Timing Is Everything in Protecting the Heart and Lungs in a "Sympathetic Storm"

α before β?

Vincent Degos, M.D., Ph.D., Martin J. London, M.D.

IN this issue of the Journal, Lu *et al.*[1] provide intriguing data on the etiologic role of excessive sympathetic activity from damage to the nucleus tractus solitarii (NTS) in rats resulting in catastrophic damage to the heart and lungs. The good news here is that such damage may potentially be effectively treated with inexpensive α-adrenergic receptor blocking agent. The NTS is a center for the processing of diverse afferent inputs responsible for maintenance of cardiopulmonary homeostasis, and this study adds to our knowledge of its importance. Given these critical functions and its diverse receptor population, it should come as no surprise that alteration or destruction of portions of the NTS has been associated with marked alterations of blood pressure, heart rate, and baroreceptor function in animal models.[2] This "sympathetic storm" is appreciated to be responsible for the now well-appreciated clinical syndromes of neurogenic-mediated stress cardiomyopathy and pulmonary edema.[3]

"New results and controversies about perioperative therapies based on sympathetic blockade or stimulation of various adrenergic receptors will likely help us customize therapies."

In a previous study,[4] these authors developed a rat model simulating their clinical observations of patients dying of fulminant cardiovascular collapse due to EV71 brainstem encephalitis in whom destructive lesions were observed in the NTS on autopsy. In this model, which uses stereotactically guided microinjection of 6-hydroxydopamine into the NTS, they were able to markedly attenuate the resulting acute hypertension, catecholamine release, pulmonary edema, and cardiac dysfunction present in control animals by early intravenous administration of the preganglionic nicotinic receptor antagonist, hexamethonium. In an accompanying editorial,[5] a recent case report[6] documenting rapid resolution of neurogenic pulmonary edema with intravenous phentolamine (acting on similar receptors) was cited as a possible human analog of this hypothesis.

In the current study, they evaluate the effects of an α1-blocker (prazosin, including a dose-response evaluation), α2-blocker (yohimbine), or a nonselective β-blocker (propranolol) as well as the specific effects of α-agonism (phenylephrine) in this model. Sophisticated physiologic, histologic, immunohistologic, and echocardiographic measurements were conducted, including novel evaluation of cell to cell signaling *via* connexin 43, a gap-junction protein which modulates cardiac electrical activity, apoptosis, and lung inflammation.[7] The findings of significant protection from the adverse pathophysiologic effects of the sympathetic "storm" by prazosin, contrasted by the rapid death within 2 h from pulmonary edema and acute ventricular dilatation with contraction necrosis *in all of the propranolol-treated rats* (despite significantly higher heart rates in the prazosin-treated rats) are striking. As well, the authors report a time-dependent increase in connexin 43, Caspase 3 expression (enzyme involved in the terminal phase of apoptosis), and TUNEL (terminal deoxynucleotidyl transferase dUTP)-positive cell, which allows detection of apoptotic cells, in the heart and lungs of these rats. To increase the plausibility of a causal link between α1-receptor overactivity and the heart and lung injuries, the authors demonstrate that phenylephrine enhanced the phenotype of lung and heart and the expression of connexin 43 and TUNEL-positive cells.

Excessive stimulation of α1-receptors results in pleiotropic effects as they are also expressed on several cell types such

Image: ©iStock.

Corresponding article on page 1192.

Accepted for publication January 24, 2014. From the Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California (V.D., M.J.L.); and INSERM, UMR 1141, Hôpital Robert Debré, Paris, France, and Department of Anesthesia and Perioperative Care, Hopital Pitié Salpetrière, Université Pierre et Marie Curie, Paris VI, Assistance Publique des Hopitaux de Paris, Paris, France (V.D.).

 Anesthesiology 2014; 120:1069-71

as cardiomyocytes, neurons, and immunocytes. The study by Lu *et al.*[1] is novel and gives clear direction for further investigations because they were neither able to delineate which cell type is a key target in their model nor able to conclusively demonstrate a precise mechanistic link between α1-receptor overexcitation and connexin 43. Furthermore, as the authors note, the long-term effects of treatment in the surviving rats on neurobehavioral function require investigation.

If this is a valid physiologic model, which clinical scenarios of acute brain injury would it best represent? The authors make a strong case in their original publication for a specific form of acute encephalitis. Sympathetic overactivity is a hallmark of subarchnoid hemorrhage and other neurologic states, but the implications of associated increase in intracranial pressure (not considered in this model) are clearly expected to complicate clinical use of potent sympathetic blocking agents. Maintenance of adequate cerebral perfusion pressure is a critical determinant of outcome in the setting of acute brain injury. Increased plasma norepinephrine seems to play a critical role in the pathogenesis of subarachnoid hemorrhage–induced neurogenic pulmonary edema and cardiac wall motion abnormalities[8,9] although both epinephrine and norepinephrine may be involved *via* multiple signaling pathways. Moreover, excessive adrenergic stimulation is well known to occur in extracerebral syndromes such as pheochromocytoma. Cases of cardiac failure due to hypertensive crisis in the context of the associated adrenergic stimulation seem to be rare but have been reported.

