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We regard these revisions as guidelines, not rigid rules. In the end, we as editors are responsible for weighing the available facts about each prospective author and for making the decisions we believe will bring the best scientific and medical information to the *Journal*. No *Journal* editor who makes these decisions has any financial relationship with any biomedical company. With these modifications in policy, we can prevent financial interests from infringing on the editorial content of the *Journal*, while at the same time acknowledging that some level of interaction between academia and industry may facilitate the dissemination of scientific knowledge and its application to patient care.

It is essential that our editorial policies allow the *Journal* to fulfill its mission to publish current, authoritative, and unbiased information about advances in medical research. We believe that the modification of our policy on the financial associations of authors of review articles and editorials will allow us to fulfill this mission more successfully. Patients, whose physicians are guided by the information in the *Journal*, will be the ultimate beneficiaries.

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CARDIAC-RESYNCHRONIZATION THERAPY FOR HEART FAILURE

THE syndrome of congestive heart failure is responsible for substantial morbidity and mortality.¹ Patients with heart failure have shortness of breath and a limited capacity for exercise, have high rates of hospitalization and rehospitalization, and die prematurely. The primary mode of therapy for this syndrome is based on antagonism of neurohormonal pathways (notably, the sympathetic nervous system² and the renin-angiotensin-aldosterone axis^{3,4}) activated in the failing cardiovascular system. Drugs that antagonize these pathways decrease mortality and morbidity²⁻⁴ and in some cases improve the underlying structural abnormalities of the heart, a process termed "reverse remodeling."⁵ On the basis of a large number of clinical trials, a regimen comprising up to six classes of drugs (neurohormonal antagonists, diuretics, and digoxin) has become the cornerstone of therapy for heart failure.¹ Mechanical support with left ventricular assist devices and heart transplantation are reserved for the minority of patients who have severely decompensated heart failure.⁶ Despite these therapeutic advances, it is generally accepted that current therapies do not adequately address the clinical need of patients with heart failure, and additional strategies are being developed.

Approximately 30 percent of patients with cardiomyopathy have intraventricular conduction delay such as left or right bundle-branch block, leading to loss of coordination of ventricular contraction.⁷ This dyssynchronous pattern of ventricular contraction is believed to contribute to the pathophysiology of heart failure, reducing the already diminished contractile reserve of the heart.⁸ Specifically, dyssynchronous contraction exacerbates inefficient use of energy by the heart (a process termed mechanoenergetic uncoupling⁹), and patients with conduction-system delays, indicated by a widened QRS interval on the surface electrocardiogram, have worse clinical outcomes than those with normal QRS intervals.⁷ Accordingly, the idea that cardiac-pacing technology might be used to restore the synchrony of ventricular contraction has been of theoretical interest for over a decade.

In this issue of the *Journal*, Abraham and colleagues report the results of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, which evaluated the effectiveness of resynchronization therapy in patients with moderate-to-severe symptoms of heart failure (90 percent of patients were in New York Heart Association class III).¹⁰ The investigators used a pacing device that has a third lead; conventional dual-chamber pacemakers have only two leads (one placed in the right atrium and the other in the right ventricle). This third lead, which is passed through the coronary sinus and placed in a vein that runs along the ventricular free wall, permits simultaneous pacing of both the left and right ventricles so as to cause resynchronization of the

left ventricular septum and free wall (Fig. 1). The study demonstrated improvement in symptoms and exercise capacity and a reduced rate of hospitalizations for heart failure over a six-month period. These findings extend the results of earlier, nonblinded clinical trials¹¹ and pathophysiological studies showing that resynchronization therapy not only improves myocardial performance but also reduces the mismatch between cardiac contractility and use of energy.⁸

These are exciting findings, since they suggest that a nonpharmacologic approach may be a useful adjunct to pharmacologic strategies, albeit only in the subgroup of patients with intraventricular conduction delay. This new form of pacing therapy is already avail-

