Reversed Reverse Remodeling
Can Biomonitoring Solve the Clinical Conundrum of the 3Rs?

James L. Januzzi Jr, MD; Paul J. Hauptman, MD

In the course of managing patients with chronic heart failure (HF) because of left ventricular systolic dysfunction (LVSD; typically defined as an LV ejection fraction [EF] ≤40–50%), the goals of care include prescription of guideline-directed medical therapy with the achievement of target doses of angiotensin-converting enzyme inhibitors or angiotensin receptor II blockers, mineralocorticoid receptor antagonists, and β-adrenergic blockers (BBs).1 Each of these guideline-directed medical therapy agents has been associated with reduction in complications of HF, improving event-free survival in a broad range of studies, particularly when titrated to target doses; together with cardiac resynchronization therapy, this represents the best care that can be delivered for our patients with HF.

However, the durability of improvement in LV size and function is not easily predicted. It is in this context that the article by de Groote et al3 in this issue of Circulation: Heart Failure provides useful insight.

In a single-center study with an approach reminiscent of methods used in the Cardiac Insufficiency Bisoprolol Study 3,4 patients with HF and an LVEF <45% received angiotensin-converting enzyme inhibitor/angiotensin receptor II blocker uptitration first, followed by delayed addition and aggressive titration of BB (mainly bisoprolol to a mean dose of 9 mg per day and carvedilol to a mean dose of 53 mg per day). Slightly more than 20% received mineralocorticoid receptor antagonist therapy, and none underwent early cardiac resynchronization therapy. Repeat echocardiography was performed a median of 6 months after medication optimization; those subjects with an LVEF >45% were subsequently followed for a median of 9 years for return of LVSD or clinical events.

Of the 174 subjects with LVRR after medication optimization, durable improvement in LVEF was seen in a substantial majority; patients with sustained LVRR had excellent event-free survival, with few events and a cardiovascular mortality rate of only 4%. However, 26% of the study subjects had an LVEF <45% during follow-up. It is worth noting that in these subjects a substantial rate of cardiovascular mortality (22%) was observed; after adjustment, LVEF deterioration was an independent significant predictor of near-term mortality. Patients in the study by de Groote et al3 were not necessarily a typical population of patients seen in contemporary clinical practice: the median duration of time from diagnosis with LVSD to BB initiation was unusually long at 14.3 months; this may have influenced responsiveness to the therapies applied. Furthermore, as noted, the use of mineralocorticoid receptor antagonist and cardiac resynchronization therapy was low, although this was fairly typical in the era these subjects were first diagnosed, and the patients did receive high-quality aggressive titration of angiotensin-converting enzyme inhibitor/angiotensin receptor II blocker and BB. Caveats notwithstanding, given the risk associated with the reversal of LV remodeling, the study highlights the need for regular monitoring of patients after recovery of LV function. This leads to a series of questions.

What Is the Best Way to Monitor Patients Who Have Demonstrated Reverse Remodeling?

Although standard 2-dimensional echocardiography is viewed as the gold standard for routine imaging in patients with HF, it provides little information about the presence and severity of biological processes involved in LV remodeling, such as hypertrophy and apoptosis of cardiomyocytes, inflammation, reinduction of fetal gene expression, and alternations in the extracellular matrix.5,6 Accordingly, another method for early

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Underlying clinical improvement is LV reverse remodeling (LVRR), characterized by decreased LV dimensions, normalization of LV shape, and improvement in systolic function; LVRR may be achieved through the application of guideline-directed medical therapy, in particular higher-dose BB therapy, and LVRR is unmistakably accompanied by improved prognosis. For example, pooled results of 22 studies about the effects of carvedilol suggest an improvement in LVEF of 6.9% during a 30-week follow-up period; in a smaller number of studies, concordant effects on LV volumes from carvedilol were also observed, with −26.7 and −33.9 mL changes in end-diastolic and end-systolic volumes, respectively, during a similar follow-up period.3 Models examining the likelihood for favorable outcome after LVRR suggested that improved LVEF or reduced LV volumes powerfully portend improved outcomes.2

Although LVRR frequently occurs during addition and up titration of HF therapy (and is among the most powerful benefits of cardiac resynchronization therapy), the precise mechanisms underlying the structural improvement are not well understood. Patients with dilated cardiomyopathy generally experience the greatest structural improvement, raising the possibility of a reversal of inflammatory or other nonischemic processes that led to LV dysfunction in the first place.

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detection of pathways leading to remodeling would be desirable. In this regard, biomarkers may represent an ideal way to detect—and possibly intervene on—remodeling before it is clinically manifest. This biomonitoring of remodeling with targeted application of therapy for its treatment may represent an attractive future application of circulating markers of HF.

Several biomarkers have been examined for their ability to presage or detect LV remodeling (Table); although most of this ever-growing list currently lack data to support their routine application in clinical practice, which leads to a sense of this ever-growing list currently lack data to support their role for biomonitoring in patients who have normalized or nearly normalized ventricular size or function is not known; could they provide an easy, straightforward way to evaluate patients at risk for reversed reverse remodeling? If so, which ones and how often should they be measured?

