other than the catheter (1). The Centers for Disease Control and Prevention guidelines further state that defervescence after removal of the catheter is indirect evidence of catheter-related infection in the absence of laboratory confirmation. Laboratory confirmation (which can be done by quantitative culture of blood or culture of a catheter segment) would have provided an even more stringent experimental definition of catheter-related bacteremia.

Our study was designed to assess the outcome of attempted catheter salvage in patients undergoing hemodialysis who have bacteremia, using systemic antibiotics alone; this practice is currently standard at our institution. We are aware of Capdevila and colleagues' data suggesting that for bacteremia caused by certain organisms, catheter salvage may be more successful when antibiotics are "locked" into the catheter in addition to being administered systemically (2–4). However, this study was limited by its small size and lack of a control group. Moreover, of the 11 patients treated with the antibiotic-lock method, 2 (18%) had recurrent bacteremia due to the same organism (and yet were considered to have had a successful outcome); in 3 patients, the catheter was still in place at the end of the study period, with no follow-up cultures documenting that the bacteremia had cleared. Finally, only 2 of the patients had bacteremia due to *Staphylococcus aureus*, the most common etiologic organism in our study and the one most likely to be associated with complications. The antibiotic-lock technique is appealing in concept, but we believe that available data are not sufficiently conclusive to justify its adoption as standard practice. The work of Capdevila and others (3, 4) should generate further study of this technique, preferably in a randomized study that compares the efficacy and safety of the antibiotic-lock technique with those of early catheter removal.

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References

1. Guideline for prevention of intravascular device-related infections. Part 1: Intravascular device-related infections: an overview. The Hospital Infection Control Practices and Advisory Committee. Am J Infect Control. 1996;24:262-93.
2. **Capdevila JA, Segarra A, Planes AM, Ramirez-Arellano M, Pahissa A, Piera L, et al.** Successful treatment of haemodialysis catheter-related sepsis without catheter removal. Nephrol Dial Transplant. 1993;8:231-4.
3. **Benoit JL, Carandang G, Sitrin M, Arnow PM.** Intraluminal antibiotic treatment of central venous catheter infections in patients receiving parenteral nutrition at home. Clin Infect Dis. 1995;21:1286-8.
4. **Krzywda EA, Andris DA, Edmiston CE, Quebbeman EJ.** Treatment of Hickman catheter sepsis using antibiotic lock technique. Infect Control Hosp Epidemiol. 1995;16:596-8.

Ultrasonographic Screening for Deep Venous Thrombosis after Arthroplasty

To the Editor: The article on ultrasonographic screening for deep venous thrombosis after arthroplasty (1) agrees completely with my experience regarding the lack of value of such screening in these patients. In a 6-month period (January through June 1995) at William Beaumont Hospital, ultrasonography was done on patients who had had arthroplasty for whom there was a definite clinical suspicion of deep venous thrombosis. Only 8% of patients had acute femoropopliteal deep venous thrombosis.

Of additional interest in Robinson and colleagues' study (1) was the length of stay, approximately 10 ± 5 days. This length of stay helped to ensure that 85% of the patients were discharged "fully mobile" (and were receiving therapeutic anticoagulation with warfarin on the day of discharge, as much as 2 weeks after surgery); this therapy should also prevent subsequent deep venous thrombosis.

Considering the current practice of discharging patients who have had arthroplasty 4 to 5 days after this surgery, this article supports not only avoiding screening tests for deep venous thrombosis but also continuing warfarin or other prophylactic

regimens at home. The literature supports the use of postoperative prophylaxis of deep venous thrombosis for 2 to 4 weeks.

Compared with the cost of arthroplasty and the potential risks and costs of deep venous thrombosis and pulmonary embolism, 2 to 3 weeks of warfarin prophylaxis and monitoring of the prothrombin time at home seem medically and financially beneficial.

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Reference

1. **Robinson KS, Anderson DR, Gross M, Petrie D, Leighton R, Stanish W, et al.** Ultrasonographic screening before hospital discharge for deep venous thrombosis after arthroplasty: The Post-Arthroplasty Screening Study. A randomized, controlled trial. Ann Intern Med. 1997;127:439-45.

To the Editor: It is interesting that Robinson and colleagues' study (1) shows a rate of deep vein thrombosis after hospital discharge (2.5%) that is lower than the rates reported by Planes (2) and Bergqvist (3) and their colleagues. The main reason for the lower incidence in Robinson and coworkers' study is the inclusion of only proximal deep venous thrombosis as diagnosed by ultrasonography. In contrast, the other two studies included both proximal and distal deep venous thrombosis diagnosed by venography. The incidence of proximal deep venous thrombosis is similar in all three studies, but undiagnosed distal deep venous thrombosis (which is asymptomatic) occurred in approximately 10% of patients in the other two studies. Distal deep venous thrombosis is clinically important because it can increase risk for proximal deep venous thrombosis and the postphlebitic syndrome. Robinson and colleagues did not consider these conditions. We agree that there is no need for screening at hospital discharge, but we believe it is important to continue prophylaxis with low-molecular-weight heparin or coumarin for up to 6 to 8 weeks. This regimen has been shown to be safe and effective in reducing risk for both proximal and distal deep venous thrombosis.