Evidence supports a similar sympathetic surge in severe sepsis,[10] a condition for which treatment strategies remain controversial. The potential impact of widely accepted but often not well delineated intensive care unit and perioperative therapies based on sympathetic blockade or stimulation of various receptors such as use of β-blockers for heart rate control and cardioprotection in patients with several heart diseases; guideline-recommended use of norepinephrine for the treatment of hypotension in septic shock, the ubiquitous use of phenylephrine to offset vasodilating effects of sedatives and analgesics in the intensive care unit, the growing use of the potent α_2 agonist dexmedetomidine for intensive care unit sedation would seem to mandate that better delineation of the status of the level of excitation of adrenoreceptors may help better customize individual patient therapy in the future.

By now, most readers of this journal are well aware of the ongoing controversy over the effectiveness and safety of perioperative β-blockade, particularly with regard to associations of their use with perioperative death and stroke.[11] More recently, the issue of precise timing of β-blockade in conditions previously considered contraindications has been widely publicized. A recent open-label, randomized study of the use of esmolol infusions in mechanically ventilated patients with septic shock, all of whom were requiring norepinephrine for hemodynamic support, demonstrated feasibility and safety of a decidedly clinically controversial approach based on the growing literature base to "protect" the β-adrenergic receptor.[12] The striking finding of a reduction in 28-day mortality from 80.5 to 49.4% in the treated group (a secondary outcome) will no doubt lead to intense clinical interest and larger, multicenter randomized controlled trials. The study by Lu *et al.*,[1] reporting profound safety hazards with the early use of β-receptor blockade in the setting of sympathetic activation, seems highly controversial. Further investigations in the context of differences in sympathetic activation between acute brain injury and sepsis will be of great interest.

Although catecholamine storm may be associated with severe myocardial and lung dysfunction, it is reassuring that the time course of this dysfunction in many studies is relatively transient with return to normal macroscopic function within a few days. However, the long-term impact on these two major organs through adrenoreceptor overexcitation and pro-apoptosis mechanisms, as reported in Lu *et al.* study,[1] has yet to be determined conclusively.

New results and controversies about perioperative therapies based on sympathetic blockade or stimulation of various adrenergic receptors will likely help us customize therapies. The study by Lu *et al.*[1] provides intriguing evidence about the role of excessive sympathetic activity and its effect on pro-apoptosis pathway. The precise timing between severe physiologic insults and pharmacological intervention need further investigation in both laboratory and clinical settings. There seems to be much to look forward to.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Degos: degosv@gmail.com

