ischemia is an incomplete gauge of the myocardial O2 demand present at the time. Perhaps the apparent changes in "ischemic threshold" during the day described by Tzivoni and colleagues may be explained in part by fluctuations in the baseline heart rate or the duration of heart rate increases at different times of the day rather than solely to changes in coronary tone, as the investigators suggest.

The results of our study underscore the complexity of the pathophysiological mechanisms leading to ischemia during daily activities and suggest that future studies investigating pathophysiology based on heart rate changes should be refined by incorporating the variables of baseline heart rate, magnitude of heart rate increase, and duration of heart rate increases before implicating changes in coronary tone.

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Unfavorable Outcome in Patients With Primary Electrical Disease Who Survive Ventricular Fibrillation

The study by Wever et al1 highlights several important features regarding patients with primary electrical disease: (1) noninducibility at baseline electrophysiological study does not necessarily predict an arrhythmia-free course; (2) such patients are at fairly high risk of major arrhythmic events during follow-up; (3) defibrillator implantation should be considered as an early management strategy. Interestingly, 2 of their 19 patients experienced ventricular fibrillation (VF)/sudden cardiac death despite receiving what was thought to be suppressive therapy (one gauged by electrophysiological study, the other by noninvasive means). The authors treated 10 of their 19 patients with an automatic (A) implantable cardioverter-defibrillator (ICD) and highly recommended that a defibrillator be implanted early in all patients with primary electrical disease who have survived VF. Their findings corroborate those of our earlier study, the first and largest systematic study of ICD therapy in VF survivors without significant structural heart disease (28 patients).2,3

The study of Wever et al was a single-center, prospective one, whereas ours was a multicenter, retrospective one that by design included only patients without significant structural heart disease treated with ICDs. In the study of Wever et al, all patients underwent, among other tests, myocardial biopsy, right ventricular cineangiography, and two-channel Holter monitoring, evaluations that were performed on many but not all of our patients. Lack of definitive arrhythmia diagnosis surrounding unmonitored shocks was a limitation of both studies, as the AICDs had no arrhythmia storage capabilities. Despite differences in the two studies, our findings were nicely corroborated by those of Wever et al. On the average, patients were relatively young (mean age, 42 years2 versus 33 years1); a high percentage of patients was noninducible for ventricular tachyarrhythmias (61%3 versus 47%2); presumably "appropriate" shocks were received by defibrillator implanters during follow-up1-3; and our 17.7% estimated 2-year actuarial sudden arrhythmic death rate was fairly similar to that of the more recent Dutch study (estimated from their Fig 2, as an actuarialized rate was not provided in the text).

The precise number and timing (relative to index arrest and date of ICD implantation) of recurrent AICD shocks in patients 7, 8, and 10 of the study by Wever et al could not be determined from the data provided. Were these all part of one shock episode, respectively? Interestingly, none of the patients in Wever's study received "undetermined" shocks, whereas the majority of shocks in our population were classified as "indeterminate." Several factors may account for the difference. Wever et al defined an appropriate shock to include one preceded by sudden onset of palpitations. By this definition, at least three and possibly five of our patients' shocks would have been reclassified from indeterminate to appropriate. Programmed AICD rate crossovers in our patients were not always set at 200 beats per minute, and, although set above maximum exercise rates, may initially still have been set lower than the heart rates ultimately achieved during vigorous activity by many of these otherwise healthy patients. The role, if any, of β-adrenergic blocking agents is uncertain. Several of our patients but apparently none of Wever's patients were receiving these drugs.

In summary, despite some methodological differences, the study by Wever et al corroborates our earlier findings concerning patients with VF in the absence of significant structural heart disease: These are patients with a risk of recurrent arrest whose fatal outcome may be avoided by ICD therapy. Baseline and posttreatment noninducibility assessed by electrophysiological or noninvasive studies does not necessarily portend an arrhythmia-free outcome.

It is hoped that our study and that of Wever et al provide complementary information that will help physicians in the optimal management of these challenging patients with idiopathic VF.

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References
Arrhythmia detection (D) and termination by shock delivery (S) in a patient with primary electrical disease in whom an automatic implantable cardioverter-defibrillator with storing capability was implanted. This patient had no complaints before shock delivery.