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References

1. **Robinson KS, Anderson DR, Gross M, Petrie D, Leighton R, Stanish W, et al.** Ultrasonographic screening before hospital discharge for deep venous thrombosis after arthroplasty: The Post-Arthroplasty Screening Study. A randomized, controlled trial. Ann Intern Med. 1997;127:439-45.
2. **Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y.** Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. Lancet. 1996;348:224-8.
3. **Bergqvist D, Benoni G, Bjorgell O, Fredin H, Hedlundh U, Nicolas S, et al.** Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med. 1996;335:696-700.

In response: As Dr. Pedell points out, the mean length of stay after total hip or knee arthroplasty has decreased since we completed our study. Our study showed that an average of 10 days of warfarin prophylaxis given in the hospital only provided safe and effective patient care. With current lengths of hospital stay after joint arthroplasty as short as 4 days, the question is raised about whether outpatient warfarin treatment is warranted to ensure that patients receive prophylaxis for at least 10 days.

Our study does shed some light on this matter. We agree with Dr. Pedell that the state of mobilization at the time of hospital discharge is likely to be a factor in the risk for the development of postdischarge venous thromboembolism. At hospital discharge, 85% of the patients in our study were "fully mobile," and no correlation was observed between length of stay and risk for subsequent postdischarge venous thromboembolism. About 15% of the patients were discharged from the hospital before day 6. On the basis of this information, we believe that patients who receive prophylaxis for 5 days and are fully mobile at hospital discharge on day 5 do not require postdischarge prophylaxis. Postdischarge prophylaxis lasting up to 5 days should be considered for patients discharged on day 5 who are not fully mobile.

As stated by Dr. Rajput and Mr. Nanavati, controlled studies have shown that prolonging prophylaxis 3 weeks beyond hospital discharge reduces the rate of venography-confirmed deep venous thrombosis after total hip arthroplasty (1, 2). However, it is uncertain whether prolonging prophylaxis for this length of time results in a clinically important reduction in the rate of symptomatic or fatal thromboembolic complications after total hip or knee arthroplasty. In the absence of outcomes data from controlled trials, the potential benefits of outpatient prophylaxis must be carefully weighed against the risks and the costs of medication and monitoring in any individual patient.

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References

1. **Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y.** Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. Lancet. 1996;348:224-8.
2. **Bergqvist D, Benoni G, Bjorgell O, Fredin H, Hedlundh U, Nicolas S, et al.** Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med. 1996;335:696-700.

Positive-Pressure Ventilation in Amyotrophic Lateral Sclerosis

To the Editor: Although Aboussouan and colleagues (1) reaffirm that assisting the ventilation of patients with amyotrophic lateral sclerosis can prolong survival, even their patients who "tolerated" nocturnal nasal positive-pressure ventilation survived only 15 months. Most untreated patients with this disease die of CO_2 narcosis or inability to clear airway secretions (2). However, patients for whom assisted peak cough flows greater than 160 L/min can be generated (that is, patients with less bulbar involvement) and who are equipped and trained in using assisted coughing, mechanical insufflation–exsufflation, and up to 24-hour noninvasive positive-pressure ventilation as needed can have prolonged survival without tracheostomy (3). In contrast, those with assisted peak cough flows less than 160 L/min will require tracheostomy (3).

Aboussouan and colleagues prevented neither daytime hypoventilation with a mouth piece or nasal positive-pressure ventilation nor respiratory failure from bronchial mucus plugging. They noted that mechanical insufflation–exsufflation was used but did not describe how or when this procedure was done. This procedure is generally not effective when severe bulbar dysfunction results in assisted cough flows less than 160 L/min (4). Furthermore, the tidal volumes used by the authors were insufficient to compensate for air leakage in this open system, and bulbar function assessment was based on an arbitrary scale rather than on peak cough flow (3, 4). Thus, the authors underestimated the potential of noninvasive aids to prolong survival. Because we maintain alveolar ventilation around the clock and create effective cough flows, some of our patients with amyotrophic lateral sclerosis have required 24-hour ventilatory support for many years but have never undergone intubation, tracheostomy, or even hospitalization (3). We recommend that all who are interested in this strategy read more on the subject (5).

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References

1. **Aboussouan LS, Khan SU, Meeker DP, Stelmach K, Mitsumoto H.** Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. Ann Intern Med. 1997;127:450-3.
2. **Bach JR, Pansit R, Ballanger F, Kulessa R, Ishikawa Y.** Neuromuscu-

lar ventilatory insufficiency: the effect of home mechanical ventilator use vs. oxygen therapy on pneumonia and hospitalization rates. Am J Phys Med Rehabil. [In press].
3. **Bach JR.** Amyotrophic lateral sclerosis: predictors for prolongation of life by noninvasive respiratory aids. Arch Phys Med Rehab. 1995;76:828-31.
4. **Bach JR, Saporito LR.** Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure: a different approach to weaning. Chest. 1996;110:1566-71.
5. **Bach JR, ed.** Pulmonary Rehabilitation: The Obstructive and Paralytic Conditions. Philadelphia: Hanley & Belfus; 1996.

In response: We agree that noninvasive positive-pressure ventilation should not be restricted to nighttime. Although we emphasized nocturnal use, we also encouraged daytime use. However, tolerance of this treatment was strictly defined as the ability to sleep nightly for at least 4 consecutive hours with the device, regardless of daytime use. We did use other interfaces, including mouth pieces for daytime ventilation. Every attempt was made to control mucus plugging and secretions by using suction devices, medications, and assisted coughing. Mechanical insufflation–exsufflation was used, but only when it became available at the end of our study.

