Vagal Nerve Stimulation in Chronic Heart Failure: An Antiinflammatory Intervention?

To the Editor:
Li et al recently reported that vagal nerve stimulation improved survival in otherwise untreated rats with heart failure secondary to left coronary artery ligation. Although this finding is indeed intriguing and of potential therapeutic importance, the authors are understandably speculative about the possible mechanisms underlying this observation.

The authors discuss that the beneficial effects seen in their study cannot solely be ascribed to vagal inhibition of myocardial presynaptic norepinephrine release or to the attenuation of cardiomyocyte G-protein interactions that normally augment β-adrenergic tone. Although the inhibition of sympathetic activity may partly account for the benefits observed, there are likely to be, we suggest, additional and important effects on the chronic inflammation seen in chronic heart failure (CHF).

It is increasingly appreciated that efferent vagal nerve stimulation can directly and rapidly regulate immune responses. Vagal nerve stimulation can inhibit the release of cytokines like tumor necrosis factor; interleukins-1, -6, and -18 (but not interleukin-10); and intracellular high-mobility group B1 protein. In particular, vagal nerve stimulation protects against endotoxia and ischemia-reperfusion injury. Tracey has termed this the “cholinergic anti-inflammatory pathway” or “the inflammatory reflex.” Mechanistically, the process seems to depend on the nicotinic acetylcholine receptor α7 subunit.

In edematous human CHF patients, increased levels of proinflammatory endotoxin (LPS) have been detected. Plausibly, we consider that among other properties, vagal stimulation was a highly effective antiinflammatory treatment that was applied to untreated CHF rats. These rats were treated from 2 weeks onward. At this time, >60% had died, and many were severely ill, as indicated by the subsequent 20-week mortality rate of 50% in the sham-treated CHF rats. Therefore, it can be considered that among other properties, vagal stimulation was a highly effective antiinflammatory treatment that was applied to animals with advanced CHF (likely equivalent to New York Heart Association class IV in humans). It is our contention that this study may have demonstrated the potential utility of antiinflammatory and particularly anti-LPS therapies in severe CHF.

Jochen Springer, PhD
Division of Applied Cachexia Research
Department of Cardiology
Charité Campus Virchow-Klinikum
Berlin, Germany

Darlington O. Okonko, BSc, MRCP
Stefan D. Anker, MD, PhD
Clinical Cardiology
National Heart & Lung Institute
Imperial College
London, UK
s.anker@imperial.ac.uk

References

Response
We, along with Drs Okonko, Onkondo, and Anker, speculate about the possibility that vagal stimulation improves survival in severe chronic heart failure (CHF) through the inhibition of the release of cytokines such as tumor necrosis factor-α (TNF-α). In an earlier cohort study, they showed that the plasma levels of the endotoxins, cytokines, and C-reactive protein were higher in edematous CHF patients than in stable CHF patients, suggesting that altered gut permeability with bacterial translocation and endotoxia triggers immune activation in CHF patients during edematous episodes. A recent clinical trial shows that pentoxifylline, an inhibitor of TNF-α synthesis at its transcriptional level, improved cardiac function and reduced the plasma level of TNF-α and C-reactive protein in CHF patients. Although we did not measure the plasma concentration of endotoxins or cytokines, there was no significant difference between the treated and untreated CHF rats in the plasma level of C-reactive protein (Li et al, unpublished observation, 2003).

At this stage, there is no supporting evidence that the immunomodulating agents and the cholinergic antiinflammatory effects improve survival in CHF. Therefore, to clarify the mechanisms for beneficial effects of vagal stimulation on CHF, further studies, including immunological assay, are needed.

Meihua Li, PhD
Can Zheng, PhD
Toru Kawada, MD
Masaru Sugimachi, MD
Kenji Sunagawa, MD
Department of Cardiovascular Dynamics
National Cardiovascular Center Research Institute
Saitama, Japan

Takayuki Sato, MD
Department of Cardiovascular Control
Kochi Medical School
Nankoku, Japan
tacsato-kochimed@umin.ac.jp

References
Vagal Nerve Stimulation in Chronic Heart Failure: An Antiinflammatory Intervention?
Jochen Springer, Darlington O. Okonko and Stefan D. Anker

_Circulation_. 2004;110:e34
doii: 10.1161/01.CIR.0000139382.42506.89
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/4/e34

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/