

**Transgenic System for Conditional Induction and Rescue of Cardiac Remodeling Provides New Insights into the Remodeling 'Point of No Return'**

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Cardiac Remodeling is the final common pathway for several cardiac diseases and considered a target for treatment in prevention of heart failure. Remodeling can be developed following cardiac dysfunction *per se* without cell death. Further, when myocyte viability is preserved (a state known as Myocardial Hibernation) remodeling is reversible. Rahimtoola *et al* have argued that there is an early 'golden time' where revascularization can reverse remodeling, an opportunity which may decline at later stages. Yet, the potential benefit of revascularization on reversing remodeling at its late stages has not been experimentally tested. We have recently developed a VEGF-based mice model system for Myocardial Hibernation. In this model, we inhibit cardiac VEGF and decrease capillary density thus inflicting progressive cardiac ischemia, without cell death. Further, we have shown that VEGF-mediated revascularization fully restores myocardial functioning. We harnessed this model system for studying cardiac remodeling and its potential reversibility. We show that left ventricle dilatation and fibrosis precedes ventricular hypertrophy and that interstitial fibrosis is progressive and upon reaching a critical level survival declines. At early stages, remodeling could be reversed by VEGF-mediated neovascularization, as well as by pharmacological inhibitors of the Renin-Angiotensin system. The latter, even in face of a remaining perfusion deficit and a compromised cardiac function. Ability to revascularize and restore contractile function were preserved even months later. However, despite rectifying its underlying causes, remodeling was no longer reversible at its end-stage, thereby demonstrating a definitive 'point-of-no-return' for heart remodeling. This study suggests that, while revascularization therapy might be beneficial even at more progressive stages of ischemic heart disease, its utility for reversing remodeling might be mostly useful if applied at earlier stages.