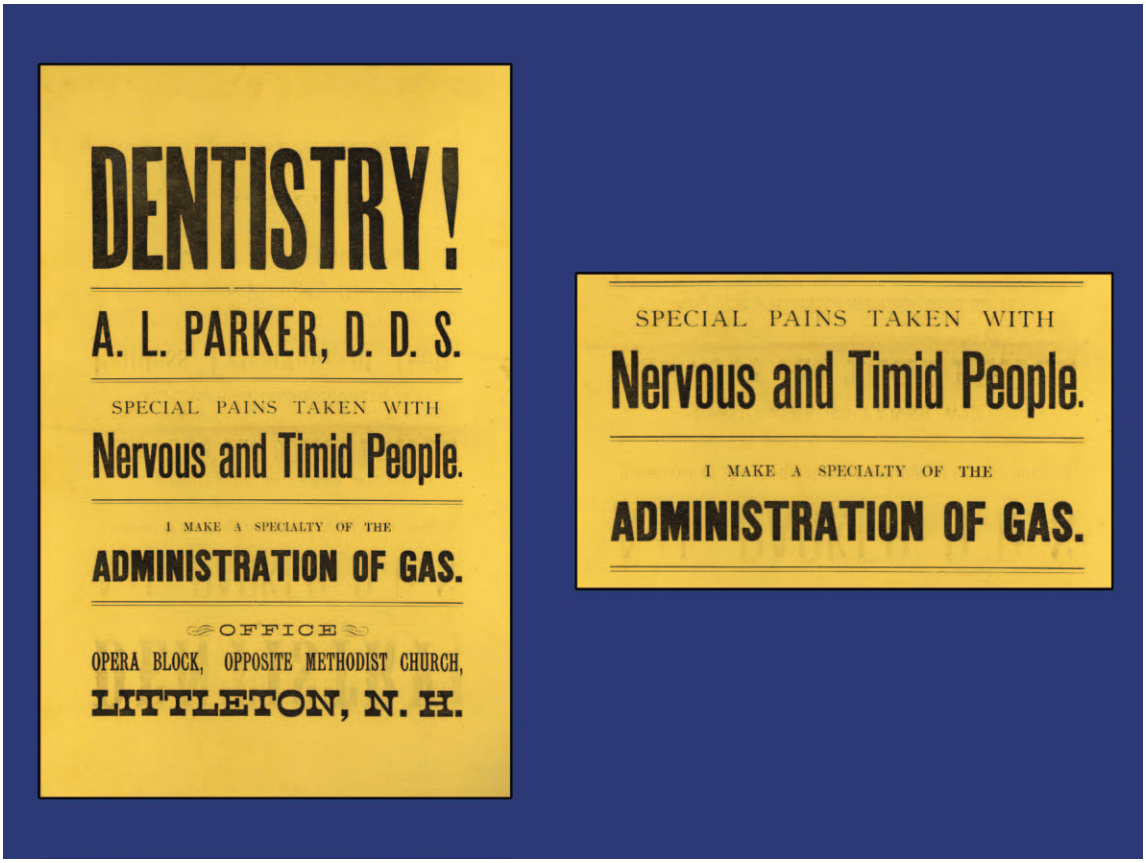
References

1. Lu WH, Hsieh KS, Lu PJ, Wu YS, Ho WY, Cheng PW, Lai CC, Hsiao M, Tseng CJ: Different Impacts of α- and β-blockers in neurogenic hypertension produced by brainstem lesions in rat. Anesthesiology 2014; 120:1192–204
2. Talman WT, Dragon DN, Jones SY, Moore SA, Lin LH: Sudden death and myocardial lesions after damage to catecholamine neurons of the nucleus tractus solitarii in rat. Cell Mol Neurobiol 2012; 32:1119–26
3. Wittstein IS: Stress cardiomyopathy: A syndrome of catecholamine-mediated myocardial stunning? Cell Mol Neurobiol 2012; 32:847–57
4. Lu WH, Hsieh KS, Lu PJ, Wu YS, Ho WY, Lai CC, Wang JS, Ger LP, Hsiao M, Tseng CJ: Hexamethonium reverses the lethal cardiopulmonary damages in a rat model of brainstem lesions mimicking fatal enterovirus 71 encephalitis. Crit Care Med 2013; 41:1276–85
5. Nyquist P: Wet lungs and a battered brain stem: Can we stop one if we cannot stop the other? Crit Care Med 2013; 41:1373–4
6. Davison DL, Chawla LS, Selassie L, Tevar R, Junker C, Seneff MG: Neurogenic pulmonary edema: Successful treatment with IV phentolamine. Chest 2012; 141:793–5

7. Xia Y, Gong KZ, Xu M, Zhang YY, Guo JH, Song Y, Zhang P: Regulation of gap-junction protein connexin 43 by beta-adrenergic receptor stimulation in rat cardiomyocytes. Acta Pharmacol Sin 2009; 30:928–34
8. Inamasu J, Sugimoto K, Yamada Y, Ganaha T, Ito K, Watabe T, Hayashi T, Kato Y, Ozaki Y, Hirose Y: The role of catecholamines in the pathogenesis of neurogenic pulmonary edema associated with subarachnoid hemorrhage. Acta Neurochir (Wien) 2012; 154:2179–84; discussion 2184–5
9. Sugimoto K, Inamasu J, Hirose Y, Ganaha T, Ito K, Watabe T, Hayashi T, Kato Y, Ozaki Y, Hirose Y: The role of norepinephrine and estradiol in the pathogenesis of cardiac wall motion abnormality associated with subarachnoid hemorrhage. Stroke 2012; 43:1897–903
10. Annane D, Trabold F, Sharshar T, Jarrin I, Blanc AS, Raphael JC, Gajdos P: Inappropriate sympathetic activation at onset of septic shock: A spectral analysis approach. Am J Respir Crit Care Med 1999; 160:458–65
11. Le Manach Y, Collins GS, Ibanez C, Goarin JP, Coriat P, Gaudric J, Riou B, Landais P: Impact of perioperative bleeding on the protective effect of β-blockers during infrarenal aortic reconstruction. ANESTHESIOLOGY 2012; 117:1203–11
12. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, Orecchioni A, D'Egidio A, D'Ippoliti F, Raffone C, Venditti M, Guarracino F, Girardis M, Tritapepe L, Pietropaoli P, Mebazaa A, Singer M: Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: A randomized clinical trial. JAMA 2013; 310:1683–91

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

A. L. Parker's Broadside: Laughing "Gas" for Littleton



Arthur Linwood Parker, D.D.S. (1868–1917) was born in Lyman, in northwest New Hampshire. From about 1880 to 1894, Parker called Littleton, New Hampshire, his hometown. After marrying Sadie Putnam in 1892, Parker began relocating his dental practice to central New Hampshire, to Penacook, the northernmost village of the state capital, Concord. Brandishing Parker's D.D.S. at fellow Littletonians, this side of his Littleton/Penacook broadsheet touts that Parker treats "Nervous and Timid" patients. Around the time he released these broadsheets, Parker lost his first wife—the first of two tragedies to impact his practicing dentistry and specializing in "the administration of [laughing] gas." This broadsheet is part of the Wood Library-Museum's Ben Z. Swanson Collection.

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.