Correspondence

Multiple Complex Coronary Plaques in Patients with Acute Myocardial Infarction

To the Editor: In their report on multiple complex coronary plaques in patients with acute transmural myocardial infarction, Goldstein et al. (Sept. 28 issue)[1] conclude that the subgroup of patients with angiographic evidence of multiple complex coronary plaques is at increased risk for adverse clinical outcomes. Although the authors assert that "angiography has a limited ability to delineate the severity and complexity of coronary disease," they have stretched the numerical interpretation of their findings beyond the limits of angiography.

In their study, Goldstein et al. considered lesions to be complex if they were associated with angiographic evidence of at least 50 percent stenosis. Intravascular ultrasound studies and postmortem observations have shown that expansive remodeling of large and complex plaques frequently leads to stenosis of less than 50 percent.[2,3] In an angiographic study, Ambrose et al.[4] reported that myocardial infarction originated from culprit lesions that were severely stenotic (more than 70 percent stenosis) in only 22 percent of patients. In a recent postmortem study,[5] we observed an association between histopathological determinants of plaque instability and expansive remodeling. In our study, the area of the lumen was not associated with histologic determinants of plaque instability. Thus, the data reported by Goldstein et al. represent a subgroup of atherosclerotic lesions selected according to angiographic criteria that are likely to miss a substantial fraction of unstable plaques.

Goldstein et al. restricted their analysis to angiographically complex lesions. It is conceivable that, irrespective of the complexity of the lesions, multiple angiographically significant lesions in general are associated with an increased risk of adverse events. The authors did not report on the outcome for patients with one or more noncomplex lesions. Therefore, their conclusion may not be limited to angiographically complex lesions.

GERARD PASTERKAMP, M.D., PH.D.
ARYAN VINK, M.D.
CORNELIUS BORST, M.D., PH.D.
University Medical Center Utrecht
3584 CX Utrecht, the Netherlands

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To the Editor: Goldstein and coworkers highlight the prognostic importance of the presence of multiple complex coronary plaques with regard to subsequent clinical events, such as repeated coronary angioplasty and bypass grafting, in patients with acute myocardial infarction. The authors discuss intraplaque lipid components or systemic lipid disorders, as well as systemic inflammatory processes, as possible contributors to the "generalized" plaque instability observed in this group of patients. However, they provide no information on previous therapy with statins in patients who already had clinical manifestations of coronary artery disease or on the initiation of statin therapy on the occasion of the myocardial infarction.

Statins have been shown to be effective for the secondary prevention of coronary artery disease in subjects with elevated low-density lipoprotein (LDL) cholesterol levels,[1] as well as in those with nearly normal levels,[2] reducing cardio-

vascular risk by about 30 percent. The rapid reduction in risk achieved with statins in patients with coronary artery disease indicates that these drugs may act by increasing plaque stability rather than through effects on atherogenesis itself. Statins may influence plaque stability through lipid-lowering effects as well as through non–lipid-related, probably anti-inflammatory, effects.[3] To exclude the possibility of treatment-related bias in this study, it is therefore important to consider LDL cholesterol levels, as well as the proportion of patients who had already been treated with a statin and the proportion with newly initiated statin therapy. In the absence of such additional information, the increased risk of adverse outcomes among patients with multiple complex coronary plaques, as reported by the authors, may be significantly overestimated or underestimated.

THOMAS C. WASCHER, M.D.
ANTONELLA DECAMPO, M.D.
ISABELLA SCHMOELZER, M.D.
Karl-Franzens University of Graz
A-8036 Graz, Austria

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The authors reply:

To the Editor: Pasterkamp et al. point out that angiography has limitations in delineating plaques that may be biologically unstable but not sufficiently severe to have angiographic features of complexity and that such lesions may progress to clinical instability. We agree that the absence of angiographic evidence of complexity does not preclude the possibility that a less stenotic, noncomplex lesion will progress and cause adverse events, and our observations cannot be construed to mean that angiographically less complex plaques are necessarily benign. In our report, we emphasized the limitations of angiography in delineating the precise architecture and biologic behavior of any given lesion, whether angiographically complex or not. Nevertheless, observations from our study and others[1-4] consistently demonstrate that complex plaques have a strong predilection to angiographic progression associated with adverse clinical events.

