Electrophysiological Testing in High-Risk Patients With Previous Myocardial Infarction

Dr. Wellens raises several important issues in his recent editorial comment regarding the role of electrophysiological testing in risk stratification and treatment of patients with previous myocardial infarction and nonsustained ventricular tachycardia presented in our article. Our study was based on the results of previous investigations in patients with remote myocardial infarction, which indicate that the inability to induce sustained ventricular arrhythmias predicts a low risk for subsequent sudden death, and thus identified a large group of patients in whom therapeutic intervention is unlikely to be beneficial. The results of our study extended these findings by demonstrating that even in the subgroup of patients known to be at highest risk of sudden death (those with impaired ventricular function), the predictive value of a negative test was excellent. We also systematically evaluated the role of electrophysiological guided antiarrhythmic drug therapy as a prophylactic treatment strategy in patients with inducible ventricular arrhythmias. Drug therapy alone was found to have serious limitations. Although drug responders had good long-term prognoses, 50% of the patients were nonresponders. The 2-year incidence rate of sudden death or cardiac arrest in these latter patients was 50%.

Dr. Wellens’ interpretations of several aspects of this study are inaccurate. No patient in our study had hemodynamically stable sustained ventricular tachycardia during follow-up. All arrhythmia-related end points were either sudden death or cardiac arrest with successful resuscitation. If the results of guided drug therapy were analyzed on an intention-to-treat basis, the three patients with inducible sustained ventricular arrhythmias and cardiac arrest during serial drug testing would have been classified as drug nonresponders (all had been nonresponders during at least one previous drug trial and certainly could not be grouped with patients without baseline inducible arrhythmias). In contrast to Dr. Wellens’ assertion, such an analysis would have magnified the difference between drug responders and nonresponders and certainly have not rendered the difference insignificant! The findings of our study do not necessarily support the universal application of serial drug testing to myocardial infarction survivors with inducible sustained ventricular arrhythmias, nor do they suggest that drug therapy alone can provide adequate prophylaxis in all patients. However, as we concluded, electrophysiological guided drug therapy in combination with implantable defibrillators for patients who are not drug responders may be a more suitable therapeutic strategy for testing in future placebo-controlled clinical trials.

A second set of issues raised by Dr. Wellens is related to the optimal method of choosing high-risk candidates and the proper timing of studies after myocardial infarction. As suggested by Dr. Wellens, electrophysiological testing in this setting should be limited to patients with impaired ventricular function and occur only after reversible myocardial ischemia has been appropriately treated. Both these conditions were met in our study population. The apparent excellent negative predictive value of the signal-averaged electrocardiogram has been established in a diverse population of patients, including myocardial infarction survivors. However, many of these patients had good ventricular function. Whether this test will remain a useful predictor of benign outcome when applied exclusively to patients with impaired ventricular function remains to be determined.

Dr. Wellens also questioned the additional requirement of nonsustained ventricular tachycardia as a criterion for study entry. The presence of nonsustained ventricular tachycardia in the post-myocardial infarction survivor increases the risk of sudden death by twofold to fourfold, independent of ventricular function. Thus, patients with both nonsustained ventricular tachycardia and impaired ventricular function form a subgroup at highest risk for sudden death and constitute an ideal population for studying the impact of therapeutic interventions. The findings of the Cardiac Arrhythmia Suppression Trial (CAST) raise serious questions regarding the suppression of spontaneous ventricular ectopy as an effective strategy for preventing sudden death. However, this latter study does not invalidate the role of spontaneous nonsustained ventricular tachycardia as a baseline predictor of risk.

Ideally, risk stratification after myocardial infarction should be performed just before hospital discharge. However, the anatomical substrate for ventricular arrhythmias undergoes considerable change in the first few weeks after myocardial infarction. The reproducibility of electrophysiological findings during this time period has received little attention. Two studies with small populations specifically addressing this issue demonstrate considerable variability in the induction of sustained monomorphic ventricular tachycardia at different points in time during the first 2 months after infarction. One prospective study with a large population demonstrated that the induction of sustained ventricular arrhythmias early after myocardial infarction in patients with normal or impaired ventricular function was associated with a significantly increased risk of sudden death. However, the stimulation protocol in this study was somewhat unusual (i.e., limited to two extrastimuli with a stimulation current of no more than 20 mA). The usefulness of more often used stimulation protocols (as many as three extrastimuli delivered at twice diastolic threshold) early after myocardial infarction in patients with impaired ventricular function has not been established. Further clarification of these problems is necessary before early postinfarction testing can be advocated routinely.