In that context, our results may not actually differ much from Bio and Bach's experience. Our patients tolerant of noninvasive positive-pressure ventilation did not survive only 15 months. Rather, the *median* survival was 15 months; as our figures indicate, more than 40% of tolerant patients remain alive 2 years after initiation of noninvasive positive-pressure ventilation. We now have 10 patients with amyotrophic lateral sclerosis, including one third (6 of 18) of the tolerant patients of our original cohort, who have progressively increased the time they spend on noninvasive positive-pressure ventilation to 24 hours a day, with only one hospitalization for deep venous thrombosis. Two patients have been successfully maintained on 24 hours of ventilation per day for more than 3 years.

To simply state that the longer survival with noninvasive positive-pressure ventilation is not surprising does not validate the statement. For instance, one study has concluded that ventilation imparted a survival *disadvantage* in patients with Duchenne muscular dystrophy (1). Our study remains one of the few (if not only) larger studies of a homogeneous group of patients with a neuromuscular disease for which noninvasive positive-pressure ventilation is proposed to prolong survival.

The absolute lack of intolerance reported by Bio and Bach is intriguing and is counter to our experience. Perhaps the discrepancy lies in our definition of tolerance.

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1. **Raphael JC, Chevret S, Chastang C, Bouvet F.** Randomised trial of preventive nasal ventilation in Duchenne muscular dystrophy. French Multicentre Cooperative Group on Home Mechanical Ventilation Assistance in Duchenne de Boulogne Muscular Dystrophy. Lancet. 1994; 343:1600-4.

Hepatitis C Virus Genotype Distribution in B-Cell Non-Hodgkin Lymphoma

To the Editor: Epidemiologic studies have shown hepatitis C virus (HCV) infection in a statistically significant proportion of de novo B-cell non-Hodgkin lymphomas that are not complicating the course of type II mixed cryoglobulinemia (1–3).

To study the influence of specific HCV genotypes on the pathogenesis of B-cell non-Hodgkin lymphoma, we analyzed 97 HCV-positive (anti-HCV antibody–positive and HCV RNA–positive) patients, including 35 patients with B-cell non-Hodgkin lymphoma that was not complicating the course of type II mixed cryoglobulinemia, 27 patients undergoing long-term hemodialysis, and 35 patients with chronic liver disease. The HCV genotype was determined by using a genotype-specific primer polymerase chain reaction method (4). Results are summarized in the **Table**. The prevalence of hepatitis C virus genotype 1b/II was unexpectedly lower in patients with B-cell non-Hodgkin lymphoma (25.7%) than in patients undergoing long-term hemodialysis (66.7%; $P = 0.0013$) and those with chronic liver disease (62.8%; $P = 0.001$). Conversely, the prevalence of genotypes 2a/III and 2b/IV was higher in patients with B-cell non-Hodgkin lymphoma (42.8%) than in the hemodialysis group (14.8%; $P = 0.01$) and chronic liver disease group (14.2%; $P = 0.008$).

Table. Hepatitis C Virus Genotype Distribution

Hepatitis C Virus Genotype	B-Cell Non-Hodgkin Lymphoma Group ($n = 35$)	Hemodialysis Group ($n = 27$)	Chronic Liver Disease Group ($n = 35$)
	n (%)*		
1a/I	2 (5.7)	0	3 (8.6)
1b/II	9 (25.7)	18 (66.7)	22 (62.8)
2a/III	8 (22.8)	3 (11.1)	4 (11.4)
2b/IV	7 (20)	1 (3.7)	1 (2.8)
3a/V	0	0	2 (5.7)
Unclassifiable	5 (14.3)	1 (3.7)	0
Mixed infections	4 (11.4)	4 (14.8)	3 (8.6)

* Numbers in parentheses are the percentage of patients with the genotype.

The possible clinical relevance of the presence of different genotypes, in terms of prognosis or therapeutic response, in HCV-associated diseases has now emerged (5). A high prevalence of genotype 2a/III in Italian patients who had cryoglobulinemia without associated liver disease but with circulating autoantibodies was recently reported; this finding suggests that this variant may have a pathogenetic role in autoimmune-lymphoproliferative disorders (4). The different genotype distribution in our series of de novo B-cell non-Hodgkin lymphoma in comparison with patients undergoing hemodialysis and patients with chronic liver disease further supports the hypothesis that different HCV variants might be related to greater lymphotropism. Moreover, our observation indicates that HCV-related factors, namely viral genotypes, may play a role in the malignant proliferation of defined B-cell subsets, in addition to unknown host-related factors.

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References

1. **Ferri C, Caracciolo F, Zignego AL, La Civita L, Monti M, Longobardo G, et al.** Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br J Haematol. 1994;88:392-4.
2. **Luppi M, Ferrari MG, Bonaccorsi G, Longo G, Narni F, Barozzi P, et al.** Hepatitis C virus infection in subsets of neoplastic lymphoproliferations not associated with cryoglobulinemia. Leukemia. 1996;10:351-5.
3. **Pioltelli P, Zehender G, Monti G, Monteverde A, Galli M.** HCV and non-Hodgkin lymphoma [Letter]. Lancet. 1996;347:624-5.
4. **Zignego AL, Ferri C, Giannini C, Monti M, La Civita L, Careccia G, et al.** Hepatitis C virus genotype analysis in patients with type II mixed cryoglobulinemia. Ann Intern Med. 1996;124:31-4.
5. **Zein NN, Rakela J, Krawitt EL, Rajender KR, Tominaga T, Persing DH.** Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity, and response to interferon therapy. The Collaborative Study Group. Ann Intern Med. 1996;125:634-9.

