

## Editorial Focus: role for neural growth factor in autonomically driven arrhythmogenesis? Focus on: “Structural neuroplasticity following T5 spinal cord transection: increased cardiac sympathetic innervation density and SPN arborization”

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THE AUTONOMIC NERVOUS SYSTEM has long been known to exert powerful influence on the genesis of and vulnerability to cardiac arrhythmias. With regard to ventricular arrhythmias, increased sympathetic outflow is generally thought to be proarrhythmic, while parasympathetic drive is thought to be antiarrhythmic. Imbalance in this relationship with a shift toward sympathetic dominance and away from parasympathetic dominance induces electrical destabilization of the myocardium, although the mechanisms of these effects remain largely unknown (14). The study by Lujan et al. (10) from Dr. Stephen DiCarlo's group suggests that neural growth factors (NGFs) may play a role in the pathogenesis of autonomically driven ventricular arrhythmias within the setting of spinal cord injury (SCI). An extension of their previous work, which established that midthoracic level 5 (T5) spinal cord transection in rats, increases vulnerability to ventricular arrhythmias (5), Lujan's study expands on these findings and provides further evidence of structural hyperinnervation of sympathetic neural supply to the myocardium following SCI in rats. Using injection of cholera toxin B into the left and right stellate ganglion, which provides over 90% of sympathetic supply to the heart, the authors determined that following SCI there was a significant increase in cardiac sympathetic preganglionic neuronal (SPN) arborization as compared to intact rats. Furthermore, there was a significant increase in left ventricular NGF content as well as increased left ventricular sympathetic density as measured through tyrosine hydroxylase immunohistochemistry. Thus, by using a combination of multiple techniques and lines of evidence, the authors concluded that SCI results in sympathetic hyperinnervation of the left ventricular myocardium.

The discovery of NGF by Levi-Montalcini (8, 9) has led to expansive study and understanding of their well-known actions on neural growth and survival, particularly during development and injury. Less well understood are their actions on nonneural targets, including the cardiovascular system. More recently, however, a number of studies have provided evidence of a critical role for NGF in the heart following myocardial injury (3, 7). This has led to the formulation of the nerve-sprouting hypothesis of sudden cardiac death. According to this hypothesis (Fig. 1) myocardial ischemia injures both the myocardium and the surrounding sympathetic innervation richly supplying the coronary arteries. Sympathetic nerve sprouting results from this injury, leading to sympathetic hyperinnervation, resulting

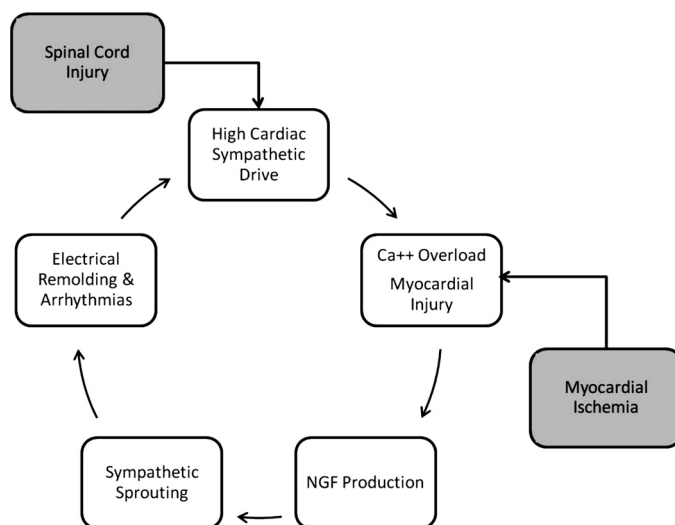


Fig. 1. Hypothesized sequence of events by which either spinal cord injury or myocardial infarction lead to increased sympathetic sprouting and thus increased vulnerability to cardiac arrhythmias.

in increasing risk for sudden fatal cardiac arrhythmias including ventricular tachycardia and ventricular fibrillation. NGF is thought to play a critical role in the cascade of these events, expressed by nonneural cells surrounding the site of injury (5).

Within the context of SCI, although not immediately obvious, evidence of myocardial injury has been postulated, likely driven by the high level of sympathetic outflow that occurs immediately following the acute SCI. SCIs at or below T5 result in loss of descending sympathetic drive to the vasculature innervated by SPNs, which exit the spinal cord below the level of transection. This results in hypotension and thus a dramatic reflex-mediated increase in sympathetic outflow to the heart, the pathways of which are preserved above the level of the transection. These levels of sympathetic outflow following SCI have been reported to be high enough to induce calcium overload (12) and induce left ventricular dysfunction and ST-segment elevation (11), thus likely establishing a setting where NGF is produced by either injured myocardium or lymphocytes recruited to the site of injury, and induces sympathetic sprouting and hyperinnervation of the heart. Although the points of entry for SCI in the hypothesized cycle of NGF-mediated increases in sympathetic hyperinnervation of the myocardium may differ from that of myocardial ischemia (Fig. 1), the result is essentially the same: establishment of electrical remodeling of the myocardium and arrhythmogenesis.

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These results have important implications in not only addressing the mechanisms responsible for the high mortality rates and incidence of cardiovascular disease in chronic SCI patients (15) but also regarding other pathophysiologic states that are accompanied by high cardiac sympathetic drive.

