Reverse Remodeling in Dilated Cardiomyopathy: Dream Come True?

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The common pathway of heart failure pathogenesis, termed the remodeling process, originally referred to alteration in the ventricular architecture, which was driven by a combination of pathologic myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation and interstitial fibrosis subsequent to myocardial infarction. The resulting increase in volume and altered chamber configuration [1-3] is readily accessible by echocardiography and other imaging modalities. The term was later generalized to reflect similar changes following a variety of acute and chronic myocardial insults, including hypertension, myocarditis, valvular heart disease and others causing myocardial injury and increased wall stress [4,5].

Acknowledging that adverse myocardial remodeling may be reversible with time and/or various interventions (drugs, devices, surgical procedures including reconstruction techniques, and temporary mechanical cardiac support devices), the term “reverse remodeling” was suggested. This phenomenon raises three main questions: the first – how to define, or rather identify reverse remodeling? The second – does it ever occur, and if it does what are its predictors? Finally, what are the clinical correlates of reverse remodeling with regard to symptoms and prognosis?

In the current issue of IMAJ, Arad and co-authors [6] report that of their patients with dilated cardiomyopathy, about a quarter eventually had reverse remodeling. Since we know that reverse remodeling is associated with a better prognosis, understanding its mechanism and identifying subgroups in which this process may or may not be relevant is obviously crucial.

Several faults should be mentioned regarding the current study. The HF patients in this study cohort are noted for their diverse etiologies of dilated cardiomyopathy and we lack data on the index time period in which the HF disease along with the remodeling process started in each patient. Of note, the authors established the diagnosis of reverse remodeling by using echocardiography rather than more definitive technologies such as magnetic resonance imaging. These pitfalls, present in real-world daily life in most HF centers around the globe, reflect the difficulties inherent in “observational clinical studies” for understanding the fundamentals of the reverse remodeling process and further explore the true prevalence of reverse remodeling as well as “preconditions” to its occurrence.

The definition of reverse myocardial remodeling is not straightforward and consequently various studies using echocardiography assessed different aspects of left ventricular systolic function and spatial configuration. Left ventricular end-diastolic size (diameter, volume) was assessed by some (correlating with LV wall stress) while others measured end-systolic size (assuming it holds geometric and functional information). LV ejection fraction was advocated by others as the easiest marker with which to assess improvement. Changes in LV mass were generally sought in patients with pressure overload (suggesting severe aortic stenosis pre- and post-valve replacement), overlooking the fact that the most important determinant of LV mass is the diastolic diameter which thus could serve as a marker in patients with dilated cardiomyopathy. LV size (by whichever method it is measured) and EF is a tricky business. Smaller ventricles uncoupled with higher EF means that stroke volume and cardiac output are actually reduced and do not imply functional “improvement.”

An increase of “15 EF percentage points” from 15 to 30% (a 100% increase in EF) cannot be assumed to be the same as from 30 to 45% (a 50% increase). In the very low EF group it is probably extremely rare to find doubling of EF, while those who do have it may clinically benefit more from the extra “15% EF points” than would patients with moderately reduced EF. Methodologically, identifying a 100% increase in function is much more robust than a 50% increase, especially if assessed by “eye-balling.” This introduces yet another bias against patients with the higher baseline EF. With declining EF improvement cutoff values (10% increases), the definition of improvement becomes even more cumbersome and may well be within the measurement error margin. Probably the best approach using conventional echocardiography would be to assess stroke volume and end-diastolic volume and define reverse remodeling as a decrease in the end-diastolic volume with...

HF = heart failure
LV = left ventricular
EF = ejection fraction
maintenance or improvement of baseline stroke volume, suggesting that stroke volume is now maintained at lower wall stress (and oxygen consumption). In their study, Arad et al. [6] were closest to that approach by defining positive reverse remodeling as the combination of increased EF and decreased end-diastolic volume rather than either alone. Contemporary approaches to remodeling include quantifiable function assessment such as systolic and diastolic strain analysis as well as changes in left atrial size and function [7-9].

The authors of this study should be congratulated for shining a spotlight on the phenomenon of reverse remodeling. Yet, crucial questions regarding reverse remodeling remain unanswered. For example, should different subgroups of patients be treated differently in order to achieve reverse remodeling (i.e., targeting higher doses of anti-remodeling medications)? Are certain etiologies of dilated cardiomyopathy associated with “spontaneous” reverse remodeling? Should we follow dilated cardiomyopathy patients with various technologies that are more suitable than echocardiography for assessing early signs of reverse remodeling? We believe that these questions will be addressed in future designated trials and will enable us to cope better with this sick HF population.

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References

Capsule

Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the USA

In assessing the association between serum 25-hydroxyvitamin D concentrations (25(OH)D) and mortality in a large consortium of cohort studies (with particular attention to potential age, gender, season, and country differences), Schöttker and team found that 25(OH)D concentrations varied strongly by season (higher in summer), country (higher in the USA and northern Europe) and gender (higher in men), but no consistent trend with age was observed. During follow-up, 6695 study participants died: 2624 from cardiovascular diseases and 2227 from cancer. For each cohort and analysis, 25(OH)D quintiles were defined with cohort and subgroup specific cutoff values. Comparing bottom versus top quintiles resulted in a pooled risk ratio of 1.57 (95% confidence interval 1.36–1.81) for all-cause mortality. Risk ratios for cardiovascular mortality were similar in magnitude to that for all-cause mortality in subjects both with and without a history of cardiovascular disease at baseline. With respect to cancer mortality, an association was only observed among subjects with a history of cancer (risk ratio 1.70, 1.00–2.88). Analyses using all quintiles suggest curvilinear, inverse, dose-response curves for the aforementioned relationships. No strong differences specific for age, gender, season, or country were detected. Heterogeneity was low in most meta-analyses. Despite levels of 25(OH)D strongly varying with country, gender, and season, the association between 25(OH)D level and all-cause and cause-specific mortality was remarkably consistent. Results from a long-term randomized controlled trial addressing longevity are being awaited before vitamin D supplementation can be recommended in most individuals with low 25(OH)D levels.

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Eitan Israeli

“The best way to be more free is to grant more freedom to others”
Carlo Doss (1849-1910), Italian writer, politician and diplomat

“Any life, no matter how long and complex it may be, is made up of a single moment – the moment in which a man finds out, once and for all, who he is”
Jorge Luis Borges (1899-1986), Argentinian writer, essayist, poet and translator, and a key figure in Spanish literature. Borges’s works have contributed to philosophical literature and also to the fantasy genre known as magical realism.