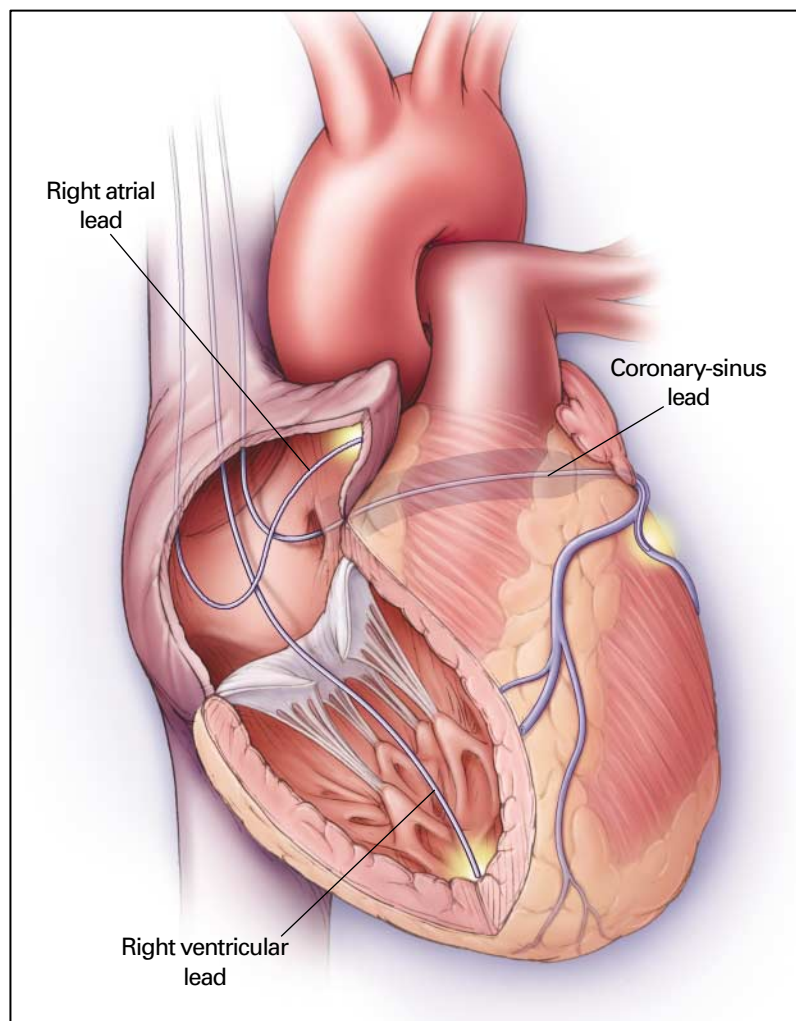


Figure 1. Placement of the Three Pacing Leads for Resynchronization Therapy.

Two leads allow pacing of the right atrium and right ventricle. The third lead, which is advanced through the coronary sinus into a venous branch that runs along the free wall of the left ventricle, allows early activation of the left ventricle, which would otherwise be activated late during conduction.

able in the United States, having received approval from the Food and Drug Administration (FDA) in August 2001. Who, then, should receive it? On the basis of the current findings, it is reasonable to implant these devices in patients who have low ejection fractions and wide QRS complexes and who remain symptomatic (New York Heart Association class III or higher) despite optimal medical therapy. Since existing pharmacologic therapies and comprehensive treatment programs effectively reduce symptoms,¹² the number of candidates for resynchronization therapy may shrink.

Although the results of the MIRACLE study are very encouraging, a note of caution is warranted. We do not yet understand whether resynchronization therapy prolongs the lives of patients with heart failure — information that is available for all other therapies for heart failure. The majority of other options available for long-term treatment of heart failure are known to improve both symptoms and survival. Perhaps the most important reason to establish the effect of a new therapy for heart failure on survival is that many initially promising therapies (most notably, drugs that have positive inotropic properties) have subsequently been proved ineffective or even detrimental in larger, longer-term studies.¹³ Moreover, the use of surrogate outcomes such as exercise capacity has a notorious history of not predicting the clinical response to cardiovascular therapies. It is also important to note that the follow-up in the current study was six months,¹⁰ and the sustainability of the clinical improvement with resynchronization therapy needs to be substantiated. Studies that will provide answers to these important questions are currently being conducted in both the United States and Europe and are near completion⁷; calls to end these trials prematurely because the FDA has approved the device should be resisted.

As the MIRACLE investigators report, placement of the resynchronization device carries a small risk of serious adverse effects, such as coronary-sinus perforation, death, or unsuccessful implantation.¹⁰ The ultimate applicability of this therapy will have to account for a balance of risks and benefits in the eligible patient population. As with all forms of interventional medicine, it is reasonable to expect that experienced operators and improved technology will lead to a greater safety profile for implantation of the device.

Another central question in the use of such devices is whether they should routinely incorporate a defibrillator. The issue of combined defibrillator therapy is an important consideration for these patients, and devices that have both capabilities have been successfully developed. Patients with structural heart disease due to myocardial infarction benefit from implantable defibrillators, as demonstrated in the Multicenter Automatic Defibrillator Implantation Trial II.¹⁴ Thus, pa-

tients with symptomatic heart failure due to ischemic cardiomyopathy and a wide QRS complex might be better served by a combined resynchronization pacer and defibrillator. Whether patients with nonischemic cardiomyopathy should receive such devices is currently being addressed in the ongoing Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure study.¹⁵

The MIRACLE trial clearly demonstrates that biventricular pacing improves symptoms and reduces the need for hospitalization for heart failure. Resynchronization therapy may therefore be viewed as a promising new mode of treatment for patients with heart failure and conduction-system delays who do not have a response to pharmacologic treatment. For this therapy to be more broadly applied, we will require additional information. The completion of studies that address questions about mortality and the role of pacemakers that are also capable of defibrillation will extend our knowledge and lead to a rational incorporation of this new therapy into practice.

