For patients with reduced ejection fraction (EF), the risk of cardiac arrest is particularly high in the healing phase after a myocardial infarction (MI). Estimates from recent clinical trials show an annualized sudden-death risk of 8% to 12% in the 3-month period after MI, even with optimal medical therapy including appropriate revascularization, β-adrenergic receptor blocker, aldosterone inhibitor, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy.1

The recently initiated Vest Prevention of Early Sudden Death Trial/Prediction of ICD Therapies Study (VEST/PREDICTS) illustrates the gravity of this situation (clinicaltrials.gov identifier NCT00628966). VEST/PREDICTS is randomizing acute MI patients with EF ≤35% to wear an external defibrillator, an apparatus that consists of a jacket containing electrodes to detect the cardiac rhythm, defibrillator patches with explosive gel packs that release conductive gel immediately before a shock is delivered, and an on-board computer to interpret and manage the rhythm.2 The device also contains 2 safety buttons that need to be pressed simultaneously to suppress a shock, in case the patient is still conscious when the tachycardia alarm goes off or in the event of a false alarm. Continued pressure on the buttons suppresses the shock, and release of the pressure allows the shock to proceed (assuming that the arrhythmia is still detected at that point). This suggests the unpleasant image of a patient squeezing the buttons with all available force in a panicked rush to the emergency room for less painful therapy, but, at the very least, the protection afforded by the vest should allow that patient to make it alive to the emergency room. Unfortunately, in 2008 this is the best we have to offer to reduce sudden-death mortality in the healing phase after MI. This is a sad state of affairs.

In recent times, when we think of reducing sudden-death risk, we assume that implantable cardioverter-defibrillators (ICDs) are the automatic solution to every problem. Clinical trials have shown convincingly and repeatedly that ICDs save lives for patients with reduced EF.3–6 The 2 patient populations that have not shown a survival benefit after ICD implantation are postrevascularization and post-MI patients. Relevant to this editorial are the post-MI patients. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and the Beta-Blocker Strategy plus Implantable Cardioverter Defibrillator (BEST + ICD) trial are 2 recently published randomized controlled clinical trials that evaluate mortality benefit for ICD implantation after acute MI.7,8 The BEST + ICD study was stopped for futility reasons after the investigators screened 15 507 patients and only managed to enroll 143 into the trial. The DINAMIT study evaluated ICD implantation in 664 low-EF patients 6 to 40 days after MI. The study found no survival benefit to ICD implantation. A reduction in the sudden-death rate was matched by a substantial increase in nonsudden cardiac death for the ICD group. Speculation has centered on the possibility that the ICD may have merely converted the cause of inevitable death from arrhythmic to heart failure. I am skeptical. No information was given on the incidence of appropriate ICD therapies for patients who died in the trial, which presumably would have been increased shortly before death if this hypothesis is correct. Other possible explanations for the absence of a beneficial effect include the possibility that something related to ICD implantation (eg, invasive procedure, defibrillation testing, inappropriate or inappropriate shocks, or dyssynchrony from RV pacing) increased the probability of heart failure death or that the enrollment requirement of either elevated baseline heart rate or decreased heart rate variability selected for a “hyperadrenergic” patient population that was predisposed to both arrhythmic and heart failure death.

The reasons for failure of the postinfarct ICD trials certainly are important to determine the role of ICD implantation in the immediate post-MI patient population, but the fact remains that this population is at very high mortality risk from both arrhythmias and heart failure. A therapy that could eliminate arrhythmias while improving (or at least not further harming) cardiac contractility could therefore be of tremendous benefit to this patient population. When faced with this type of challenge, a common strategy is to go to animal models in order to assess disease mechanisms in a relatively controlled environment. Armed with the knowledge gained from these models, new therapeutic strategies can be devised. This approach was taken by Lau et al in the current issue of Circulation.9

A canine model has been used for several decades to assess mechanisms of ventricular tachycardia (VT) in the healing phase after MI. The typical protocol includes ligation of the left anterior descending coronary artery, followed days or weeks later by electrophysiological analysis. Early work by Ursell et al and Gardner et al showed that physiological
disturbances occurred over a narrow window of time after infarction. A modest loss of resting membrane potential (RMP) and a reduction in the amplitude and rate of rise for the action potential (AP) were apparent in infarct border cells 5 days after left anterior descending artery ligation. In animals studied 2 or more weeks after MI, these changes had largely normalized. In the same model, Lue et al observed similar changes in AP upstroke characteristics, but they found no change in RMP in this early post-MI period, suggesting that there might be some variability in this response. Later mechanistic investigations found that a reduction in peak sodium current with kinetic changes including faster inactivation and slower recovery from inactivation explained the reduction in the excitation phase of the AP. In this issue of Circulation, Lau et al take these observations to the next step by devising a novel therapy to circumvent the RMP effects on native ion channel behavior and cellular excitability. They hypothesized that expression of a sodium channel isoform that retained activity in the relatively depolarized environment of the healing infarct would improve cellular excitability and conduction velocity at the infarct border. The overriding hypothesis was that improved conduction velocity would interrupt reentrant VT circuits.

