Although the concept of remodeling is well established with respect to heart muscle, the importance of a restructuration of cardiac innervation, or “rewiring,” after myocardial infarction (MI) has only recently received due attention. Pioneering contributions in this regard have emerged from the laboratories of Zipes\(^1\) and Chen.\(^2\)–\(^5\) Recently, Cao, Chen, and coworkers\(^2\)–\(^5\) provided evidence implicating nerve sprouting in ventricular arrhythmogenesis and potentially sudden cardiac death (SCD). These investigators reported a significant correlation between increased sympathetic nerve density as reflected in immunocytochemical markers with history of arrhythmias including ventricular tachycardia and SCD in native hearts of human transplant recipients with severe heart failure.\(^3\) Their observations suggested an association between postinjury sympathetic nerve density and susceptibility to life-threatening ventricular arrhythmias in these patients. In a canine post-MI model, they demonstrated that induction of nerve sprouting by infusion of nerve growth factor (NGF) into the left stellate ganglion (LSG) resulted in increased incidence of ventricular tachycardia and fibrillation.\(^4\) Significantly, the predisposition to arrhythmias was again linked to immunocytochemical evidence of a heterogeneous pattern of sympathetic reinnervation. In a similar conscious canine model, the group reported the frequent occurrence before ventricular tachycardia (VT) of visible T-wave alternans,\(^5\) a noninvasive marker of risk for ventricular arrhythmias in the post-MI population.\(^7,8\) More recently, Liu et al\(^6\) demonstrated in rabbits that hypercholesterolemia induces proarrhythmic neural and myocardial remodeling. Nerve sprouting and sympathetic hyperinnervation were associated with dispersion of repolarization, changes in calcium currents, and increased ventricular fibrillation incidence. Collectively, this evidence indicates that heterogeneous remodeling and hyperadrenergic innervation are likely to play significant adverse roles in the increased risk of life-threatening arrhythmias after MI.

In this issue of *Circulation Research*, Zhou et al\(^7\) report on the trophic factors that initiate and influence the pattern of sympathetic reinnervation as a function of time after MI in a canine model. To accomplish this goal, they focused on NGF and growth associated protein (GAP43) because of their established roles in the synthesis of neurotactin and tubulin proteins, effects on Schwann cell migration, and influence on synaptic transmission between sympathetic neurons and cardiac myocytes. Blood, left ventricular (LV) tissue, and stellate ganglia were sampled at different time points after MI. Specifically, the authors tested the hypothesis that elevations in local NGF production underlie the triggering sequence of sympathetic nerve sprouting after infarction.

The signaling sequence that was elucidated is depicted schematically in the Figure. Essentially, infarcted myocardial cells locally release NGF and GAP43, setting in motion a cascade of increased regionalized expression of neurotrophic substances and their retrograde transport to the left stellate ganglion (LSG) and presumably to other thoracic ganglia. The effects at the ganglionic level trigger more extensive growth of cardiac sympathetic neurons. The nerve sprouting occurs primarily in noninfarcted LV free wall, although some occurs in the damaged tissue. Limited growth in the infarcted region is probably attributable to the lack of blood supply. Cardiac nerve growth was verified both histologically and by the demonstration of increased neurofilament, tyrosine hydroxylase, and synaptophysin expression. The sympathetic nerve sprouting and hyperinnervation were evident by 3 days and persisted beyond the first week after MI. Interestingly, there were sizeable interindividual differences in systemic serum NGF concentration, a factor that is consistent with genetic control of cardiac nerve density and individual magnitude of nerve sprouting after infarction.

This elegant study appears to support the fundamental hypothesis tested, namely, that NGF and GAP43 constitute the underlying signals responsible for nerve growth in this post-MI experimental model. As the authors acknowledge, direct proof of causality is not established, as the inferences were based primarily on the temporal sequence of neurotrophic release and upregulation, retrograde transport, and subsequent nerve sprouting. Nevertheless, this group’s previous demonstration that NGF infusion into the LSG can directly elicit nerve sprouting in canines\(^8\) after MI lends strength to their central hypothesis. Potential sympathetic afferent pathways also require study. Overall, this investigation provides new insights bolstering the concept that after MI, there is heterogeneous sympathetic hyperinnervation, a condition known to be arrhythmogenic.

Intriguing questions arise as to whether neural remodeling is adaptive or maladaptive and whether manipulating this
process has therapeutic potential. Clinically, it has been demonstrated that cardiac reinnervation improves hemodynamic function. After cardiac transplantation, reinnervation is associated with significant improvement in exercise performance, as evaluated by heart rate response, aerobic threshold, and oxygen consumption. However, the main concern is whether the improved hemodynamic function is achieved at the cost of heightened risk for life-threatening arrhythmias because of heterogeneous adrenergic hyperinnervation. Indeed, antagonizing the proarrhythmic effect of excessive adrenergic tone is the likely basis for the reduction in SCD by \( \beta \)-adrenergic blockade. It remains to be determined whether achieving more uniform nerve growth can optimize contractility without increasing electrical instability and risk for life-threatening arrhythmias.

Zhou et al. have significantly advanced our understanding of the rewiring process that is integral to recovery from MI. It may not be premature to incorporate the term “neural remodeling,” introduced by these investigators, alongside “myocardial remodeling” into the conceptual framework of the pathophysiology of acute infarction.

**References**


**Key Words:** myocardial infarction, nerve growth factor, nerve sprouting, neural remodeling, sympathetic nerve, ventricular arrhythmia
Frayed Nerves in Myocardial Infarction: The Importance of Rewiring
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