Validation of electrophysiological guided therapy as an effective method for preventing sudden death in patients with previous myocardial infarction awaits the results of several well-designed placebo-controlled trials that are currently planned or under way. As Dr. Wellens correctly points out, if maximum benefit is to be derived from interventional strategies after myocardial infarction, careful consideration must be given to the characteristics of patients selected for these potentially time-consuming and expensive therapeutic interventions.

David J. Wilber, MD
Loyola University Medical Center
Maywood, Illinois

References
3. Denniss AR, Richards DA, Cody DV, Russell PA, Young AA, Cooper MJ, Ross DL, Uther JB: Prognostic significance of
ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal-averaged electrocardiograms of survivors of myocardial infarction. Circulation 1986;74:731–745

Ticlopidine in Unstable Angina

In response to the editorial comment by Dr. FitzGerald concerning our article, we have some observations. The purpose of our study was not to compare the clinical efficacy of ticlopidine with that of aspirin but rather to evaluate whether an antiplatelet drug with a mechanism of action different from that of aspirin could reduce cardiovascular complications in patients with unstable angina. Such a study could be useful to reaffirm the role of platelets in the evolution of unstable angina and to consequently define another therapeutic approach that, like aspirin, could improve the clinical course of such patients. Our study provides affirmative feedback to both points but does not indicate that ticlopidine is better than aspirin. We agree with Dr. FitzGerald that further study is necessary to assess the latter possibility. Nevertheless, from the clinical practice viewpoint, the data from our study should be carefully considered, especially as 10–20% of patients with unstable angina cannot be treated with aspirin.

Concerning the potential contamination of the trial results by the use of aspirin, as either prescribed or consumed independently by the patients, it can easily be argued that if there was contamination in the two groups, it would have been at the same or higher level in the control group. In that case, the comparison between the two treatments can be reasonably considered unbiased. Moreover, it should be pointed out that in Italy the use of aspirin in the prevention of occlusive ischemic events in patients with unstable angina is not a common practice, and that aspirin associated with ticlopidine markedly increases bleeding time. If there had been contamination, many bleeding disorders would have been observed in the ticlopidine group, but this did not occur.

With regard to the fact that our study was not controlled, we reply that the trial was a controlled, multicenter, and completely and centrally randomized trial; the routine therapy used in every center was compared with the same therapy plus ticlopidine. In this way, it was not necessary to modify the common therapeutic policy followed in the individual centers, and data were quickly obtained that could be transferred to clinical practice. Confirmation of this advantage is demonstrated by the 10 months of recruitment in our study compared with the 4 and 7 years of the studies of Lewis et al and Cairns et al, respectively, necessary to enroll a comparable number of patients. Our methodologic approach was consequently of a pragmatic type, like the model adopted by GISSI. For the same reason, the standard therapies adopted by the centers (calcium antagonists in 86% of the cases) were a spontaneous choice and not based on the meta-analysis of Held et al, which was published after our study concluded.

The decision to prematurely interrupt enrollment of patients was made not by the sponsor but by the study executive committee in accordance with the protocol (see “Sample Size”).

Dr. FitzGerald also stresses that ticlopidine did not appear to have any preventive effect in our study during the first 20–30 days of treatment. This may be true, but it may not be correct to make such an extrapolation after the fact, keeping in mind that the scope of the study was to verify the efficacy of the drug in the prevention of fatal occlusive ischemic events within 6 months. In fact, many primary end points were observed in the control group after 16–180 days of treatment. This causes us to at least consider using antiplatelet treatment for a prolonged period of time, not just in the acute phase. Moreover, heparin may be preferable to aspirin in the early phase.

The “canard” of the possible different efficacy of aspirin with respect to sex could provide a basis for discussion, and we respect the opinion of Dr. FitzGerald. However, we would like to emphasize, as we stated, that Table 6 (concerning the frequency of events in relation to sex and to previous myocardial infarction) had only a descriptive purpose. In fact, we did not make any evaluation of such subgroups.

Finally, with regard to the increased risk of hemorrhagic complications and of gastrointestinal bleeding with the use of ticlopidine observed in a US study and in a Swedish study, the effect has not been confirmed in both the unstable angina study or in our previous short- and long-term experiences.

Francesco Balsano, MD
Francesco Violi, MD
University “La Sapienza”
Rome
Claudio Cimminiello, MD
Internal Medicine Department
Ospedale S. Carlo Borromeo
Milan

References
Electrophysiological testing in high-risk patients with previous myocardial infarction.

D J Wilber

_Circulation._ 1990;82:2281-2282
doi: 10.1161/01.CIR.82.6.2281

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/6/2281.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/