Anemia Secondary to Vitamin D Intoxication

To the Editor: Anemia is not usually mentioned as a complication of vitamin D intoxication but has been described in patients with and without renal failure (1). We report on a woman with vitamin D intoxication and anemia not caused by renal failure.

A 66-year-old woman was admitted to the emergency department with hypercalcemia diagnosed after 3 weeks of severe con-

stitutional symptoms. Three years earlier, osteoporosis had been diagnosed and a rheumatologist had prescribed an extemporaneous formulation (200 IU of vitamin D and 1 g of calcium glucobionate twice daily), which was prepared by a pharmacist. Blood tests at admission showed a calcium level of 4.04 mmol/L, a hemoglobin concentration of 103 g/L, a urea concentration of 11.2 mmol/L, and a creatinine level of 146 μmol/L. After rehydration, the hemoglobin concentration decreased to 83 g/L. Anemia was nonspecific and nonregenerative, and results of additional tests (chest radiography, mammography, abdominal ultrasonography, bone scintigraphy, fibrogastroscopy, and colonoscopy) were normal. Parathyroid hormone was undetectable, and the plasma 25-hydroxyvitamin D level was 696 nmol/L (normal range, 15 to 125 nmol/L). Two months later, while the patient was receiving a milk-free diet, plasma 25-hydroxyvitamin D levels were high, serum calcium levels were normal, and anemia had resolved. Symptoms had begun roughly when a new bottle of pills with a vitamin D content of 200 μg (8000 IU) was started.

The association of hypercalcemia and anemia suggested a neoplastic origin; this idea was rejected when results of additional examinations became available. High vitamin D levels could directly affect hematopoietic cells (2) or act through high calcium levels, which inhibit erythroid colony formation in vitro (3) and erythropoietin production in vitro (4) and in vivo (5). That calcium is more important than vitamin D itself is supported by the course of our patient, whose anemia subsided after normalization of calcium levels, despite high vitamin D levels.

In addition to the danger of extemporaneous formulations, which carry a higher risk for error than factory-made pills, anemia is another potential complication of vitamin D intoxication.

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References

1. **Scharfman WB, Proop S.** Anemia associated with vitamin D intoxication. N Engl J Med. 1956;255:1207-12.
2. **Reichel H, Koeffler HP, Norman AW.** Production of 1a,25-dihydroxyvitamin D3 by hematopoietic cells. Prog Clin Biol Res. 1990;332:81-97.
3. **Misiti J, Spivak JL.** Erythropoiesis in vitro. J Clin Invest. 1979;64: 1573-9.
4. **Nagakura K, Ueno M, Brookins J, Beckman BS, Fisher JW.** Effects of low calcium levels on erythropoietin production by human renal carcinoma cells in culture. Am J Physiol. 1987;253:797-801.
5. **McGonigle RJ, Brookins J, Pegram BL, Fisher JW.** Enhanced erythropoietin production by calcium entry blockers in rats exposed to hypoxia. J Pharmacol Exp Ther. 1987;241:428-32.

The Toxic Shock Syndrome and *Staphylococcus lugdunensis* Bacteremia

To the Editor: The toxic shock syndrome is often associated with *Staphylococcus aureus* and is mediated by toxic shock syndrome toxin-1 (TSST-1) and other enterotoxins. We describe the first case of the toxic shock syndrome associated with a coagulase-negative staphylococcal species, *S. lugdunensis.*

A 33-year-old, otherwise healthy woman developed nausea, vomiting, diffuse abdominal pain, myalgias, and confusion within 48 hours of tooth extraction and Gelfoam packing (Pharmacia-Upjohn, Kalamazoo, Michigan). Evaluation in the emergency department revealed a faint erythematous macular rash of the chest and livedo reticularis of the legs. General and pelvic examination were otherwise normal. Admission data (**Table**) fulfilled the criteria for the toxic shock syndrome. Cultures of blood and purulant right maxillary sinus aspirate showed coagulase-negative staphylococcal species, and the species of the blood isolates was identified *S. lugdunensis*. Tests for coagulase, TSST-1, staphylococcal enterotoxins A to E, and exfoliatin toxin A were negative. No *S. aureus* or *S. pyogenes* were isolated from blood, urine, sputum, or sinus or vaginal secretions. The patient improved with medical treatment. Desquamation of the palms and soles was noted before discharge.