Wascher et al. emphasize the important relation of LDL cholesterol levels and statin therapy to the outcome of acute coronary syndromes. We used a retrospective analysis of a data base that included total cholesterol levels but did not include detailed data on the responses of cholesterol fractions (LDL and high-density lipoprotein) over time to therapy with cholesterol-lowering medications. Therefore, we cannot with certainty exclude the remote possibility that in our study the strong association between multiple complex plaques and clinical adverse events was influenced by LDL cholesterol levels and statin therapy.

JAMES A. GOLDSTEIN, M.D.
CINDY GRINES, M.D.
WILLIAM W. O'NEILL, M.D.
William Beaumont Hospital
Royal Oak, MI 48073-6769

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Zanamivir to Prevent Influenza

To the Editor: Hayden et al. (Nov. 2 issue)[1] identified an index case with an influenza-like illness in 337 families, and assigned the family contacts to prophylaxis with either zanamivir or placebo. Among the 414 family contacts who received zanamivir, influenza developed in 7 (1.7 percent), as compared with 40 of the 423 contacts who received placebo (9.5 percent). Prophylaxis reduced the transmission of influenza by about 80 percent. But there are some problems. Although subjects with index cases of influenza-like symptoms were selected, only 165 of the 337 (49 percent) actually had influenza. Hence, as the accompanying editorial notes, 10 contacts have to receive prophylactic treatment to prevent 1 case of influenza.[2] The wholesale cost of zanamivir is $44.40 per 10-day course of prophylaxis.[3] Thus, the risk of influenza is small after an exposure at home, and prophylaxis is expensive. Moreover, immediately after completing the prophylaxis, the patient is again at risk for influenza. Patients and families may therefore request multiple courses of prophylaxis during an influenza season.

There is another strategy — to vaccinate the exposed family members with influenza vaccine. Antibodies develop in vaccinated persons within one week after vaccination, and the concentration of antibodies peaks in four weeks.[4] The vaccine provides approximately 80 percent protection during the entire influenza season.[5] Those in whom influenza-like symptoms developed within the first week after exposure to an index case (the incubation period of influenza is one to three days) could be treated with antiviral drugs.

Influenza vaccination is 80 percent effective for preventing influenza, costs $6.00, and lasts throughout the influenza season. Zanamivir is 80 percent effective for preventing influenza, costs $44.40, and lasts 10 days. Influenza vaccination is the best way to prevent influenza.

HENRY M. FEDER, JR., M.D.
University of Connecticut Health Center
Farmington, CT 06030

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To the Editor: Hayden et al. report a 79 percent reduction (from 19 percent to 4 percent) in the occurrence of influenza infection in the group that received prophylaxis with

zanamivir as compared with the group that was assigned to placebo. In the base-line characteristics we noticed a difference in the number of household contacts that were already infected at base line. The proportion is 16 percent in the placebo group and only 6 percent in the group assigned to zanamivir. As a consequence, the chance for other healthy family members to become infected differed between the groups. The difference that the authors found in the outcomes may, at least in part, have resulted from this difference that existed at base line. Although it was probably not foreseen, we believe that the analysis should have adjusted for this substantial difference at base line.