Reply

Results of the study by Meissner et al.2 are in accordance with our findings that patients with primary electrical disease who have survived an episode of ventricular fibrillation are at high risk of recurrence of a life-threatening arrhythmia.3 In this predominantly young group of patients, strict measures are necessary to prevent a lethal outcome. As in our study, Meissner et al conclude that the automatic implantable cardioverter-defibrillator (AICD) is the preferable measure. The estimated 2-year actuarial major arrhythmic event rate in our study was 24%, with a 95% confidence interval of 10 to 53, similar to the estimated 2-year actuarial sudden arrhythmic death rate of 17.7% in the study from Meissner et al. Thus, this category of patients with no impairment of cardiac pump function may be the group to benefit most from AICD therapy.

Five patients (6, 7, 8, 10, and 15) from our study received (pre)syncope-triggered shocks to terminate a first recurrent arrhythmic event at 17, 7, 36, 7, and 21 months after the index episode, respectively. Patients 7, 8, and 10 received recurrent shocks, not in the same episode. According to the predefined protocol, appropriate shocks in our study were defined as documented shocks preceded by either a syncopal attack, sudden and transient dizziness (presyncope), or sudden onset of palpitations. Shocks were associated with termination of presyncope in three patients (patients 7, 10, and 15) and syncope in two (patients 6 and 8). According to their definitions, Meissner et al would also have considered these shocks appropriate. Moreover, in none of our AICD patients did heart rate (during sinus rhythm in nine patients, and atrial fibrillation in one) ever exceed the programmed rate cutoff during continuous telemetry preoperatively or during Holter monitoring and exercise testing preoperatively and postoperatively. The implanted devices also monitored electrogram morphology by means of a probability density function. This function was omitted in one patient, who had a wide QRS during sinus rhythm (patient 12). We saw no direct reason for the use of β-blocking agents in any of the AICD patients in this study. As discussed in the “Study Limitations,” there was no indication that any shock was elicited by a supraventricular tachyarrhythmia. In all of our AICD patients, rate cutoff was set at 200 per minute, as the rate of a recurrent life-threatening arrhythmia would not be expected to be less than 200 per minute in this patient category. Interestingly, one patient, who was later included in our study (patient 20), received a shock not preceded by symptoms. This patient had undergone implantation of an AICD with an electrogram storing function. The Figure shows the recorded electrogram of the event. In the absence of storing capabilities, this shock would have been considered undetermined.

The major finding of both studies is the high risk of unfavorable outcome, in contrast to the general belief expressed in previous reports of a benign prognosis in such patients. For a better understanding of this fascinating patient group, data concerning larger numbers of patients are essential. For this purpose, the Unexplained Cardiac Arrest Registry of Europe (U-CARE)4 has been initiated.

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Atrial Natriuretic Peptides Are Stable in Plasma for 7 Years

Because of the continuing controversy on how long atrial natriuretic factor (ANF) is stable in plasma, as reflected by the letters in the October 1993 issue of Circulation,1,2 plasma in which ANF was measured in 1986 was reevaluated in 1993. The levels of ANF in healthy human volunteers measured in 1986 and published in Circulation3 were re-assayed in 1993, and nearly identical (±5%) concentrations were found. There was no significant decrease in the ANF concentration found in the plasma samples that had been stored at -80°C for this 7-year period. Thus, I completely agree with Flynn et al4 and Tan et al4 that there is no deterioration in immunoreactive ANF in plasma when stored for a period of as long as 6 months at -80°C. Furthermore, as outlined above, there is no significant deterioration in immunoreactive ANF when it is stored for very long periods of time (ie, 7 years) if these samples are not thawed and refrozen on several occasions. Atrial natriuretic peptides derived from the N-terminus of the ANF prohormone (ie, proANF 1-30 and proANF 31-67, the numbers reflecting the amino acids starting with the N-terminus of the ANF prohormone being number 1) were also measured in 1986,3 and the same plasma samples were reevaluated in October 1993. Their concentrations were also essentially the same (±5%) 7 years later. Our proANF 1-30 assay immunologically recognizes proANF 1-30 (25%) and proANF 1-98 (the N-terminus of the ANF prohormone, 75%) in plasma as determined by high-performance gel permeation chromatography,5 whereas our proANF 31-67 assay immunologically recognizes proANF 31-67 (96%) and proANF 1-98 (4%).6 Thus, each of these atrial natriuretic peptides is stable in plasma for prolonged periods if stored at -80°C. Tan et al4 and Nelesen et al2-3 both have shown that frequent thawing and refreezing of plasma samples degrade atrial natriuretic peptides and decrease their measured concentrations. This is an important point to remember when assaying plasma for the concentration of these peptides.

As opposed to the above stability of atrial natriuretic peptides in plasma samples, when the pure human or rat sequenced atrial
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