Staphylococcus lugdunensis has been associated with other severe infections, including prosthetic and native valve endocarditis, peritonitis, infective arthritis, vascular prosthesis infection, osteomyelitis, brain abscess, bacteremia, septicemia, and septic shock. Previous reports implicated coagulase-negative staphylococcal species in the pathogenesis of the toxic shock syndrome (1, 2) and suggested TSST-1 production (1, 2), although subse-

Table. Laboratory Data in Woman with the Toxic Shock Syndrome and *Staphylococcus lugdunensis* Bacteremia*

Variable	Hospital Day				
	1	2	3	5	7
Temperature, °F	102.0	100.4	101.6	99.5	99.6
Heart rate, *beats/min*	134	118	102	92	98
Blood pressure, *mm Hg*	93/53†	110/58†	110/50†	114/41†	125/55
Cardiac output, *L/min*	9.51	6.13	6.19	7.05	5.52
Cardiac index, *L/min per m²*	4.73	2.84	2.87	3.65	2.80
Systemic vascular resistance, *dyne/sec per cm²*	294	609	982	828	793
Pulmonary capillary wedge pressure, *mm Hg*	22	21	18	14	13
Pulmonary artery pressure, *mm Hg*	39/25	36/22	34/19	35/21	35/21
pH	7.16	7.37	7.44	7.39	7.37
P_{CO_2}, *mm Hg*	24	16	26	27	21
P_{O_2}, *mm Hg*	452	192	107	202	125
HCO_3, *mm/L*	9	10	17	17	19
Pa_{O_2}: Fi_{O_2} ratio	452	384	268	404	313
Lactate (lower limit of detection < 1.0), μmol/L	3.8	–	–	–	–
Creatinine level, *mg/dL*	7.4	7.5	8.0	7.1	6.1
Creatine phosphokinase level, *mU/mL*	14030	12990	16840	20760	–
AST level, *mU/mL*	1128	810	478	346	234
ALT level, *U/L*	–	524	337	157	–
Lactate dehydrogenase level, *mU/mL*	4450	–	4220	2870	1660
Leukocyte count, *cells/mm³*	44.8	35.8	39.4	–	26.9
Platelet count, *cells/mm³*	14	<10	<10	22	<10
Prothrombin time, *s*	23.9	16.1	12.7	16.7	13.9
Fibrinogen, *mg/dL*	76	–	–	137	–
D-dimer level, *μg/mL*	>8	–	–	>4 and <8	–
Serum calcium level, *mg/dL*	5.6	5.3	4.4	5.5	–
Serum phosphate level, *mg/dL*	6.3	4.0	3.6	5.4	3.2

* ALT = alanine aminotransferase; AST = aspartate aminotransferase; Fi_{O_2} = fraction of inspired oxygen.
† While patient was receiving multiple vasopressors.

quent analysis of select coagulase-negative staphylococcal species isolates failed to demonstrate TSST-1 or a TSST-1 gene (3).

This case expands the spectrum of severe infections associated with *S. lugdunensis*. Reports of *S. lugdunensis* endocarditis after tooth extraction (4) and the toxic shock syndrome associated with Gelfoam nasal packing (5) suggest a portal of entry in this case. The absence of a toxic shock syndrome–associated enterotoxin does not exclude the possibility of a novel virulence factor. As gram-positive organisms are increasingly identified in the bacteremic sepsis syndrome, the possibility that subspecies of coagulase-negative staphylococcal species may have different virulence patterns should be recognized.

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References

1. **Kahler RC, Boyce JM, Bergdoll MS, Lockwood WR, Taylor MR.** Case report: toxic shock syndrome associated with TSST-1 producing coagulase-negative staphylococci. Am J Med Sci. 1986;292:310-2.
2. **Crass BA, Bergdoll MS.** Involvement of coagulase-negative staphylococci in toxic shock syndrome. J Clin Microbiol. 1986;23:43-5.
3. **Kreiswirth BN, Schlievert PM, Novick RP.** Evaluation of coagulase-negative staphylococci for ability to produce toxic shock syndrome toxin 1. J Clin Microbiol. 1987;25:2028-9.
4. **Kralovic SM, Melin-Aldana H, Smith KK, Linneman CC Jr.** *Staphylococcus lugdunensis* endocarditis after tooth extraction. Clin Infect Dis. 1995;20:715-6.
5. **Ramzi TY, Gross CW, Rande HL.** Toxic shock syndrome following functional endonasal sinus surgery: a case report. Head Neck. 1991;13:247-8.

Clarithromycin and Digoxin Toxicity

To the Editor: Case reports describing clarithromycin and its probable effect on digoxin metabolism have been sporadically described in the literature (1, 2). These findings have important implications for patient care because both digoxin and clarithromycin are commonly prescribed medications. We report a case of digoxin toxicity during clarithromycin therapy.

A 70-year-old woman had been receiving digoxin, 0.25 mg/d, for the past 4 years for idiopathic cardiomyopathy. Other medications included hydrochlorothiazide, 25 mg/d; isosorbide mononitrate, 30 mg/d; and captopril, 50 mg every 8 hours. The patient began receiving clarithromycin, 500 mg twice daily, for bronchitis. After 4 days of this treatment, the patient was hospitalized because of nausea, vomiting, weakness, and the presence of brown spots in the patient's field of vision for 4 days. Physical examination was unremarkable except for mild dehydration. An electrocardiogram showed sinus rhythm, borderline first-degree atrioventricular block, and left bundle-branch block. The serum digoxin level was 4.8 ng/mL (normal, 0.8 to 2.4 ng/mL) on admission and increased to 5.4 ng/mL 2 hours after admission. On admission the blood urea nitrogen level was 29 mg/mL, creatinine level was 1.4 mg/dL, and potassium level was 4.9 mEq/L.