JOHANNES C. VAN DER WOUDEN, PH.D.
REINOUT D.W. VAN BENTVELD, M.D.
ROOS M.D. BERNSEN, M.SC.
Erasmus University Rotterdam
3000 DR Rotterdam, the Netherlands

The authors reply:

To the Editor: We fully agree that preseason immunization is the most cost-effective and preferred measure for the prevention of influenza. Unlike influenza vaccine, however, antiviral drugs such as zanamivir offer the possibility of immediate protection for nonimmunized persons who are exposed in settings such as households. Most household cases develop in the first week after exposure (Fig. 1). Zanamivir does not interfere with the immune response to the vaccine,[1] so the combination of short-term prophylaxis with antiviral drugs and concurrent immunization can provide protection for exposed persons. This approach is particularly useful for high-risk patients who receive immunization after the start of the influenza season.[2]

In Table 1 of our article, the percentage of contacts with laboratory-confirmed influenza infection refers to those in whom infection developed after they were enrolled in the prophylaxis phase of the study — not those who were already infected at base line. At the start of prophylaxis, there were only four contacts who had symptoms and in whom laboratory-documented influenza subsequently developed (three in the zanamivir group and one in the placebo group); of these, two (one in the zanamivir group and one in the placebo group) had infections that met the definition of influenza illness that we used for the primary end point and were included in the intention-to-treat analysis of efficacy.

Wright's editorial raised a number of pertinent questions.[3] Zanamivir provides protection from influenza only during the dosing interval, and our primary efficacy analysis was limited to the first 11 days after the administration of the drug was begun. In the subsequent 10-day period there were only three new cases of symptomatic influenza in contacts (one in the zanamivir group and two in the placebo group), a result consistent with the conclusion that most transmission occurs quickly within households (Fig. 1).

Prophylaxis with zanamivir was associated with amelioration of illness. Among the contacts in whom influenza infection developed despite prophylaxis, illness meeting the primary end-point definition developed in 40 of the 66 in the placebo group (61 percent) and only 7 of the 26 in the zanamivir group (27 percent). Furthermore, in those in whom illness developed while they were receiving daily prophylaxis, the median time to resolution of symptoms was 5.5 days for the 7 contacts in the zanamivir group and 8.0 days for the 40 contacts in the placebo group. This 2.5-day difference in the duration of illness is similar to that observed for the subjects with index cases of influenza who were receiving treatment twice daily.

The potential efficacy of zanamivir in providing additional protection beyond that provided by vaccine was examined in a small subgroup of immunized contacts. Laboratory-confirmed infection developed in 8 of the 78 contacts in the placebo group who had been vaccinated (10 percent) and in 2 of the 57 vaccinated contacts in the zanamivir group (3.5 percent); influenza illness developed in 5 of the 78 vaccinated contacts in the placebo group (6 percent) and in none of the vaccinated contacts in the zanamivir group. Although the small numbers of vaccine failures preclude a formal efficacy analysis, these findings suggest that the protective ef-

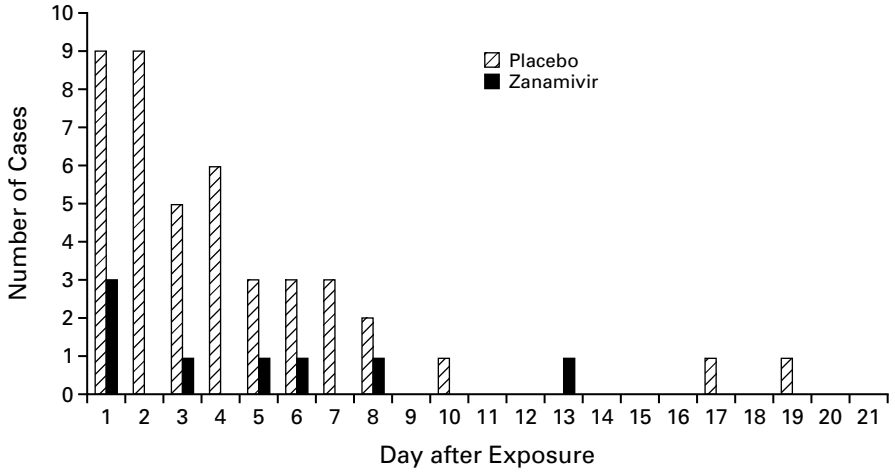

Figure 1. Number of Cases of Influenza That Developed in Household Contacts, Treated with Zanamivir or Placebo, during the First 21 Days after Exposure.

