Congestive heart failure is a burgeoning problem, especially in older adults, affecting nearly 0.1% of subjects >65 years old, accounting for nearly 20% of all hospitalizations in this age group, and costing the healthcare system a bundle.1 Several experimental observations have demonstrated an important role for progressive dilation and geometric remodeling of the left ventricle in worsening cardiac pump function.2 The results of experimental studies on the adverse implications of ventricular dilation and remodeling have been confirmed in clinical and epidemiological studies of depressed ventricular function and congestive heart failure in humans.2,3 Studies of the natural history of left ventricular dysfunction provide evidence to directly implicate left ventricular dilation and remodeling to an adverse clinical outcome in patients with congestive heart failure. Ventricular dilation and remodeling impose an increased mechanical disadvantage to the pump function by increasing wall stress and consequently the hemodynamic load and by contributing to mitral regurgitation and possibly arrhythmogenesis in patients with congestive heart failure independently of the neurohormonal status. Therapeutic trials have also shown that the majority of clinically useful and approved treatment modalities in heart failure attenuate or reverse ventricular dysfunction, and hemodynamics are concerned without raising concerns about significant side effects.13,14

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These encouraging observations led to a randomized trial, the results of which were presented at the late-breaking clinical trials session of the annual scientific sessions of the American Heart Association in November 2004. The multicenter prospective trial randomized 300 patients with NYHA class II, III, or IV heart failure and dilated cardiomyopathy to undergo mitral valve repair/replacement (MVR) alone (n=102), MVR plus CSD placement (n=91), continued optimal medical therapy alone (n=50), or continued optimal medical therapy plus CSD placement (n=57). The primary end point of the trial was a clinical composite, with patients classified as improved, the same, or worse, based on the occurrence of death, a major cardiac procedure indicative of progression of heart failure, or a change in NYHA class. Compared with the control group, the CSD group had more “improved” patients (38% versus 27%) and fewer “worse” patients (37% versus 45%), yielding an odds ratio of 1.73 (P=0.02) in favor of the CSD group. The improvement in the primary end point was mainly the result of fewer major cardiac procedures (19 versus 33; P=0.01). There were no significant differences in mortality, rehospitalization, or ejec-

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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...ion fraction even though the CSD group had a greater reduction in left ventricular end-diastolic \( (P=0.009) \) and end-systolic \( (P=0.017) \) volumes, a greater improvement in sphericity index \( (P=0.026) \), and an improvement in quality-of-life measures \( (P=0.05 \) for Minnesota Living with Heart Failure Index). Thus, the results to date suggest a modest overall benefit of CSD in heart failure; however, it is unclear whether certain subgroups of patients are likely to derive greater benefit than others and whether a longer period of follow-up will reveal additional improvement in clinical outcomes. The precise cellular mechanism by which the ACORN device attenuates remodeling and preserves ventricular function remains unclear.

In this issue of Circulation, Blom et al provide new and interesting data on the effects of passive ventricular restraint with the ACORN device in a model of postmyocardial infarction ventricular dysfunction in sheep. The authors produced a large myocardial infarction in sheep through coronary branch ligation and randomized the animals to placement of passive restraint 7 days after infarction or no restraint. The authors demonstrate that in untreated sheep, 3 months after the myocardial infarction, the left ventricle dilated, myocyte length increased, isolated myocyte velocity of contraction was depressed, and myocyte responsiveness to \( \beta \)-adrenergic stimulation was reduced. Placement of the CSD resulted in attenuation but not complete prevention of ventricular dilation, less decline in ejection fraction, reduction in myocyte length, and improvement in \( \beta \)-adrenergic responsiveness in myocytes from regions at the border of and remote from the infarct zone. Furthermore, the authors show that in addition to these cellular effects, extracellular matrix turnover was altered by passive restraint resulting in a net accumulation of collagen in the vulnerable peri-infarction zone. Although there were heterogeneous changes in the content of various matrix-degrading metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs), the authors attribute the increased collagen accumulation to the downregulation of matrix-degrading enzyme MMP-9.