Digoxin and clarithromycin therapies were discontinued, and the patient was admitted to a telemetry bed. In 2 days, her symptoms improved, and the digoxin level decreased to 1.7 ng/mL. The medical record showed that 6 months before admission, the digoxin, blood urea nitrogen, creatinine, and thyroid-stimulating hormone levels were normal. At hospital discharge, the patient's digoxin level was 1.7 ng/mL and the electrocardiogram had not changed. Therapy with digoxin, 0.125 mg every other day, was restarted, and the digoxin level was 0.8 ng/mL 1 week later.

Erythromycin prolongs the clearance of digoxin and allows more of an active drug to be absorbed by altering the colonic flora that metabolizes digoxin to various inactive compounds (3). We believe that clarithromycin has a similar effect on digoxin. Serum digoxin levels should be closely monitored when a patient begins receiving clarithromycin and other macrolide antibiotics.

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References

1. **Midoneck SR, Etingin OR.** Clarithromycin-related toxic effects of digoxin [Letter]. N Engl J Med. 1995;333:1505.
2. **Brown BA, Wallace RJ Jr, Griffith DE, Warden J.** Clarithromycin-associated digoxin toxicity in the elderly. Clin Infect Dis. 1997;24:92-3.
3. **Lindenbaum J, Rund DG, Butler VP Jr, Tse-Eng D, Saha JR.** Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. N Engl J Med. 1981;305:789-94.

AL Amyloidosis Combined with Acquired Factor V Deficiency

To the Editor: Many coagulation disorders have been described in patients with AL amyloidosis (for example, factor X deficiency, factor IX deficiency, and disseminated intravascular coagulation). We report the first case of AL amyloidosis combined with acquired factor V deficiency.

In May 1990, a 33-year-old man had splenectomy after polytraumatism. The prothrombin rate was 91%. In August 1994, gastrointestinal hemorrhage occurred. The surgeon found a voluminous hematoma of the lesser peritoneal sac, but laparotomy and gastrointestinal endoscopy could not trace the origin of the bleeding. The prothrombin rate was 35%, factor V level was 25%, and antiprothrombinase antibody was present. Bleeding time, fibrinogen levels, and platelet counts were normal. Neither disseminated intravascular coagulation nor anti–factor V antibody was seen. The patient received packed red blood cells, prothrombin, and fresh frozen plasma; none of these affected prothrombin rate or factor V level. Laboratory values indicated inflammation, a pure nephrotic syndrome, and liver abnormalities with cytolysis and cholestasis. The patient did not have hypertension or renal failure. Ultrasonography showed two normal kidneys without dilatation of the urinary tract and showed hepatomegaly without thrombosis of the portal, hepatic, or renal veins. The patient was negative for serologic markers of hepatitis B and C. Prothrombin rate was 33%, and the factor V level was 17%. Antiprothrombinase antibody was detected. Bleeding time and platelet counts were normal, and no anti–factor V antibody was seen.

Liver and renal biopsies permitted diagnosis of AL amyloidosis. The patient did not have myeloma but did have a medullary infiltration with plasmocytes expressing only κ light chain. Cutaneous biopsy and electromyography yielded normal results. Echocardiography showed alterations of left ventricular relaxation. Monthly courses of vincristine, melphalan, cyclophosphamide, and prednisone were started in December 1994. Three months later, a 54% prothrombin rate and a 60% factor V level were noted, without renal improvement. Bone marrow transplantation was done in May 1995, but the patient died in June 1995 after massive gastrointestinal hemorrhage without ulceration.

This patient had AL amyloidosis with renal, liver, medullary, and probably gastric involvement. There was no obvious myeloma, but a plasmacyte dyscrasia was seen. Factor X deficiency during amyloidosis is well known and seems to be due to an immobilization of the coagulation protein in the vasculature (1). This explains why patients are refractory to factor X concentrates. Another study (2) showed that amyloid fibrils bind factor X and, to a much lesser extent, factor IX and prothrombin. Factor V deficiency in our patient was probably linked to amyloidosis because the patient had neither a congenital deficiency nor a deficiency due to hepatocellular deficiency, disseminated intravascular coagulation, splenomegaly, or anti–factor V antibody. Moreover, measurement of factor V levels before and after infusions of fresh frozen plasma showed that factor V levels did not increase. The mechanism of factor V deficiency may be linked to the fixation of this factor in the amyloid fibrils.

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References

1. **Furie B, Greene E, Furie BC.** Syndrome of acquired factor X deficiency and systemic amyloidosis: in vivo studies of the metabolic fate of factor X. N Engl J Med. 1977;297:81-5.
2. **Furie B, Voo L, Keith PW, McAdam J, Furie BC.** Mechanism of factor X deficiency in systemic amyloidosis. N Engl J Med. 1981;304:827-30.

Cardiac Rupture during Dobutamine Stress Test

To the Editor: Dobutamine stress echocardiography is widely used to diagnose coronary artery disease (1), but the safety of this testing procedure is uncertain. Major life-threatening complications—primarily sustained ventricular tachycardia, ventricular fibrillation, myocardial infarction, and cardiac asystole—have been reported to occur in 1 of 300 tests in large series (2, 3). We report one case of cardiac rupture and death during low-dose dobutamine stress echocardiography done in a 66-year-old patient with recent myocardial infarction admitted to a coronary care unit.

