CARDIAC RESYNCHRONIZATION therapy (CRT) is a major advance in the treatment of heart failure (HF), and thus far the most important HF therapeutic modality identified in the 21st century. When applied to patients with left ventricular dyssynchrony, CRT immediately improves chamber contractile performance and myocardial efficiency. These salutary effects eventually result in reverse remodeling, improved functional capacity and symptoms, and a reduction in the major clinical outcomes of mortality and hospitalizations. The mechanisms that link the immediate effects of CRT and the chronic beneficial effects on myocardial and clinical end points have not been identified, however. One of the candidates for this linkage is a reduction in myocardial adrenergic stimulation, or normalization/attenuation of a mechanism known to promote progressive remodeling and HF. This possibility is raised by recent data in support of an “antiadrenergic hypothesis” of CRT (13).

Unlike other HF treatments, CRT produces major improvements in all dimensions (1) of the heart failure syndrome, including mortality (2, 3), hospitalizations (2, 3), exercise tolerance (2–4), and quality of life (2–4). Beyond the absolute therapeutic benefit, CRT also demonstrates that devices, in addition to drugs, may have a profound impact on HF natural history.

How does CRT work? In a general sense, it partially reverses chamber contractile dysfunction caused by regional delays in left ventricular conduction, typically to the lateral wall in the setting of a left bundle branch block. The result of resynchronizing ventricular conduction and subsequent cardiac myocyte depolarization is more efficient and simultaneous contraction of the entire left ventricle, compared with the dyssynchronous, to-and-fro wall motion characteristic of regional conduction delays. This resynchronization of contraction immediately improves systolic function and myocardial efficiency, reduces wall stress, and reduces mitral regurgitation (5, 6). Later, when measured at 3–6 mo (7), ventricular remodeling (pathological hypertrophy/chamber dilation) improves. The later favorable effects are likely due to the reduction in wall stress (8), but details of the therapeutic mechanisms are yet to be determined.

From a HF clinical care standpoint, CRT is an example of the future of medical therapy: specific targeting of a subpopulation based on a surrogate marker (electrocardiographic QRS lengthening) that identifies a responsive subpopulation. That is, if this therapy were applied to the general HF population, where dyssynchrony amenable to correction by biventricular pacing may be present in only a minority of patients, CRT would likely not be efficacious, at least demonstrable within the sample sizes that are usually within reach of sponsors’ budgets. There now is a very concerted effort to identify biomarkers, particularly pharmacogenetic, to accomplish the same thing with pharmacological therapy. This has already met with some success (9, 10) and is being incorporated into the drug development process (11). As it stands, the clinical response rate to CRT in a population of patients enriched in mechanical dyssynchrony by electrocardiographic criteria appears to be in the 60–70% range (12, 13), but this figure incorporates a relatively high placebo response rate (12).

With CRT therapy, one of the remaining challenges is to thoroughly investigate and elucidate the precise mechanisms by which clinical and remodeling improvements occur. These are almost certainly linked phenomena, and so studies of remodeling should be considered clinically relevant. It would seem likely that the favorable antiremodeling effects of CRT are derivative of the initial favorable effects on chamber contractile performance (8). However, there are multiple possible cardiac myocytic signaling processes involved, as well as novel, yet to be identified mechanisms. A mechanism known to be extremely important in the natural history of HF is cardiac adrenergic mechanisms, and an effect of CRT on adrenergic activity has been suggested by some (14) but not all (15) previous studies. In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Najem et al. (13) provide evidence that a favorable effect on adrenergic drive may be an important determinant of CRT response. In this study, “responders” to CRT (as determined by New York Heart Association Class improvement) demonstrated an increase in microneurographically measured femoral sympathetic nerve activity (MSNA) when the biventricular pacing mode of CRT was turned off, leaving the patient with a left bundle branch block and presumed left ventricular dyssynchrony. No such increase in MSNA occurred in nonresponders when biventricular pacing was stopped. Although there are design weaknesses in the Najem et al. (13) study, such as the method of identification of responders and the lack of any baseline myocardial functional or adrenergic data, the results clearly suggest an antiadrenergic role of CRT in producing a favorable clinical response. The confirmation of this hypothesis and the explanation for a reduction in adrenergic drive in some patients but not others will need to be determined in future studies. Finally, there are several possible mechanisms by which CRT could reduce adrenergic drive, including a lowering of ventricular filling or central venous pressures (16) that are excitatory to adrenergic activity, and/or a resetting of impaired baroreflexes (17). These and other possible mechanisms also need to be investigated in additional studies.

REFERENCES


