Nearly 3 decades ago, this journal reported the seminal discovery by Murry et al1 of ischemic preconditioning, a phenomenon in which several episodes of brief ischemia followed by reperfusion protected cardiac muscle cells from a subsequent prolonged ischemic insult. Since then, a similar protective effect of ischemic preconditioning has been observed in many organs, including brain, liver, and kidney, supporting the notion that ischemic preconditioning is a fundamental property shared by different cell types. Given the obvious clinical implications, intense research efforts have been devoted to dissecting the mechanisms and identifying the putative mediators underlying the short-term or long-term cardioprotective effects induced by preconditioning.2 Different forms of nonischemic preconditioning have been demonstrated in the heart, including mechanical stretch, heat stress, metabolic challenge, and pharmacological agents.3,4 The cardioprotective effects have also been extended beyond myocyte viability to pathological hypertrophy and remodeling.5,6 However, the vast majority of studies investigating preconditioning have focused on the protective effects of ischemic preconditioning against subsequent ischemia/reperfusion injury–induced myocyte death. In contrast, other nonischemic types of preconditioning have received relatively little attention,7 and whether the principles of preconditioning can be applied to other pathological cardiac states remains unexplored and nonischemic preconditioning remains a vastly underexplored area in cardiac biology. A report in this issue of Circulation by Wei et al8 proves a bold hypothesis that, similar to mechanisms of ischemic preconditioning, transient hypertrophic stimulation to the heart would make the heart more resistant to the development of pathological hypertrophy against sustained hypertrophic stress.

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In this body of work, Wei et al, in elegant experiments, provide proof of concept of hypertrophic preconditioning as a mechanism to decrease pathological hypertrophy in the presence of sustained hypertrophic stimuli.8 Both in vitro and in vivo systems were used in the study. In vitro, pretreatment of cultured cardiomyocytes with norepinephrine for 12 hours followed by 12 hours of withdrawal resulted in a significant reduction in the subsequent hypertrophic responses at both the morphological and molecular levels with decreased expression of fetal myocyte genes such as β-myosin heavy chain and atrial natriuretic peptide. In vivo, the authors first used 2 cycles (1 and 2 days) of mini-pump–mediated phenylephrine administration before a final 4-day phenylephrine treatment. Comparing this group with the simple 4-day treatment group, they observed a significant attenuation in cardiac hypertrophy by phenylephrine pretreatment, although in this model cardiac fibrosis was not significantly reduced. Next, the authors examined the effects of hypertrophic preconditioning in a model of sustained pressure overload with transaortic constriction (TAC). Quite remarkably, the authors show that by implementing short-term TAC followed by a brief period of recovery, subsequent cardiac hypertrophy with prolonged TAC could be significantly attenuated. The beneficial effects of TAC-induced hypertrophic preconditioning appeared to affect many pathological features in addition to myocyte hypertrophy. In contrast to phenylephrine-mediated preconditioning in which fibrosis was not significantly affected, pressure-overload preconditioning significantly decreased both perivascular and interstitial cardiac fibrosis. In addition, cardiac function was better preserved and remodeling of the preconditioned ventricle was significantly better with less ventricular dilatation. Moreover, animals that received pressure overload–mediated preconditioning exhibited significantly greater survival rates after prolonged TAC. This observation is consistent with an earlier report demonstrating that exercise-induced preconditioning protected against the development of pressure overload–induced hypertrophy.

The authors provide some insight into potential mechanisms mediating hypertrophic preconditioning. They focus on 2 genes, S100A8 and S100A9, with S100A9 previously shown to be correlated with regression of hypertrophy.9,10 The authors show that the expression of these genes increases in cardiomyocytes after norepinephrine-mediated hypertrophic preconditioning as well as in mouse hearts after TAC-induced preconditioning. Finally, the authors used gain- and loss-of-function experiments in vitro to show the importance of these genes in mediating hypertrophic preconditioning (Figure).

The study by Wei et al also highlights some important characteristics about hypertrophic preconditioning and how it may be mechanistically different from ischemic preconditioning. Unlike ischemic preconditioning, in which the preconditioned state can be established in a matter of minutes after very short episodes of ischemia/reperfusion, hypertrophic preconditioning revealed in this study is established by relatively long-term hypertrophic stimulations over days.
It is therefore not totally unexpected that hypertrophic preconditioning requires the expression of new genes critical to cardiac protection. It is quite surprising, however, that the potential mediators for hypertrophic preconditioning identified in this report are S100A8 and S100A9, a pair of genes originally implicated in activating inflammatory response secondary to tissue damage. S100A8 and S100A9 can form multiplex protein complexes to exert different functions, including as ligand for the Toll-like receptor 4 in immune modulation. In fact, several lines of evidence suggest that elevated S100A8/A9 can be detrimental to cardiac hypertrophy and promotes pathological remodeling in heart. Therefore, it is intriguing that this report showed that S100A8/A9 treatment was sufficient to attenuate hypertrophy in cardiomyocytes and to reduce fibrotic response in fibroblasts. These results certainly raise many interesting questions about S100A8/A9–mediated hypertrophic preconditioning: What would be the active forms of S100A8 and S100A9? What are their interacting partners responsible for the antihypertrophic effect? What are the downstream mechanisms involved in S100A8/A9–mediated antihypertrophic effect? Are they important in mediating an antihypertrophic effect against different insults? For instance, the antifibrotic effect was not observed in phenylephrine-induced preconditioning, in contrast to TAC-induced preconditioning. Additional investigations are needed to establish their role during hypertrophic preconditioning in vivo when different cell types, including inflammatory cells, are involved in the complex process of cardiac hypertrophy and remodeling. As authors correctly pointed out, there must be many other factors involved in hypertrophic preconditioning, and more layers of signaling complexity in this process are yet to be uncovered.

Nearly 30 years after the original report of ischemia preconditioning, we continue to face the challenging issue of translating an elegant discovery into new treatment. Much of the insights we have learned from the cardioprotective effects of ischemic preconditioning remain distant from direct clinical applications. Therefore, the clinical implication of hypertrophic preconditioning in the management of hypertrophic cardiomyopathy and congestive heart failure may prove to be equally challenging. Unlike cardiac injury experienced during acute ischemia/reperfusion process, pathogenesis of cardiac hypertrophy and heart failure is a chronic process, requiring months to years to manifest. The effective window of hypertrophic preconditioning is unclear but, as inferred from the persistent expression of S100A8/S100A9, may last only a few weeks. As indicated also by the authors, the dose and cellular targets of S100A8/S100A9 may have different outcomes in cardiac hypertrophy regulation. Finally, in hypertrophic hearts, the effectiveness of ischemic preconditioning is significantly attenuated. It is unclear whether hypertrophic preconditioning can remain intact with the presence of underlying cardiac pathology such as a pre-existing state of dilated, hypertrophic, or ischemic cardiomyopathy. Nevertheless, the findings by Wei et al offer a new possibility of hypertrophic suppression through preconditioning. The clinical translation of these findings will undoubtedly depend on identifying downstream targets that prepare not just the myocytes but also the interstitium to respond favorably to sustained increases in afterload. Revealing the underlying mechanisms for this phenomena, albeit in small steps, may put us closer to achieving a therapeutic goal of preventing cardiac hypertrophy and retarding the development of heart failure. Prevention is better than cure.

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