fects of immunization and prophylaxis with antiviral drugs are additive. Moreover, inhaled zanamivir is effective in protecting immunized nursing home residents during outbreaks of influenza.[4]

FREDERICK G. HAYDEN, M.D.
University of Virginia
Charlottesville, VA 22908

MICHAEL J. ELLIOT, M.D.
Glaxo Wellcome
Research Triangle Park, NC 27709

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Treating Opioid Dependence

To the Editor: The article by Johnson et al. on the treatment of opioid dependence (Nov. 2 issue)[1] and the accompanying editorial by O'Connor[2] serve an important purpose in making physicians and, one hopes, the public more aware of the effectiveness of methadone maintenance for heroin dependence. It is discouraging, however, that the ineffectiveness of low-dose methadone therapy still has to be demonstrated. The effectiveness of methadone, at an average dose of 100 mg per day, was shown by Dole et al.[3] more than 30 years ago and has been repeatedly confirmed since then, with some patients needing a dose higher than 100 mg per day.[4] If the high-dose group in the study by Johnson et al. had actually received a high dose of methadone (i.e., higher than 100 mg per day), its effectiveness might have been even more impressive. The low-dose group received a daily dose of 20 mg of methadone, which would not even be an analgesic dose if used for chronic pain. Unfortunately, most programs are using inadequate doses of methadone with, not surprisingly, poor results.

Buprenorphine has been shown to be effective as maintenance therapy for heroin dependence; however, the authors do not mention its high potential for abuse. It is one of the most frequently abused drugs in Australia and Scotland.[5] It would have been helpful if Johnson et al. and O'Connor had mentioned the risk of addiction with buprenorphine as well as its effectiveness as maintenance therapy.

BARRY STIMMEL, M.D.
Mount Sinai School of Medicine
New York, NY 10029-6574

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To the Editor: A maintenance dose of 20 mg of methadone per day is homeopathic. A dose of 60 to 100 mg per day is not high; it is a standard dose. Daily doses above 110 mg are high. The state of California permits a dose of up to 180 mg per day.

A policy of allowing private physicians to prescribe methadone to addicts has both positive and negative aspects. It assists addicts who live in states that do not have methadone treatment programs, and it is appealing because of the dosing schedule and privacy. But how many private physicians want patients with opioid dependence in their waiting rooms or want to assume the responsibility for their primary care?

As methadone maintenance has evolved, we now realize that opioid dependence is a complex problem and needs more attention. It is not enough to give an addict methadone every day. There are other, large problems associated with opioid dependence. Most heroin addicts did not graduate from high school, are functionally illiterate, do not have job skills, and have serious emotional problems, and at least a third of them abuse alcohol. (This last fact is not mentioned in the article or editorial, nor is the fact that most heroin addicts are positive for hepatitis C virus.) Few medical offices are equipped to address these problems. Addicts need help in learning the coping skills required for living in the community. In the past decade, treatment centers began seeing the addict as a whole person, not just a needle user. The problems associated with opioid dependence are addressed in many of the large clinics, with even dietary counseling provided.

THOMAS V. REESE, SR., M.D.
3120 Nahenahe Pl.
Kihei, HI 96753

The authors reply:

To the Editor: Both Stimmel and Reese object to the term "high dose" for a dose of 60 to 100 mg of methadone per day. We used the term in its relative, not absolute, sense, and we agree that for some patients, even higher doses may be necessary and appropriate.

Both Stimmel and Reese also criticize our use of a lower-dose control treatment. However, inclusion of this treatment was critical for documenting the effectiveness of the other study treatments, and our rescue procedure made it ethically acceptable. We agree that higher doses should be considered, and our findings support their use. It is our hope that well-controlled clinical trials[1,2] will help accomplish what 35 years of uncontrolled clinical experience has not.

Stimmel and Reese err in suggesting that a 20-mg dose of methadone is ineffective or homeopathic. In the group of patients who received this dose, there was a large reported reduction in heroin use, and in an earlier study, patients who received this dose reported substantial improvements in both symptoms and drug use.[3] The effectiveness of low methadone doses in suppressing opioid withdrawal prob-

ably contributes to the frequent failure of physicians to increase doses to a level that optimally reduces heroin use.

