Deciphering Gene Expression Profiling in Cardiac Resynchronization Therapy

We read with interest the article by Vanderheyden et al. (1). We applaud the authors for an ambitious study and the first report of gene expression in human cardiac resynchronization therapy. The limitations of the work were elucidated by both the authors and the editorial commentator (2). However, we have questions about several aspects of the article concerning both the functional as well as the gene expression measurements that make interpretation of the work problematic.

First, the magnitude of the effect of cardiac resynchronization therapy in all patients (Table 3 in Vanderheyden et al. [1]) and responders (Table 4 in Vanderheyden et al. [1]) is quite striking. More disturbing, however, is that the magnitude of the beneficial response, on average, was greater in the overall group than in the subset of responders. This result was true for ejection fraction (EF), left ventricular (LV) end-diastolic volume, several measures of dysynchrony, and phospholamban.

Some, but not all, of these differences may be accounted for by baseline differences between responders and nonresponders, which raises other issues regarding the findings. However, it is difficult to imagine how the overall increase in EF exceeds that in the responder group despite the similarity in baseline EF in both responders and nonresponders. The same is true of the decrement in LV end-diastolic volume.

Finally, the definition of responders raises some questions. There are clear differences in estimates of improvement in LV ejection fraction and changes in chamber size in the 2 groups, but there is also evidence for mechanical synchronization of LV, interventricular, and atrioventricular contraction in both groups. Thus, the mechanism of clinical improvement likely involves more than simple mechanical resynchronization, and the gene expression signature is likely a manifestation of more than resynchronization alone.

Takeshi Aiba, MD, PhD
Andreas Barth, MD, PhD
“Gordon F. Tomaselli, MD

*Department of Cardiology
Johns Hopkins University School of Medicine
720 Rutland Avenue, Ross 844
Baltimore, Maryland 21205
E-mail: gtomasel@jhmi.edu


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Reply

We thank Dr. Aiba and colleagues for discussing the pivotal findings described in our article (1) with regards to the effects of chronic cardiac resynchronization therapy (CRT) on myocardial gene expression. They question the magnitude of the effect of CRT in our study. The effect in responders is indeed robust and may be related to the prudent definition of responders. In fact, patients were categorized as responders only if they exhibited a relative increase in left ventricular ejection fraction (LVEF) of ≥25% together with an improvement in New York Heart Association functional class score >1 (2). This categorization may account for the rather large improvements in LVEF and left ventricular (LV) dimensions compared with other studies that did not include both reverse remodeling and clinical improvement as an indicator of response.

We acknowledge their concern about the paradoxically greater change in ejection fraction as well as in end-diastolic volumes in the whole study population compared with the responders group. After reviewing the data, we noticed typing errors in Table 3 of our article (1) that were responsible for the concern. The individual LVEF and end-diastolic volume at baseline and follow-up in all patients, responders, and nonresponders are summarized in Figure 1. In the whole study population, LV end-diastolic volume and ejection fraction at follow-up were 215 ± 20 ml and 31 ± 3%, respectively. This error is truly regretful, and we apologize. Nevertheless, we would like to point out that the error does not alter the data on the functional or molecular comparisons between the responders and nonresponders. In this regard, we respectfully point out that the magnitude of specific changes in LV dysynchrony and phospholamban as being reported in the entire population is not greater than in any subgroup.

A recent study also corroborated our finding that mechanical dysynchrony itself might not favorable predict a successful response to CRT, but merely acts as an indicator for the presence of “hemodynamic reserve” in the setting of advanced heart failure (3). Therefore, less mechanical dysynchrony, as evidenced in the nonresponders in our study, would indicate a more advanced degree of myocardial remodeling, less prone to favorably respond to CRT.

In addition, the paradox between the CRT effect on mechanical resynchronization and different impact on LV remodeling and function in responder versus nonresponder groups has been described previously (4). Similarly in the current study, although interventricular dysynchrony decreased in both groups, baseline intraventricular LV dyssynchrony was greater in responders and decreased only in this group. This observation supports the hypothesis that although mechanical resynchronization may be
required to reverse chamber dilation, the extent of the resynchronization alone does not always correlate with the therapeutic effect (5). Other contributing factors may be related to underlying disease, fibrosis, scar tissue, or the severity of molecular abnormalities governing excitation-contraction coupling (1,6). Therefore, it is interesting to emphasize that nonresponders had a greater baseline gene expression of \( \alpha \) and \( \alpha/\beta \) major histocompatibility complex ratio as well as a trend toward greater gene expression of sarcoendoplasmatic reticulum \( \text{Ca}^{2+} \) ATPase. Thus, despite a similar degree of LV dysfunction, dyssynchrony, and clinical heart failure class, and a comparable extent of resynchronization, nonresponders were deemed “less sick” in terms of “molecular remodeling” and less likely to be responsive to CRT therapy. We do acknowledge this to be a provocative hypothesis; it obviously requires prospective validation in a larger cohort of patients in addition to the application of a more comprehensive assessment of transcriptional and translational changes before and after CRT.

*Marc Vanderheyden, MD  
Wilfried Mullens, MD  
Jozef Bartunek, MD, PhD

*OLV-Clinic, Cardiovascular Center Aalst  
Cardiovascular Center  
Moorselbaan 164

Aalst, 9300  
Belgium  
E-mail: marc.vanderheyden@olvz-aalst.be


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