Adaptation to a number of persistent physiologic and environmental stresses results in increased cardiac sympathetic drive, autonomic imbalance, and myocardial electrical destabilization. These include states, such as chronic stress, psychological depression, and orthostatic tachycardic syndromes (1, 4, 6). The study by Lujan et al. (10) provides evidence for a mechanism whereby initial sympathetic surges are maintained and augmented through a NGF-mediated mechanism, resulting in sustained sympathetic innervation of the myocardium even though the initial insult or injury is removed or ameliorated.

Although this study provides support for this hypothesis, further questions remain, and a number of potential mechanisms are left unidentified. For instance, Lujan et al. (10) only evaluated the changes in NGF, density of sympathetic innervation, and SPN arborization within the left ventricle, thus providing only a snapshot of neuroplastic changes within a discrete area of the left ventricle induced by SCI. Autonomically driven arrhythmogenesis may not purely be a function of the gross level of sympathetic innervation but rather may be most sensitive to the degree heterogeneity of that innervation. The relationship between regional heterogeneity of sympathetic innervation and vulnerability to ventricular arrhythmias has been established in both humans (2) and animal models (13). Thus, further examination of neuroplasticity within distinct and diverse regions of the myocardium may provide further insight into these mechanisms. In addition, in order to firmly establish NGF as a critical mediator of the sympathetic sprouting following SCI, further study in which the expression of NGF is blocked would be required to determine a definitive mechanistic role by this growth factor. Further remaining to be identified is the source of NGF within this process. Whether NGF is produced from the myocardium or possibly released from lymphocytes that infiltrate areas of injury, remains to be determined. Although questions remain, Lujan et al. (10) provides important new insight into the neuroplastic changes that occur within the myocardium following SCI with implication in the areas of both SCI and cardiovascular autonomic control and provides a robust model in which to investigate the role of growth factors in the pathogenesis of automatically mediated arrhythmogenesis.

## REFERENCES

1. Brady PA, Low PA, Shen WK. Inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, and overlapping syndromes. *Pacing Clin Electrophysiol* 28: 1112–1121, 2005.
2. Cao JM, Fishbein MC, Han JB, Lai WW, Lai AC, Wu TJ, Czer L, Wolf PL, Denton TA, Shintaku IP, Chen PS, Chen LS. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. *Circulation* 101: 1960–1969, 2000.
3. Caporali A, Sala-Newby GB, Meloni M, Graiani G, Pani E, Cristofaro B, Newby AC, Madeddu P, Emanueli C. Identification of the pro-survival activity of nerve growth factor on cardiac myocytes. *Cell Death Differ* 15: 299–311, 2008.
4. Carney RM, Freedland KE, Rich MW, Smith LJ, Jaffe AS. Ventricular tachycardia and psychiatric depression in patients with coronary artery disease. *Am J Med* 95: 23–28, 1993.
5. Chen PS, Chen LS, Cao JM, Sharifi B, Karagueuzian HS, Fishbein MC. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res* 50: 409–416, 2001.
6. Grippo AJ, Santos CM, Johnson RF, Beltz TG, Martins JB, Felder RB, Johnson AK. Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression. *Am J Physiol Heart Circ Physiol* 286: H619–H626, 2004.
7. Hasan W, Jama A, Donohue T, Wernli G, Onyszchuk G, Al-Hafez B, Bilgen M, Smith PG. Sympathetic hyperinnervation and inflammatory cell NGF synthesis following myocardial infarction in rats. *Brain Res* 1124: 142–154, 2006.
8. Levi-Montalcini R. Growth control of nerve cells by a protein factor and its antiserum: discovery of this factor may provide new leads to understanding of some neurogenetic processes. *Science* 143: 105–110, 1964.
9. Levi-Montalcini R, Angeletti PU. Essential role of the nerve growth factor in the survival and maintenance of dissociated sensory and sympathetic embryonic nerve cells in vitro. *Dev Biol* 7: 653–659, 1963.
10. Lujan HL, Palani G, DiCarlo SE. Structural neuroplasticity following T5 spinal cord transection: increased cardiac sympathetic innervation density and SPN arborization. *Am J Physiol Regul Integr Comp Physiol* (July 28, 2010). doi:10.1152/ajpregu.00329.2010.
11. Morita S, Inokuchi S, Yamagiwa T, Aoki H, Nakagawa Y, Yamamoto Tako-tsubolike I. Left ventricular dysfunction with ST-segment elevation after central spinal cord injury: a case report. *J Emerg Med* 2008.
12. Sharov VG, Galakhin KA. [Myocardial changes after spinal cord injuries in humans and experimental animals]. *Arkh Patol* 46: 17–20, 1984.
13. Tsai J, Cao JM, Zhou S, Swissa M, Cates AW, KenKnight BH, Chen LS, Karagueuzian HS, Chen PS. T wave alternans as a predictor of spontaneous ventricular tachycardia in a canine model of sudden cardiac death. *J Cardiovasc Electrophysiol* 13: 51–55, 2002.
14. Verrier RL, Antzelevitch C. Autonomic aspects of arrhythmogenesis: the enduring and the new. *Curr Opin Cardiol* 19: 2–11, 2004.
15. Whiteneck GG, Charlifue SW, Frankel HL, Fraser MH, Gardner BP, Gerhart KA, Krishnan KR, Menter RR, Nuseibeh I, Short DJ. Mortality, morbidity, and psychosocial outcomes of persons spinal cord injured more than 20 years ago. *Paraplegia* 30: 617–630, 1992.