To the Editor:

In the October 2006 issue of *Heart Rhythm,* Sinha and Calkins[1] provide an editorial of our report on a novel investigational therapy for heart failure based on cardiac contractility modulation.[2] We would like to respond to several of the points raised.

The first specific comment of Sinha and Calkins is that we focused on event-free survival instead of the 6-minute walk test, New York Heart Association (NYHA) functional class, and Minnesota Living with Heart Failure Questionnaire, as was done in the MIRACLE study of cardiac resynchronization therapy (CRT). This statement is inaccurate because, in fact, there was no such focus; all of the noted study endpoints were examined and treated equally.

The next criticism deals with the presence of a placebo effect. Although we agree that our study shows a significant placebo effect, *we do not view this as a problem.* We believe that our finding is reassuring and speaks to the integrity of the study, because every important, double-blind study of heart failure treatment examining functional capacity and quality-of-life measures (especially with a device) should identify a placebo effect. For example, in the MIRACLE study, NYHA functional class improved by one or more classes in fully 38% of control patients. The omnipresent and prominent placebo effects in these parameters contribute importantly to the need for pivotal studies of devices of this nature to include relatively large numbers of patients.

More importantly, Sinha and Calkins were critical that our data did not demonstrate any statistically significant differences in these parameters between the control and the Optimizer (cardiac contractility modulation) group. However, our study was a small feasibility study (25 patients per arm) designed to obtain initial clinical experience with multiple safety and efficacy endpoints. As such, the study was intentionally underpowered and would not be able to identify statistically significant differences between treatment and control groups. Nevertheless, our study shows trends that are in favor of the device for most of the parameters and, in fact, are of a magnitude that is only slightly less than those observed in studies of CRT in patients with prolonged QRS duration.

Based on the lack of statistical significance of changes in efficacy parameters, Sinha and Calkins state that ". . . given the neutral results of this pilot study, we remain skeptical that the OPTIMIZER system will definitively prove to be of significant clinical benefit." The lack of statistical significance is neither good nor bad in a pilot study of this size; overanalysis of our findings can lead to premature conclusions. It would seem to be too hasty to conclude from the results of a pilot study, with trends favoring the therapy in almost every parameter examined, that a larger study would be negative.

In the end, Sinha and Calkins suggest that it would be "more rewarding" for patients to be enrolled in the CRT–defibrillator study sponsored by St. Jude of patients with NYHA III symptoms, normal QRS duration, and echocardiographic evidence of left ventricular mechanical dyssynchrony. This is potentially misleading because the percentage of congestive heart failure patients with normal QRS width who have mechanical dyssynchrony by echocardiography currently is unknown. Therefore, a majority of such patients may not qualify for such a study.

The purpose of reporting the results of small feasibility studies as we did is to provide accurate information about new treatments currently under development and evaluation. In the case of cardiac contractility modulation, additional information is available from prior preliminary studies. Identification of positive trends in several parameters in multiple studies, although encouraging, must be tempered by the knowledge that it is only through appropriately powered studies that definitive conclusions (positive **or** negative) can be made. Premature conclusion in either direction can disrupt the equipoise necessary for appropriate conduct of definitive studies as well as potentially disrupt ongoing studies of a potentially beneficial treatment for a group of patients with no other treatment option.

Daniel Burkhoff, MD

IMPULSE Dynamics, Cardiovascular Research Foundation
Orangeburg, New York
Columbia University
New York, New York

Koonlawee Nademanee, MD

Pacific Rim EP
Inglewood, California
On behalf of the authors
wee@pacificrimep.com

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To The Editor—Response:

We appreciate the perspective provided by Dr. Neelagaru and colleagues of our editorial commentary.[1] We recognize that their trial[2] was a small pilot study and hence was "underpowered" with regard to appropriately interpreting the "significant placebo effect" observed. Nevertheless, we hope they experience rapid enrollment in their currently ongoing larger randomized controlled trial (FIX-HF-5) of the implantable OPTIMIZER system (IMPULSE Dynamics, Orangeburg, NY, USA) and look forward to its results examining this exciting new therapy.