Stimmel suggests that buprenorphine may have a high potential for abuse. It does have a potential for abuse, but it is probably less than that of methadone or heroin. Buprenorphine has typically been abused in circumstances of limited regulation, limited availability of other opioids, or both. Once it has been approved by the Food and Drug Administration (FDA), the primary formulation for the treatment of heroin dependence will be a combination product containing the antagonist naloxone, which dramatically reduces the potential for abuse through injection by opioid-dependent persons.[4]

Reese notes that many heroin-dependent patients have serious behavioral and medical problems. We certainly concur. Increasing the array of treatment options should result in a larger proportion of patients who receive some form of treatment and should enhance opportunities to address these problems.

ROLLEY E. JOHNSON, PHARM.D.
ERIC C. STRAIN, M.D.
GEORGE E. BIGELOW, PH.D.
Johns Hopkins University School of Medicine
Baltimore, MD 21224

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The editorialist replies:

To the Editor: As Stimmel and Reese point out, the dose of methadone is clearly related to its effectiveness in treating opioid dependence.[1] For example, one study found that a "high" dose, in the range of 80 to 100 mg per day, was superior to a "moderate" dose, in the range of 40 to 50 mg per day, in reducing illicit opioid use.[2] Even higher doses (more than 100 mg per day) may be necessary for some patients.

Like other opioids, buprenorphine has a potential for abuse, although as a partial opioid agonist, buprenorphine may have less potential for abuse than pure opioid agonists such as methadone. A preparation that is likely to be approved in the United States is a combination of buprenorphine and naloxone, which may further decrease (but not eliminate) the potential for abuse, especially among opioid-dependent injection-drug users.[3]

Office-based maintenance therapy for opioid dependence has the potential to provide greatly increased access to treatment. Although I agree with Reese that this approach may be especially useful in areas that do not have maintenance programs, it will also be useful in areas where programs exist but access to them is limited because of an insufficient number of treatment slots or other barriers. Studies of office-based methadone maintenance in Connecticut and elsewhere suggest that finding private physicians who are willing and able to provide such treatment and primary care for stabilized patients may not be difficult. I agree that the simple act of dispensing a medication is generally not sufficient and that counseling and other services are critical elements of treatment for opioid dependence and other medical disorders. However, studies of office-based methadone maintenance suggest that selected patients can do well in the office setting.[1,4] Nonetheless, it is unlikely that office-based methadone maintenance will be broadly available in the near future.

In 2000, President Bill Clinton signed legislation (Public Law 106-310) that authorizes appropriately trained physicians to prescribe Schedule III, IV, and V controlled substances that have been approved for the treatment of opioid dependence. Although as of this writing the FDA has yet to approve such medications, it is likely that buprenorphine will eventually be approved for this purpose.[5] Critical issues remain to be addressed. These include the training of physicians, the selection of patients, the appropriate level of counseling, the effectiveness and safety of office-based treatment, satisfaction on the part of patients and physicians, and links with substance-abuse programs.

PATRICK G. O'CONNOR, M.D., M.P.H.
Yale University School of Medicine
New Haven, CT 06520-8025

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Obesity, Hypertension, and Renal Cancer

To the Editor: We disagree with Dr. Chow and colleagues, who stated in their recent article (Nov. 2 issue)[1] that "epidemiologic studies have not been able to distinguish the effects of hypertension from those of diuretics or other antihypertensive drugs on the risk of renal-cell cancer. . . . In addition, although our results provide strong evidence of a dose–response relation with body-mass index and blood pressure in men, they may not apply to the same extent in women."

