Ganglionitis and Genetic Cardiac Arrhythmias
More Questions Than Answers

Arthur J. Moss, MD; Daniel H. Ryan, MD; Gabrielle A. Yeaney, MD

In 1968, Zipes et al reported surgical sympathectomy for the control of ventricular tachyarrhythmias in patients with ischemic heart disease. In 1971, our research group reported the effectiveness of surgical left cervicothoracic sympathetic ganglionectomy for the treatment of a patient with long-QT syndrome (LQTS) who experienced recurrent syncope related to ventricular tachyarrhythmias. This patient is still alive 43 years later without recurrent cardiac events, and she, her daughter, and her grandson have genotype-confirmed type-1 LQTS. In 1995, we reported the use of this ganglionectomy technique in 10 patients with LQTS. In all these patients, the removed lower half of the left stellate ganglion and the second and third left thoracic ganglia were reported as normal by routine histological analysis by our pathologists. Subsequently, this ganglionectomy technique, now called left cardiac sympathetic denervation, has been performed in several arrhythmia centers throughout the world. The major investigators who have reported their ganglionectomy experience in addition to ourselves include Drs Schwartz et al and Collura et al, and in none of the published reports have ganglionitis been documented in the removed stellate or thoracic ganglia.

In the current publication by Rizzo et al from the Amsterdam group, the lower half of the left stellate ganglion and the left second through fourth thoracic ganglia were removed through a videoendoscopic transthoracic approach in 8 patients with LQTS and 4 patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). All patients were severely symptomatic before the ganglionectomy and had experienced multiple syncopal episodes, with 7 of the 12 patients having had multiple shocks from a previously implantable cardioverter defibrillator. Detailed histological examination was performed on the removed stellate and thoracic ganglia, including routine hematoxylin-eosin and Masson trichrome stain plus immunohistochemical studies including antigen and T-cell activation studies to analyze inflammatory reactions in the ganglia. Molecular studies for viral genomes were also performed and were uniformly negative. Control stellate ganglia were examined in a similar fashion from patients of roughly the same age who died in accidents.

The histopathologic studies in the Rizzo et al study were thorough and well done. The removed ganglia from the patients with LQTS and CPVT revealed low-grade signs of chronic ganglionitis manifest by elevated numbers of activated T lymphocytes and cytoplasmic vacuoles in ganglion cells. Of note, the ganglia removed in the normal controls also displayed some inflammatory activity but to a lesser extent. The authors considered a number of possibilities to explain their findings, and they favored an infectious process as the most probable explanation. Furthermore, the authors speculated that the ganglionic inflammation might contribute to the cardiac electric instability in subjects with LQTS/CPVT, and particularly in those who are heavily symptomatic.

There is no question about the presence of the low-grade ganglionitis as documented in the publication by Rizzo et al in the 12 patients with life-threatening arrhythmogenic cardiac events in 2 very different genetic cardiac disorders. So how do we explain the presence of the ganglionitis in these patients? It is unlikely that the similarity of the ganglionitis in the 2 genetic disorders occurred by chance alone. First, it should be noted that the ganglionitis in the patients with LQTS and CPVT is categorized as low grade in severity, and there was evidence of minor inflammatory changes in the ganglia from the normal controls. Thus, the ganglionitis described in the affected patients reflects, at most, only a mild reaction. It seems to us that an infectious pathogenesis, although possible, is unlikely for we would expect the ganglionitis and the ganglioic injury to be more prominent, perhaps with hypercellular clusters of lymphocytes (nodules of Nageotte). Although an infiltration of predominantly CD8+ cytotoxic T lymphocytes would be reasonably anticipated in viral and autoimmune responses, we would hesitate to rule out on this basis neuronal injury from other causes. For instance, hippocampal CD8+ T-cell infiltration has been observed after electrically induced seizures in mice. What is common to all 12 patients is that they had recurrent syncope and many implantable cardioverter defibrillator shocks before the ganglionectomy. Syncopal events are associated with transient generalized hypoperfusion, and implantable cardioverter defibrillator shocks can result in injury to the myocardium.