In addition, Blom and colleagues noted increased myofibroblast cell density within the mesh device with significant organized matrix accumulation around individual mesh fibers and speculated that contraction of such myofibroblast and force generation through engagement to the extracellular matrix may also have contributed to the salutary effects of the passive restraint. The hypothesis that net extracellular matrix accumulation within the peri-infarct and remote zones may account for the antiremodeling effect of passive myocardial restraint is indeed plausible. During the last several years, it has become clear that the cardiac extracellular matrix, predominantly composed of fibrillar collagen and synthesized by cardiac fibroblasts, is not simply a passive scaffold but a dynamic tissue that is constantly, albeit slowly, turning over (replaced at the rate of 0.6%/day) and regulating cardiac structure, geometry, cellular interaction, structure, signaling, and function. Alterations in quantity, quality of collagen (specific isoforms), and in enzymatic and nonenzymatic collagen cross-linking have been demonstrated in experimental models of heart failure. The turnover of the extracellular matrix in the heart is regulated by not only collagen synthesis but also collagen breakdown, which in turn is primarily dependent on the coordinated activities of MMPs and serine proteases (plasmin and thrombin). The cardiac fibroblast and mast cells are the predominant source of MMPs in the heart. There are >20 known members of the MMP family, and their function is tightly regulated at the level of gene transcription, through their secretion in an inactive zymogen form, requiring extracellular activation and through the activities of a family of TIMPs. The MMPs and closely related molecule ADAMs (a disintegrin and metalloproteinase) not only influence matrix turnover but also may activate bioactive molecules through cleavage of their inactive precursors with a significant impact on cell–cell interaction and cellular function. In the heart, MMPs produced by cardiac fibroblasts and myocytes, are activated in response to a variety of cardiac injuries including myocardial ischemia/infarction and heart failure. Similarly, expression of TIMP, especially the matrix-bound TIMP-3, which is specifically active against MMPs and ADAM-17, is reduced in remodeling associated with heart failure. Several experimental studies have shown that the extracellular matrix plays an important role in preserving myocardial architecture and normal geometry and that thinning, remodeling, and rupture of the ventricle after myocardial infarction, all part of the adverse remodeling process, are reduced when cardiac extracellular matrix degradation is suppressed through overexpression of TIMPs or targeted deletion of specific matrix-degrading enzymes such as MMP-9. Conversely, overexpression of MMPs or targeted deletion of TIMPs enhance ventricular dilation and increase the risk of postinfarction cardiac rupture. Thus, a body of evidence implicates excessive cardiac matrix degradation in ventricular enlargement and adverse remodeling in ischemic and nonischemic cardiac injuries. Thus, the inhibitory effects of passive ventricular restraint on MMP-9 expression with net collagen accumulation reported by Bolt et al are likely related, at least in part, to the observed salutary effects on ventricular size and remodeling. Matrix preservation may explain why a restrained heart is a better pump. Even if the randomized clinical trial of CSD demonstrates efficacy, widespread use of this device will prove to be somewhat challenging in view of the need for major surgery for placement of this device. The new and emerging paradigm that links the adverse remodeling and progression of heart failure, at least in part, to excessive degradation of the cardiac extracellular matrix, has potential therapeutic implications that go beyond those of passive ventricular restraint. A number of selective and broad-spectrum MMP inhibitors for potential clinical use for a variety of clinical disorders have been developed and tested, but limited bioavailability, toxicity, and uncertain efficacy have plagued the field. Nevertheless, the possibility that drug-induced inhibition of matrix degradation with MMP inhibitors could provide a novel strategy for prevention and management of adverse ventricular remodeling and congestive heart failure is supported by experimental studies and continued exploration of this novel therapeutic paradigm is warranted.
References

Key Words: Editorials  ■ remodeling  ■ heart failure  ■ metalloproteinase
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