Three years ago, we reported the findings of a large, population-based, case–control study designed specifically to examine the association of renal-cell carcinoma with the use of diuretics and antihypertensive agents and its association with the conditions (hypertension and obesity) that call for the use of these drugs.[2] The study involved 1204 patients with histologically confirmed, newly diagnosed renal-cell carcinoma (781 men and 423 women) and an equal number of age-, sex-, and race-matched controls from the same neighborhood. Self-reported use of all pre-

scription diuretics and antihypertensives was validated, whenever possible, against physicians' records for both the patients with renal-cell carcinoma and the controls. We noted that obesity and a history of hypertension were strong and independent risk factors for renal-cell carcinoma in both men and women. There was little evidence that the use of diuretics was directly related to the development of renal-cell carcinoma. The use of diuretics for reasons other than hypertension (primarily weight control) was unrelated to risk among subjects who described themselves as having normal blood pressure; among subjects with hypertension, subjects with a high cumulative lifetime dose of diuretics had a risk similar to that in subjects with a low cumulative lifetime dose. Similarly, subjects with normal blood pressure who regularly took nondiuretic antihypertensive agents were not at increased risk for renal-cell carcinoma, and among hypertensive subjects, intake did not further increase the risk.

MIMI C. YU, PH.D.
RONALD K. ROSS, M.D.
University of Southern California
Los Angeles, CA 90033

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The authors reply:

To the Editor: We appreciate the comments of Drs. Yu and Ross on our recent cohort study. In earlier case–control studies of renal-cell cancer based on interview data, it was difficult to disentangle the risks associated with hypertension, use of antihypertensive medications, or both. The challenge of obtaining accurate and complete histories of hypertension, fluctuations in blood pressure, and use of antihypertensive medications over long periods would, at least in part, explain the inconsistent findings reported in the literature.

In their large and well-designed case–control study of renal-cell cancer, Yu and Ross and their colleagues were able to limit the potential for bias by contacting physicians to verify the use of prescription medications. However, the rates of response from physicians ranged from 35 percent to 40 percent, and it seems likely that only recent prescriptions could have been verified and that the severity and control of hypertension were difficult to evaluate.

We agree from the sum of the epidemiologic evidence that hypertension and obesity are important risk factors in both sexes. Since our study population consisted of male construction workers who had periodic measurements of height, weight, and blood pressure, we could not claim that the observed levels of risk associated with variations in weight and blood pressure would be similar in women.

WONG-HO CHOW, PH.D.
JOSEPH F. FRAUMENI, JR., M.D.
National Cancer Institute
Bethesda, MD 20892-7240

Transplantation of a Tissue-Engineered Pulmonary Artery

To the Editor: Various vascular grafts are commonly used in the reconstruction of cardiovascular tissues. However, prosthetic or bioprosthetic materials lack growth potential and therefore in children require replacement as the children grow. Tissue engineering offers the potential to create replacement structures from autologous cells and biodegradable polymer scaffolds. Since they contain living cells, these structures have the potential to grow, to repair themselves, and to remodel themselves.[1-4]

A four-year-old girl had been found to have a single right ventricle and pulmonary atresia and had undergone pulmonary-artery angioplasty and the Fontan procedure at the age of three years, three months. Angiography seven months later revealed total occlusion of the right intermediate pulmonary artery. The application of tissue engineering in this patient was approved by the ethics committee at Tokyo Women's Medical University in April 1999. The patient's parents were thoroughly informed and consented to the procedure.

An approximately 2-cm segment of peripheral vein was explanted, and cells from its walls were isolated. The cells were cultured and expanded as previously described. The cell count in the culture increased substantially, to approximately 12×10^6 cells, by eight weeks. A tube that served as a scaffold for these cells was composed of a polycaprolactone–polylactic acid copolymer (weight ratio, 1:1) reinforced with woven polyglycolic acid (Fig. 1). The biodegradable polymer conduit (10 mm in diameter, 20 mm in length, and 1 mm in thickness) was designed to degrade within eight weeks.