### Table. Candidate Biomarkers of LV Remodeling

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Extracellular matrix remodeling</th>
<th>Neurohormones</th>
<th>Myocyte injury and apoptosis</th>
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<tbody>
<tr>
<td>Osteoprotegerin</td>
<td>Matrix metalloproteinases</td>
<td>Adrenomedullin/midregional proadrenomedullin</td>
<td>Troponins I and T</td>
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<td>Adiponectin</td>
<td>Tissue inhibitor of metalloproteinases</td>
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<td>Myosin light-chain kinase I</td>
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<td>Interleukin-6</td>
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<td>Heart-type fatty acid–binding protein</td>
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<td>Collagen propeptides</td>
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<td>Creatine kinase-MB fraction</td>
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<td>N-terminal collagen type III peptide</td>
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<td>Myostatin</td>
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<td>Heat shock protein-60</td>
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<td>Syndecan-4</td>
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<td>Galectin-3</td>
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<td>Growth differentiation factor-15</td>
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The most widely studied biomarkers to assess remodeling in patients at risk (eg, post-myocardial infarction) or in large epidemiological studies are B-type natriuretic peptide (BNP) and amino-terminal pro-BNP (NT-proBNP). Highly sensitive troponin, as well as the so-called fibrosis markers galectin-3 and soluble ST2, also seems to be particularly promising.

A broad range of cardiac structure and functional correlates determines the concentrations of BNP and NT-proBNP, which, although by no means specific for LVEF or LV volumes, may identify those patients undergoing cardiac remodeling especially when measured serially over time. Conversely, a stable or falling concentration for either peptide may offer reassurance about the stability of LVEF. It has been suggested that a stable, low concentration of either BNP or NT-proBNP may obviate the need for imaging, reserving such investigation for patients with a high or increasing BNP or NT-proBNP concentration. Furthermore, the link between reduction in natriuretic peptide concentration and LVRR may explain the benefit observed in some trials specifically aimed at lowering the concentrations of these peptides. However, although currently supported by clinical practice guidelines for prognostication in chronic HF, it is not yet clear whether BNP or NT-proBNP is appropriate for use as a biomonitor for remodeling, reverse remodeling, or reversed reverse remodeling.

In chronic LVSD, higher concentrations of highly sensitive troponin have been linked to the likelihood for worsening ventricular function. Given the association between cardiomyocyte death and likelihood for fibrosis and remodeling, this is not surprising. Besides highly sensitive troponins, both galectin-3 and soluble ST2 are intriguing candidates for biomonitoring of LV remodeling; additionally, a rise in soluble ST2 may have the potential to trigger more precise therapy to prevent remodeling. Both galectin-3 and soluble ST2 have biological links to the development of myocardial fibrosis, and both peptides are prognostic in chronic HF, although a recent comparative study suggested superiority of soluble ST2 for prognosis.

When measured serially, a rise in either soluble ST2 or galectin-3 identifies a patient more likely to develop consequent remodeling. Although therapies for HF do not appreciably seem to reduce the risk for adverse outcome predicted by galectin-3, patients with elevated concentrations of soluble ST2 seem to profit from higher-dose BB therapy or addition of mineralocorticoid receptor antagonist treatment; additionally, the ValSartan Heart Failure Trial investigators recently found that the use of angiotensin receptor II blocker may reduce soluble ST2 concentrations. Taken together, we can posit that the use of soluble ST2 may not only identify the risk or presence of LV remodeling, it may ultimately prove as a trigger for therapy to improve the deleterious prognosis reported by de Groote et al' in subjects with recurrent LVSD.

Ultimately, we think that a formal study will be necessary, with sufficient longitudinal follow-up to assess the predictive value of biomonitoring in patients who have normalized or nearly normalized LV structure and function. It is certainly possible that not all biomarkers have the same importance in this cohort; however, carefully defining the population (eg, de novo HF that improves LVEF by ≥20%) in an observational registry may help to guide subsequent diagnostic and therapeutic interventions.
What Is(Are) the Biological Process(es) Underlying Reversed Reverse Remodeling?

On a fundamental level, this question is pivotal to understanding how we might monitor patients. In all likelihood, multiple processes are involved. As the data from de Groote et al1 demonstrate, it is not enough to simply suggest that stopping medication (either as suggested by the physician or instigated by the patient) is the root cause of reversed reverse remodeling. At the same time, their study provides limited insight into overall medication adherence; we learn only that the prescription of renin inhibitors and BBs at last follow-up was similar in patients with and without LVEF deterioration. Because there is obviously a difference between drug prescribing and drug taking, we cannot be certain that medication nonadherence played no role in the reversed reverse remodeling. Nevertheless, recurrent inflammation, fibrosis, and other related primary biological processes are probably important, although their relative contributions remain unknown. In the best case scenario, serial endomyocardial tissue would be available at diagnosis, on improvement in LVEF, and then on the recurrence of LV remodeling.18 However, in lieu of such data, serial evaluations of a comprehensive biomarker panel could shed light on the underlying pathophysiology.6

In summary, as we enter the era of precision medicine—the use of strategies to personalize health care to the individual patient, including the application of biomonitoring tools to more precisely recognize the presence of disease earlier than with standard means—the data of de Groote et al1 will take on even more significance. Future studies to better understand the value of circulating biomarkers to more efficiently recognize—and ultimately treat—the 3Rs in a more timely fashion would be enormously helpful.

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References


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