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MUPIROCIN TO PREVENT *S. AUREUS* INFECTIONS

INFECTIONS at surgical sites remain an important cause of illness and death and substantially increase health care costs.¹ Prevention is thus important not only for the safety of patients, but also in terms of cost effectiveness. In this issue of the *Journal*, Perl and colleagues² report the results of a randomized trial that sought to prevent surgical-site infections due to *Staphylococcus aureus*. *S. aureus* is the most frequent cause of surgical-site infections and is more virulent than other frequent causes, such as coagulase-negative staphylococci and enterococci. *S. aureus* therefore accounts for a large proportion of the morbidity and mortality due to surgical-site infections. *S. aureus* infections at surgical sites often occur in patients with nasal colonization by *S. aureus* and frequently involve the same strain as that found in the patient's nose. In multiple studies, suppression or eradication of *S. aureus* in a patient's nose has been associated with reduced rates of *S. aureus* infection.

Perl and colleagues report that according to an intention-to-treat analysis, intranasal application of mupirocin twice a day, beginning up to five days before surgery, had no significant effect on the rates of nosocomial infections, nosocomial *S. aureus* infections, or *S. aureus* surgical-site infections. These findings may not prompt many physicians to consider using this approach to prevent *S. aureus* surgical-site infections. However, the sample-size calculation for this study yielded 85 percent statistical power to detect a relative reduction of 50 percent in the rate of *S. aureus* surgical-site infections, which was the primary outcome. Hence, there was no guarantee that there would be a significant result even if the approach worked, since there was a 15 percent chance that the results would be negative. Because fewer patients than expected actually remained in the study (see Table 4 of the article) and a smaller-than-expected proportion of the patients in the placebo group had *S. aureus* surgical-site infections (2.4 percent), the statistical power for the primary outcome was even lower than anticipated

(75.6 percent); in other words, there was a one-in-four probability that the results would be negative by chance alone, even if the approach was effective.

Does focusing on the subgroup of patients who were colonized with *S. aureus* before surgery alter any of these perceptions? The rate of nosocomial *S. aureus* infections after surgery was significantly reduced by 51 percent among the 23 percent of patients with nasal carriage of *S. aureus* before surgery, but the 37 percent reduction in *S. aureus* surgical-site infections was not statistically significant ($P=0.15$). It appears that this reduction in surgical-site infections was smaller than expected because in some patients, *S. aureus* came from reservoirs other than the nose. In this study, 53 percent of *S. aureus* surgical-site infections occurred in patients who did not have nasal carriage of *S. aureus* before surgery, and 15 percent of the *S. aureus* surgical-site infections in patients who did have nasal colonization were due to a strain other than the one that had colonized their nose. Hence, 60 percent of the *S. aureus* infections at surgical sites appear not to have originated from the patient's nose.

Nevertheless, the finding by Perl et al. that the use of mupirocin to suppress or eradicate *S. aureus* in patients with postoperative nasal colonization significantly reduced nosocomial *S. aureus* infections is supported by the results of four open trials involving surgical patients, one randomized and three open trials involving patients receiving hemodialysis, and two randomized and four open trials involving patients receiving continuous ambulatory peritoneal dialysis. The credibility of these results is further supported by a randomized, placebo-controlled trial of rifampin in patients receiving hemodialysis and another in patients receiving continuous ambulatory peritoneal dialysis. A randomized, controlled trial comparing oral rifampin with topical mupirocin ointment at the exit site of the dialysis catheter in patients undergoing continuous ambulatory peritoneal dialysis also demonstrated significant reductions in the rates of exit-site infections, peritonitis, and catheter loss in both treatment groups, as compared with historical controls. Most clinicians would not now use rifampin in this manner, however, because of the risk that resistance to rifampin — a clinically useful antibiotic with some unusual therapeutic features — might develop in patients receiving such monotherapy. This risk makes the topical use of mupirocin more attractive for the purpose of preventing infection at surgical or catheter-exit sites.

Given the results of the 18 prospective epidemiologic studies mentioned above, it seems clear that nasal colonization with *S. aureus* is an important risk factor for infection and that suppression or eradication of this organism can help prevent serious *S. aureus* infections. Important questions remain concerning the cost effectiveness of this approach, whether other species