Ten days after seeding, the graft was transplanted. The occluded pulmonary artery was reconstructed with the tissue-

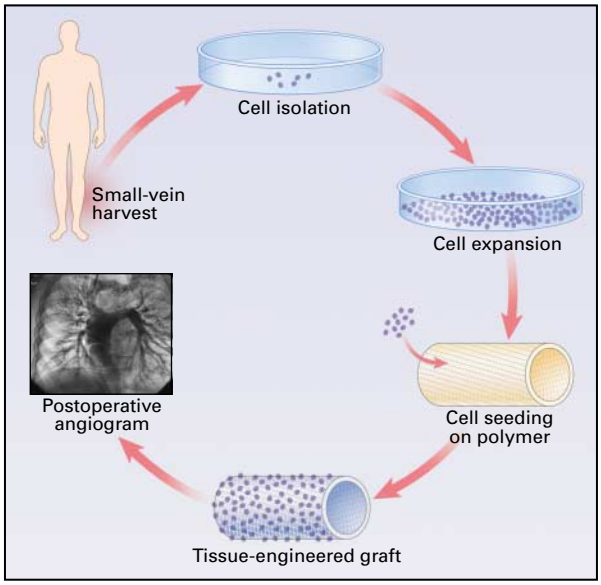

Figure 1. The Tissue-Engineering Technique.
Venous-wall cells were isolated and expanded in vitro and seeded on a biodegradable polymer scaffold. The construct of cells and polymer was implanted as autologous tissue.

engineered vessel graft. No postoperative complications occurred. On follow-up angiography, the transplanted vessel was noted to be completely patent (Fig. 1). Seven months after implantation, the patient was doing well, with no evidence of graft occlusion or aneurysmal changes on chest radiography. We suggest that in pediatric cardiovascular surgery, tissue engineering may have an important role as an alternative to transplantation and the use of artificial organs.

TOSHIHARU SHIN'OKA, M.D.
YASUHARU IMAI, M.D.
Tokyo Women's Medical University
Tokyo 162-8666, Japan

YOSHITO IKADA, PH.D.
Suzuka University of Medical Science
Mie 510-0226, Japan

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A Fatal Complication of Noninvasive Ventilation

To the Editor: Noninvasive positive-pressure ventilation is widely used in patients with chronic respiratory failure due to neuromuscular diseases such as amyotrophic lateral sclerosis.[1] Noninvasive positive-pressure ventilation can be used intermittently, the equipment is portable, and ventilation does not interfere with eating and speaking. It is considered safe, and most problems that occur are related to the fit of the mask and the risk of aspiration pneumonitis.[2] We describe a complication we have not previously seen reported.

The patient was a previously healthy 53-year-old man with amyotrophic lateral sclerosis who was started on nocturnal noninvasive positive-pressure ventilation (inspiratory pressure, 10 cm of water; expiratory pressure, 2 cm of water). He tolerated this well and decided that he did not want invasive mechanical ventilation in the future. The patient's disease progressed, but he continued to work full-time and used noninvasive positive-pressure ventilation all night and most of the day. He obtained a second ventilator, which he kept at work.

More than a year after noninvasive ventilation was initiated, the patient's ventilating unit failed. The machine's error code indicated that there had been a power-supply failure. Respiratory distress quickly developed, and the patient was taken to a local hospital but died of respiratory failure before ventilation could be reinstituted.

This case demonstrates a problem that is likely to become more common as increasing numbers of patients with chronic respiratory failure use noninvasive positive-pressure ventilation. It is important to realize that technical failures of the machines in these cases can be catastrophic. Patients and their caregivers should be counseled that noninvasive positive-pressure ventilation is not a substitute for tracheostomy and mechanical ventilation. Patients need to be made aware of the consequences of ventilator failure. We recommend that our patients consider making the transition to tracheostomy if they require full-time ventilatory support. Although this event has not decreased our use of noninvasive positive-pressure ventilation, we have begun to teach caregivers how to provide bag-and-mask ventilation to patients in the event of an emergency. If the equipment is available, this simple technique may be lifesaving.

NOAH LECHTZIN, M.D., M.H.S.
CHARLES M. WEINER, M.D.
LORA CLAWSON, M.S.N., C.R.N.P.
Johns Hopkins University School of Medicine
Baltimore, MD 21287

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