During the first 3 days after admission, mild left ventricular failure requiring diuresis and an episode of atrial fibrillation treated with amiodarone complicated the infarction. On the twelfth day after infarction, dobutamine stress echocardiography was requested because the exercise stress test result was nondiagnostic. At baseline, the resting stress echocardiography showed dyskinesia and diastolic thinning of the proximal inferior wall with preserved global function (ejection fraction, 55% by area length method) (**Figure**). At 5 μg of dobutamine, no change in wall motion was detected. At 10 μg, in the absence of significant changes in heart rate, the patient suddenly had atypical chest pain at the base of the right hemithorax. Simultaneously, a new-onset pericardial effusion was detected by echocardiography. After a few seconds, the patient lost consciousness and pulse. Pericardiocentesis was done immediately, but pericardial effusion continuously recurred. All attempts at cardiopulmonary resuscitation—which were started immediately and performed in cooperation with the anesthesiologists—failed, and the patient died.

This case dramatically emphasizes three obvious, albeit sometimes neglected, points. First, pharmacologic stress tests should be done with an attending physician present, which apparently is not always the case in some institutions in the United States (4). Second, every stress test carries a definite, albeit small, risk. Third, not all stress tests carry the same risk for major adverse reactions, and dobutamine stress testing may be more dangerous than other forms of physical or pharmacologic stress, such as those produced by exercise, dipyridamole, or adenosine (5).

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References

1. **Picano E, Mathias W Jr, Pingitore A, Bigi R, Previtali M.** Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, large scale, multicentre trial. Lancet. 1994;344:1190-2.
2. **Secknus MA, Marwick TH.** Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3,011 studies over 5 years. J Am Coll Cardiol. 1997;29:1234-40.
3. **Cheitlin MS, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, et al.** ACC/AHA guidelines for the clinical application of echocardiography: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). J Am Coll Cardiol. 1997;29:862-79.
4. **Don Michael AT.** Implications for cost-effectiveness. Am J Cardiol. 1996;77:190.
5. **Bernardino L.** Dobutamine, dipyridamole and stress echocardiography [Letter]. Circulation. 1996;94:2989.

Encouraging Physical Activity

To the Editor: I heartily endorse Andersen and colleagues' message in the article on the physician's role in encouraging patients to become more physically active (1). The authors provide evidence for the medical benefits of regular exercise and

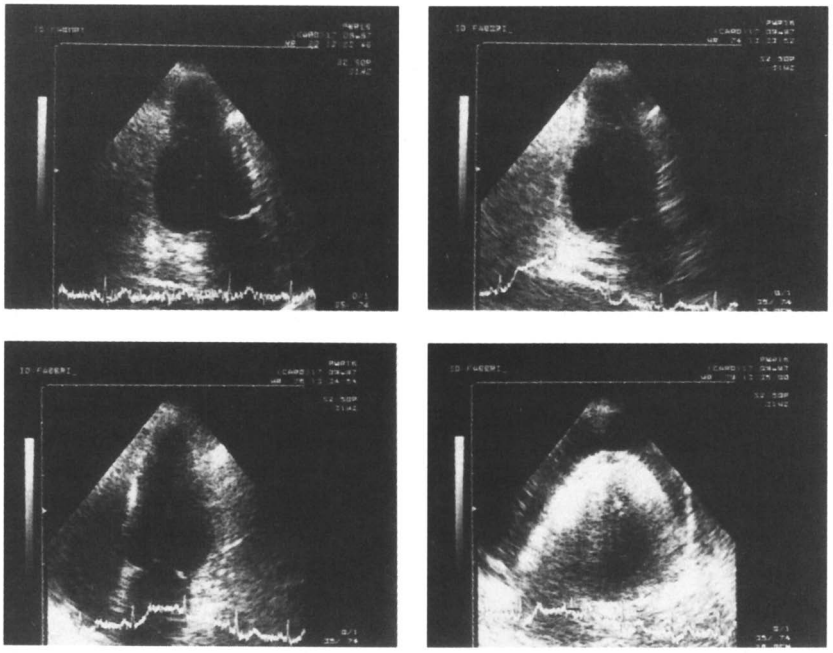

Figure. End-systolic frames of an apical view taken at rest (*top left*), after 4 of 10 μg of dobutamine per kg of body weight per minute (*top right*), after 4 minutes 54 seconds of 10 μg of dobutamine per kg per minute (*bottom left*), and after 5 minutes of 10 μg of dobutamine per kg per minute (*bottom right*). In resting conditions, there is dyskinesia of the inferobasal segment, virtually unchanged after 4 minutes of dobutamine, 10 μg. In the apical four-chamber view, no effusion is detectable at 4 minutes 54 seconds of 10 μg of dobutamine per kg per minute, and a massive pericardial effusion is obviously present 6 seconds later, producing sudden, catastrophic tamponade.

provide useful advice for physicians in getting their patients to cooperate in such programs. Only in the last sentence, however, do they refer to one of the most important elements in persuading patients to follow such a program—the physicians' own commitment to such a program themselves.