Lau et al first used a mathematical model of the cardiac myocyte to assess the effect of membrane polarization on activity of either SCN5A (the cardiac isoform of the sodium channel) or SkM1 (the skeletal muscle isoform of the sodium channel) when expressed in addition to endogenous SCN5A. They found that additional SCN5A provided additional current with the same kinetics as the endogenous channel. SkM1 had the same effect as SCN5A in fully polarized myocytes, but the sustained availability of SkM1 channels at relatively depolarized potentials maintained fast AP activation kinetics even with the reduction in endogenous SCN5A function. In a mathematical model of tissue conduction, they further found that expression of SkM1 in the cardiac myocyte environment would maintain conduction velocity at the depolarized membrane potentials typical of the early post-MI time period.

To assess viability of this approach in vivo, Lau et al used gene transfer technology, injecting recombinant adeno-viruses encoding the SkM1 gene into the epicardium during left anterior descending artery occlusion in the canine model. They evaluated efficacy 5 to 7 days after infarction and found inducible VT in 6 of 8 control animals but in only 2 of 12 SkM1 gene transfer animals. Assessment of conduction also indicated improvement in the SkM1 animals: Local electrograms were less broad and less fragmented than control infarct animals. Electrogram duration in the SkM1-treated group was only slightly broader than that in normal uninfarcted animals. Microelectrode studies showed modest depolarization of RMP in both groups, but the SkM1-treated animals had almost twice the AP upstroke velocity as the controls under these conditions.

These data are the first step toward developing a novel therapy to address the unmet need of reducing death from ventricular arrhythmias in the immediate postinfarct period. Important elements of this treatment strategy include the focality of the manipulation (unlike systemically administered drug therapy) that matches the highly localized nature of the underlying problem and the recovery of cellular excitability that has the theoretical potential of improving regional contractility. A particularly advantageous element of this approach is the nondestructive nature of the treatment, which is distinct from ablative and possibly defibrillation therapies for this problem.

A potential limitation of this strategy is that cellular depolarization and reduction of sodium current are temporary findings in the canine model. If the same finding holds true in humans, then efficacy of this therapy would be limited in duration. Still, the duration of efficacy is a time period for which no viable options currently exist. Another limitation to the study is the absence of direct measurement of conduction velocity to directly address the principle hypothesis. This measurement is not trivial in the infarct border. de Bakker et al have previously shown that fibrosis prevents conduction from proceeding along a straight path in the mature infarct scar. From that observation, we can interpolate that cellular necrosis and the beginning vestiges of fibrosis would likewise prevent straight-line conduction in the subacute infarct period tested in the Lau study. One almost needs a map of the conduction path to correctly measure conduction velocity.

Given the small number of animals in the study by Lau et al, an important consideration is the cause of failed therapy in the 2 treated animals with inducible VT. Were the animals inducible because the VT originated outside the treatment zone? Did SkM1 therapy cause a recovery of conduction that perhaps converted an otherwise nonconducting region into a region with safe slow conduction (ie, proarrhythmia)? Was therapy ineffective because RMP polarity was not reduced in these animals (similar to the Lue study and unlike the Gardner and Ursell studies)? Or was this just a matter of VT continuing to exist in spite of the improved conduction brought about by the therapy? No information is presented to answer these questions, but the answer is important to assess the translational viability of this therapy.

What of gene transfer as a therapeutic modality? In some quarters, the field of gene therapy was given up for dead years ago, but in my view it remains a viable entity. The 2 principle limitations of cardiac gene therapy are vector and delivery technology. This study does not address those issues, but it is not clear that they are relevant here. Gene expression only needs to last a few weeks, which is possible with most gene-transfer vectors. The delivery method of intramyocardial injection seemed sufficient in this study to reach the target area, and intracardiac catheter technology has already been shown in a clinical trial to be adequate for this purpose. As such, gene transfer for arrhythmias in the healing phase of an MI may be more readily achievable than gene therapy strategies that require diffuse or long-lasting gene expression.

Overall, Lau et al give us an important proof-of-concept work. They have shown that targeting the slow conduction component of a reentrant circuit can eliminate VT inducibility in a large percentage of subjects. Like any provocative and important work, their study raises new questions as it answers established questions. Given the track record and capabilities of this investigative team, it is likely that they are already
working on these answers. Ultimately, the most important question is whether or not any strategy affecting sudden-death risk will also improve mortality in the healing phase of an MI. There are several steps between us and that answer, but with the work of Lau et al we appear to have an important new therapy that will help us answer that question.

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