Progressive cardiac dysfunction after a myocardial infarction (MI) is a major contributor to the high incidence of heart failure in many parts of the world. The initial myocardial injury and the resulting decrease in left ventricular (LV) function activate a variety of systems to sustain the cardiovascular homeostasis. However, in the long-term their activation contributes to adverse cardiac remodeling and a further decrease in LV function. In recent years it has become apparent that the central nervous system (CNS) plays a pivotal role in this regard. Post-MI, several stimuli can activate CNS-angiotensinergic sympathoexcitatory pathways and as a result not only cause sympathetic hyperactivity but also activate the circulating and cardiac renin-angiotensin-aldosterone system, cytokines, and vasopressin, all contributing to further myocyte loss and decreased myocyte function.1 No braking, that is, balancing mechanisms are apparently being activated, and this is considered the main reason for progressive cardiac dysfunction leading to clinical heart failure and death. Drug therapy involving β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II type 1-receptor blockers, and mineralocorticoid receptor blockers has a marked impact, but heart failure remains a major problem. The study by Okada et al2 in the current issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* provides a new perspective and suggests that cardioprotective mechanisms are actually being activated and can attenuate heart failure post-MI, at least in mice.

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Brain-derived neurotrophic factor (Bdnf) and its receptor, tropomyosin-related kinase receptor B (TrkB), are present both in the CNS and in the heart. Okada et al2 showed that in mice with a marked decrease in LV ejection fraction (≈20%) at 2 weeks post-MI, brain and plasma Bdnf, as well as cardiac TrkB expression are clearly increased, but cardiac Bdnf expression markedly decreased. Destruction of the cardiac terminals of sensory afferent neurons from the heart by local treatment with capsaicin prevented the increase in neuronal expression of Bdnf, as well as the increase in plasma Bdnf, after MI. Interestingly, despite possibly lower sympathetic activity,3 these mice exhibited a further decrease in ejection fraction, a larger area of myocardial fibrosis, and impaired vascularization of the peri-infarct zone. Using state-of-the-art genetic targeting technology, Okada et al further dissected the role of specific components of the CNS-blood-heart Bdnf-TrkB axis. Mice with systemic deletion of the *Bdnf* gene at 2 weeks post-MI exhibited a further decrease in LV ejection fraction, as well as more fibrosis, and terminal deoxyribonucleotidyl transferase dUTP nick-end labeling–positive cardiomyocytes associated with increased expression of the proapoptotic B-cell lymphoma 2–associated X protein and decreased expression of the prosurvival molecule B-cell lymphoma protein 2. Impaired vascularization and decreased vascular endothelial growth factor expression were also apparent.

Cardiac-specific deletion of the *Bdnf* gene did not affect cardiac remodeling and dysfunction post-MI. In contrast, after genetic disruption of neuronal *Bdnf* expression, plasma Bdnf levels did not increase post-MI and adverse cardiac remodeling and dysfunction were again apparent. Specific disruption of the *TrkB* gene in the myocardium was also associated with adverse cardiac remodeling and dysfunction. Finally, intraperitoneal injection of Bdnf recombinant protein on day 0 and day 1 increased plasma Bdnf levels 4- to 5-fold above those in control MI mice and restored the cardiac phenotype in either mice treated with capsaicin or those with neuronal-specific deletion of the *Bdnf* gene. The authors conclude that Bdnf via the cardiac TrkB receptor plays a protective role in the heart post-MI by inducing angiogenesis and upregulating expression of prosurvival factors. In addition, the findings suggest that post-MI cardiac afferent nerve fibers relay mechanosensitive or chemosensitive information to the CNS, possibly the paraventricular nucleus,3 and thereby increase neuronal Bdnf expression, which in turn causes an increase in plasma Bdnf levels. The authors state—Bdnf release from the brain—but do not speculate on possible mechanisms through which release of this protein into the circulation may occur.

The study has some limitations. MI sizes are presumably large considering the low ejection fraction. However, the actual MI sizes were, surprisingly, not reported; effects of Bdnf deficiency on MI size can, therefore, not be excluded. Cardiac function was only assessed by echocardiography. This provides limited information and assessment of LV function by, for example, Millar Catheter, in at least some of the experiments would have been much more informative. Finally, some of the mice groups exhibited very low ejection fraction (≈10%), and presumably increased mortality. This is a critical end point, but unfortunately no data on mortality were provided.

Irrespective of these limitations, the present study by Okada et al2 clearly demonstrates that the ischemic myocardium sends signals to the CNS not only to increase sympathetic activity and other mechanisms to maintain cardiovascular homeostasis but also to activate cardioprotective mechanisms, such as the Bdnf-TrkB axis. The latter may serve to dampen the adverse effects of, for example, the sympathetic tone on the heart (see

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*Arterioscler Thromb Vasc Biol* is available at [http://atvb.ahajournals.org](http://atvb.ahajournals.org)

DOI: 10.1161/ATVBAHA.112.252627
schematic outline in Figure). If this concept also applies to humans, decreased activity of the Bdnf-TrkB axis in humans with neurodegenerative diseases, depression, or metabolic disorders may contribute to increased risk for heart failure post-MI. If so, plasma Bdnf levels may become another risk factor/marker and drugs to stimulate cardiac TrkB receptors may become a novel strategy to inhibit progressive cardiac dysfunction post-MI.

Acknowledgments
The authors acknowledge Danielle Oja for her excellent skills in assisting in the preparation and formatting of this article.

Sources of Funding
Dr Leenen holds the Pfizer Chair in Hypertension Research, an endowed chair supported by Pfizer Canada, the University of Ottawa Heart Institute Foundation, and the Canadian Institutes of Health Research. Research from the authors discussed in this Editorial was supported by operating grants from the Heart and Stroke Foundation of Ontario and the Canadian Institutes of Health Research.

Disclosures
None.

References

Key Words: angiogenesis • central nervous system • echocardiography • genetically altered mice • heart failure
Cardioprotective Brain Mechanisms
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