I am a 73-year-old physician in full-time active practice who runs 35 miles a week, works out for 45 minutes four times a week in the weight room, and runs 15 to 20 road races each year. There is no doubt in my mind that my ability to keep working at a high level depends on the fact that I do exercise regularly, maintain my weight, and have a full corps of energy. As a result, I am encouraged to, and am able to, preach to my patients about the virtue of exercise, to question them regularly as to how they are doing in keeping up their promises to me, and in helping them find a level of exercise that fits their particular ability. This is a special problem because I am a rheumatologist and most of my patients have musculoskeletal conditions or pain that limit what they can accomplish. Nonetheless, I am gratified that the many patients who can cooperate admit to benefit.

When smoking was more prevalent in the United States, there were many stories about physicians urging their patients to quit smoking while they were obviously enjoying a cigarette themselves. The same criticism can be leveled at us with regard to exercise. Unless we follow the precepts we teach, we are going to be unenthusiastic, ineffective counselors.

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Reference

1. **Andersen RE, Blair SN, Cheskin LJ, Bartlett SJ.** Encouraging patients to become more physically active: the physician's role. Ann Intern Med. 1997;127:395-400.

To the Editor: In Andersen and colleagues' paper on the physician's role in encouraging patients to be more physically active (1), I found three gems of statements. None was referenced, and I assume that each was the authors' common sense opinion.

1. "Writing the recommendation [for exercise] on a prescription pad may increase the likelihood that the recommendation will be followed."

2. "A physician's active interest and encouragement in how the patient is succeeding in becoming more physically active can be very helpful in increasing adherence."

3. "Physicians who set a good example themselves further enhance the importance of the message they wish to send to patients."

The third statement is arguably the most important of the three (2), but it can be made even more potent with a change in format. Physicians usually counsel their patients one at a time in a consultation room. It is more effective and efficient to invite all the patients to a seminar on exercise as preventive medicine. The physician should dress not in a white coat but in sneakers and athletic clothes. The seminar would be held not at a medical facility but in a YMCA facility or public park. The physician would discuss choice of exercise and frequency, distance, and intensity (3), with special attention to the importance of technique to increase aerobic effectiveness (4). A follow-up weekly program in aerobic walking, preferably physician-instructed, would improve compliance. The weekly program should be graduated in distance and intensity to prevent musculoskeletal injury. After a few weeks, when metabolic and brain chemistry changes occur, motivation will become self-sustaining.

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References

1. **Andersen RE, Blair SN, Cheskin LJ, Bartlett SJ.** Encouraging patients to become more physically active: the physician's role. Ann Intern Med. 1997;127:395-400.
2. **Simon HB.** Physician-al fitness: setting an example. Physician and Sports Medicine. 1989;17:45-6.
3. **Rippe J, Ward A, Porcari MS, Freedson P, O'Hanley S, Wilkie S.** The cardiovascular benefits of walking. Practical Cardiology. 1989;15:66-72.
4. **Malkin M.** Aerobic Walking—The Weight Loss Exercise. New York: Wiley; 1995.

In response: We appreciate Dr. McDuffie's and Dr. Malkin's interest in our recent paper. Both have reiterated the importance of being a good role model for patients. We commend Dr. McDuffie on his own commitment to regular vigorous physical activity. He addresses the key point of tailoring and individualizing exercise prescriptions to meet the individual health needs of each patient. Our paper focused on how to help apparently healthy adults adopt a more active lifestyle. However, as Dr. McDuffie notes, patients with musculoskeletal limitations or other medical ailments can also get symptom relief through regular activity.

Dr. Malkin suggests that physicians offer seminars stressing the importance of exercise while dressed in athletic clothing. This may be an effective strategy for some physicians to encourage patients who wish to become more vigorously active. We caution, however, that many sedentary adults without a history of physical activity do not enjoy vigorous activity (1) and may find this intimidating (2). Specialty seminars attract a biased group, probably those already predisposed to be physically active. Moreover, we think many sedentary people find that the need to change into athletic clothing and special footwear is a barrier to participation.

Although not optimal, a quick message delivered during a routine office visit that addresses the importance of increasing physical activity can elevate activity levels (3). Furthermore, patients report being receptive to this type of brief counseling. We believe that routinely delivering such messages to all patients ensures that the maximum number of people will hear this from their care provider, thus offering the potential to spread the word to the largest possible audience. More research is clearly needed to specifically document the effectiveness of physician counseling to increase activity. Making physical activity counseling as much a part of each office visit as hypertension checks will also emphasize the reciprocal relation between health and physical activity.

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References

1. **Andersen RE, Brownell KD, Haskell WL.** The Health and Fitness Club Leader's Guide: Administering a Weight Management Program. Dallas: American Health Publishing; 1992.
2. **Long BJ, Calfas KJ, Wooten W, Sallis JF, Patrick K, Goldstein M, et al.** A multisite field test of the acceptability of physical activity counseling in primary care: project PACE. Am J Prevent Med. 1996;12:73-81.
3. Physical Activity and Health: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.

Correction: Physician Workforce

In a recent position paper on physician workforce and graduate medical education (1), the first sentence of the first paragraph of the second column on page 144 should read, "Meanwhile, the total number of physicians in postgraduate residency training has ballooned from 69 142 in 1982 to 98 076 in 1996–1997, *and the number of first-year residents* is now more than 140% of the annual number of U.S. graduates from schools of allopathic and osteopathic medicine."

Reference

1. **American College of Physicians.** The physician workforce and financing of graduate medical education. Ann Intern Med. 1998;128:142-8.