
REPLY
The letter by Dr. Erdogan made some good points that, although in our view do not detract from the results and conclusions of our study, are of general interest to the issue of defibrillation success. We appreciate the opportunity to clarify the purpose of our study, which may have eluded some other readers as well.

Most patients in our study were free from antiarrhythmic drugs for five half-lives, except for two patients who had received prior amiodarone therapy that failed to suppress the targeted arrhythmia. Though we do not necessarily subscribe to the value of the 12-lead electrocardiogram as a means to demonstrate the dispersion of repolarization at the myocardial level (1,2), it is quite possible, as Dr. Erdogan states in his letter, that residual amiodarone and other factors such as anesthesia, electrolytes, autonomic tone, etc., may have influenced the dispersion of repolarization in our patients. Any of these influences might enter into the equation that governs the probabilistic nature of the defibrillation threshold (DFT), and that of the fibrillation threshold as well. However, it was not the purpose of our study to discern the effects of such factors on the DFT or ventricular fibrillation (VF) inducibility by ICD shocks.

Instead, our purpose was to show that, in a single patient and at a given time, the probability of inducibility of VF by a T-wave shock and the failure to terminate VF by a second shock were strongly associated with the extent of myocardial repolarization dispersion immediately following the shock (either caused by the shock in case of VF induction, or due to lack of synchronization by the shock in case of VF termination failure). Our intent was directed purely at the mechanistic aspects of VF induction and termination, and to demonstrate and extend for the first time, the probability of inducibility of VF by a T-wave shock in case of VF induction, or due to lack of synchronization by the shock in case of VF termination failure). Our intent was directed purely at the mechanistic aspects of VF induction and termination, and to demonstrate and extend for the first time, the probability of inducibility of VF by a T-wave shock in case of VF induction, or due to lack of synchronization by the shock in case of VF termination failure).

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C-Type Natriuretic Peptide and Vascular Remodeling
Morishige et al. (1) have reported local adenovirus-mediated transfer of C-type natriuretic peptide (CNP) to porcine coronary arteries, resulting in reduced stenosis of balloon-injured segments. This is an exciting development with obvious therapeutic potential. The investigators suggest several mechanisms by which CNP might regulate vascular remodeling, but they fail to mention the effects of CNP on the vascular renin-angiotensin system. Many studies have demonstrated that the natriuretic peptides have a tonic effect at various sites in the renin-angiotensin-aldosterone cascade (2), and we have demonstrated that CNP inhibits local conversion of angiotensin I to angiotensin II in the human forearm vasculature (3). These vascular effects of CNP in man in vivo are particularly relevant to the therapeutic potential of the technique described by Morishige, because of the known interspecies variability in the effects of the natriuretic peptides (2). The effects of angiotensin II on vascular remodeling are well-documented, and a reduction in local angiotensin II production is a potentially important mechanism for some of the observed effects of CNP.

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REPLY
We are grateful for the opportunity to respond to the valuable comments by Drs. Davidson and Struthers concerning our recent article in the Journal (1). In our article, we showed that adenovirus-mediated overexpression of C-type natriuretic peptide (CNP) in the porcine coronary artery suppresses vascular constrictive remodeling after balloon injury in vivo. However, as the authors pointed out, we did not mention the possible effect of CNP on the renin-angiotensin-aldosterone system, mainly because we did not specifically examine this system in our study.

It is indeed possible that CNP/cGMP cascade may suppress the vascular remodeling through various mechanisms, including smooth muscle relaxation and inhibition of proliferation and migration of smooth muscle cells and subsequent extracellular
matrix deposition. Vascular remodeling appears to be caused by complicated processes, in which the renin-angiotensin-aldosterone system is involved. In this sense, we fully agree with Drs. Davidson and Struthers that CNP should be regarded as an endogenous regulator of the vascular renin-angiotensin-aldosterone system (2).

In our porcine model of inflammatory coronary arteriosclerosis, which is characterized by constrictive remodeling and neointimal formation, a complex cytokine network appears to be involved, including several growth factors and inflammatory cytokines (3). Furthermore, recent studies suggested that other mechanisms, such as endothelial dysfunction, collagen accumulation, and matrix-metalloproteinase activity, may also be involved in the pathogenesis of vascular remodeling (4,5). We have recently demonstrated that small GTP binding protein Rho and its target Rho-kinase play an important role in the molecular mechanism of vascular hyperreactivity as well as vascular remodeling in our porcine model (6,7). Importantly, the Rho/Rho-kinase pathway is involved in the cardiovascular effects of angiotensin II (8).

Taken together, it is highly possible in our study that the inhibitory effect of CNP on the development of vascular remodeling was mediated, at least in part, by its modulatory effect on the vascular renin-angiotensin-aldosterone system. However, it remains to be examined whether adenovirus-mediated overexpression of CNP in the coronary artery actually reduces the local production of angiotensin II in our porcine model in vivo.

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**Stress Testing and Electron Beam Computed Tomography for Evaluation of Patients With Suspected Coronary Artery Disease**

I read with interest the study by Shavell et al. (1) on the value of exercise testing and electron beam computed tomography (EBCT) in the evaluation of coronary artery disease (CAD). The investigators report that when applied to a population referred for angiography, EBCT has a sensitivity of 96% and a specificity of 47% for detection of significant CAD (defined as ≥50% diameter stenosis), and they conclude that “Electron beam computed tomography has a higher diagnostic ability than either treadmill ECG or technetium-stress for the detection of obstructive angio- graphic CAD.” They also suggest that a combination of EBCT (for optimal sensitivity) with ECG stress testing (for improved specificity and functional information) might be the preferred approach for evaluating patients with suspected CAD.

Both these conclusions have to be viewed with skepticism: The sensitivity of nuclear stress testing in their study (78%) is low, almost equal to that of treadmill ECG (76%). When a broader definition of “positive scan results” was used (either fixed or reversible perfusion defects), the sensitivity was even lower (75%). Other than a typographic error, I can see no explanation to this paradox. Several studies have demonstrated that nuclear stress testing has a significantly higher sensitivity for detection of CAD than hereby presented. Even in the meta-analysis that the investigators quote (2), an almost 10% higher sensitivity (87%) was reported, despite the inclusion of several older studies and some with a stricter definition of “significant CAD” (≥70% diameter stenosis).

The investigators identify a number of reasons that could explain the lower than expected specificity of nuclear testing in their study, including the absence of ECG-gating and the high likelihood of attenuation-induced defects. However, the low sensitivity in the study is not adequately explained: If both fixed and reversible defects were considered as abnormal, the underestimation of reversibility that the authors quote (3,4) (and which has been described for assessment of myocardial viability) should not underestimating the sensitivity for detection of CAD. Moreover, the potential Tc-99m redistribution that the researchers consider as a source of decreased test sensitivity is minimal (3,5), if any at all (6,7), and is unlikely to completely normalize significant perfusion defects. In any case, the reference that Shavell et al. quote (8) to support their contention that redistribution might account for their low Tc-99m stress test sensitivity does not address this issue.

Finally, the combined assessment of EBCT and treadmill ECG should be evaluated with caution. In the Shavell et al. study, 27 patients with a positive EBCT scan, one third of all positive EBCT scans, were considered as having a negative “test.” What was the severity of coronary calcification in these patients? Should not the extent of calcification also be taken into account, if a combined test approach were to be used?

The utility of EBCT as a research tool is unquestionable. However, the clinical utility of EBCT, and for that matter any