It is reasonable to think that both the transient hypoperfusion and the direct current shocks could cause ganglionic cell injury because the ganglionic nerves are directly connected to the myocardium. Ganglionic protein damage might well result in a secondary autoimmune reaction with manifestations of ganglionitis. It is interesting that in 1978 Dr James et al described postmortem intracardiac ganglionitis in 8

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Cardiology Division, Department of Medicine (A.J.M.) and Department of Pathology (D.H.R., G.A.Y.), University of Rochester Medical Center, Rochester, NY.

Correspondence to Arthur J. Moss, MD, Heart Research Follow-Up Program, University of Rochester Medical Center, PO Box 653, Rochester, NY 14642. E-mail heartajm@heart.rochester.edu

(Circ Arrhythm Electrophysiol. 2014;7:190-191.)

© 2014 American Heart Association, Inc.

Circ Arrhythm Electrophysiol is available at http://circres.ahajournals.org

DOI: 10.1161/CIRCEP.114.001589

190
patients with LQTS who had syncopal spells and died from their disease. It may well be that intracardiac and extracardiac neurogenic ganglionic cells are particularly susceptible to hypoperfusion or defibrillator shock injury with resultant intracellular protein damage and secondary inflammatory ganglionitis. We would suggest this as a possible explanation for the ganglionitis findings because they pertain to the descriptions of similar finding in patients with LQTS in 2 publications separated by >35 years.

Could the observed stellate and thoracic ganglionitis, whether a primary or secondary phenomenon, play a triggering role in the precipitation of life-threatening ventricular tachyarrhythmias in these 2 different genetic disease states? Although anything is possible, we think it is unlikely that the minor degree of ganglionitis as described is stimulating the vulnerable myocardium in these patients with high-risk genetic disorders. One would think it is at least as likely that the minor inflammatory damage to the ganglia would reduce transmission of nerve traffic through the ganglia from higher centers rather than exacerbate the sympathetic stimulation to the myocardium. Of course, our comments are speculative, but we suspect the ganglionic findings are minor and are not playing a causal role in the disease process. However, cervical thoracic ganglionectomy should dramatically reduce normal sympathetic traffic to the heart with resultant rhythm stabilization, and this is what was observed in almost all the patients reported in the article by Rizzo et al.6

The type of gangliocytic injury described by the authors as vacuolation may be subtle and is difficult to discern from figures provided.6 Vacuolation of ganglion cells has been described in several instances from toxic exposure, to trauma, to aging and is considered nonspecific.10,11 It should be noted that stellate and thoracic ganglia are not routinely examined in postmortem examination by pathologists, so there is a paucity of available data on the histological findings in these tissues among patients who die suddenly from cardiac arrhythmias. It might be useful to examine ganglia from patients who die in clinical settings involving multiple electric shocks or syncopal episodes unrelated to congenital arrhythmia to sort out the secondary versus primary nature of the histopathologic findings observed in these ganglia.

The authors are to be congratulated for providing a new orientation to the inflammatory activity of the cardiac ganglia in patients with LQTS and CPVT and recurrent cardiac events. The authors have raised more questions than can be answered at this time, and their approach opens the door for further investigations into the role of altered ganglionic structure and function involved in the mechanistic complexities of inherited and acquired cardiac rhythm disorders.

Disclosures
Dr Moss is a consultant to Gilead Sciences, Foster City, CA, and has received research grant for long-QT syndrome investigations from BioReference Laboratories, Inc, Elmwood Park, NJ. The other authors report no conflicts.

References

Key Words: Editorials ▪ arrhythmias, cardiac ▪ long QT syndrome ▪ polymorphic catecholaminergic ventricular tachycardia
Ganglionitis and Genetic Cardiac Arrhythmias: More Questions Than Answers
Arthur J. Moss, Daniel H. Ryan and Gabrielle A. Yeaney

*Circ Arrhythm Electrophysiol.* 2014;7:190-191
doi: 10.1161/CIRCEP.114.001589
*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/7/2/190

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Arrhythmia and Electrophysiology* 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: Arrhythmia and Electrophysiology* is online at:
http://circep.ahajournals.org//subscriptions/