



# A new mechanism for diverticular diseases: aging-related vagal withdrawal

Anthony J. Yun<sup>a</sup>, Kimberly A. Bazar<sup>b,\*</sup>, Patrick Y. Lee<sup>a</sup>

<sup>a</sup> *Stanford University, USA*

<sup>b</sup> *Department of Dermatology, San Mateo Medical Center, 222 West, 39th Avenue,  
San Mateo, CA 94403, USA*

Received 19 June 2004; accepted 5 July 2004

---

**Summary** It is widely believed that diverticulosis, a common condition among the elderly, results from repeated colonic barotrauma related to low dietary fiber and low stool bulk. Recent evidence has challenged the dietary-barotrauma hypothesis. We propose an alternative hypothesis that diverticulosis may be attributable to colonic smooth muscle dysfunction that results from vagal attrition associated with aging. We previously proposed that broad aging-related attrition of autonomic nerves may unmask intrinsic sympathetic bias of end-organs, leading to the compendium of familiar conditions associated with senility. Unexplained cholinergic hypersensitivity and receptor over-expression in bowel affected by diverticulosis have recently been observed. These findings are highly suggestive of a compensatory response to loss of vagal innervation. The resulting autonomic dysregulation may induce bowel smooth muscle dysfunction, setting the stage for diverticula formation. Thus, diverticular bowel disease may be a manifestation of the aging-related systemic vagal withdrawal. The framework may extend to diverticula formation in other parts of the gastrointestinal and genitourinary tracts. For instance, aging-related vagal attrition may represent the common upstream mechanism that induces both sphincter of Oddi dysfunction and peri-ampullary duodenal diverticula, conditions that frequently occur together. Novel approaches to preventing and treating diverticular diseases by promoting vagal activity are proposed including the electrical or pharmacologic modulation of the autonomic system.

© 2004 Elsevier Ltd. All rights reserved.

---

## Hypothesis

It is generally believed that diverticulosis, a common malady of the elderly, reflects mucosal

herniation that results from repeated colonic barotrauma related to low dietary fiber and low stool bulk [1,2]. Recently, however, the dietary hypothesis has been challenged [3], and questions have been raised regarding the methods used to measure colonic intraluminal pressure in earlier studies [4]. We propose an alternative hypothesis that diverticulosis may be attributable to colonic smooth

---

\* Corresponding author. Address: 987 Addison Avenue, Palo Alto, CA 94301, USA. Tel.: +1 650 280 9116; fax: +1 650 325 5028.  
E-mail address: [kbazar@sbcglobal.net](mailto:kbazar@sbcglobal.net) (K.A. Bazar).

muscle dysfunction that results from vagal attrition associated with aging.

## Evidence for the hypothesis

We previously hypothesized that broad aging-related attrition of autonomic nerves may unmask intrinsic sympathetic bias of end-organs, leading to the compendium of familiar conditions associated with senility [5]. In this paper, we extend the concept to diverticular diseases. In the normal gastrointestinal tract, vagal activity is involved in the regulation of exocrine function, promotion of bowel motility, and initiation of feedback signals to the central nervous system. Vagal signal is carried through cholinergic and muscarinic pathways while sympathetic signal is carried through adrenergic pathways.

Various emerging evidence provides indirect support for the notion that vagal attrition may play a role in diverticular bowel disease. For instance, reduction of choline acetyltransferase activity in affected bowel has recently been noted [4]. Furthermore, the unexplained enhancement of acetylcholine sensitivity and over-expression of M3 receptors in the smooth muscle of affected bowel would be consistent with compensatory adaptation to reduced vagal nerve innervation [4,5]. Supporting the view of reduced vagal innervation is the observation that PGP 9-5 immunoreactivity is diminished in diverticular disease [4]. Reduction in PGP 9-5, a ubiquitin hydrolase present in axons or normal neural tissue, is generally seen in areas of neuronal degeneration [6,7]. The view that attrition of vagal innervation leads to end-organ vagal hypersensitivity may explain why baseline motility is normal in diverticular disease, but heightened colonic motility mimicking irritable bowel syndrome is seen post-prandially. Notably, the heightened smooth muscle contractions in diverticular disease have been attributed to cholinergic receptor overexpression, not excess vagal innervation [8]. In the setting of vagal attrition, dysfunctional bowel contractions are thought to contribute to gaps in tissue planes between muscle fibers, through which mucosal herniations are thought to occur [9]. That irritable bowel syndrome, another disease associated with vagal hypersensitivity and bowel hypermotility, is associated with diverticular disease is perhaps not surprising [10,11].

This collection of findings is suggestive of reduced vagal innervation, but does not explain why cholinergic innervation diminishes [12]. In our view, the vagal withdrawal of diverticulosis

may represent a specific local manifestation of the global withdrawal of vagal innervation from end-organs during aging, as was recently proposed [5]. This global phenomenon is likely an evolutionary maladaptation that has been unmasked by the rapid expansion of human lifespan during the last few centuries [5].

## Implications

Additional work is necessary to validate our hypothesis that age-related vagal withdrawal plays a role in colonic diverticular disease. A peculiarity that remains to be explained is the differential distributions of diverticulosis in the sigmoid colon among Caucasians and in the cecum among Asians [13,14]. Is there underlying variation of vagal function and age-related withdrawal that varies within an organ system, among different organ systems, and across populations?

The aforementioned data regarding the association of vagal impairment and diverticular disease is currently limited to colonic diverticulosis. Diverticular disease, however, can occur anywhere in the gastrointestinal tract. Examples include Zenker's diverticulum in the esophagus, duodenal diverticulum, and Meckel's diverticulum in the small bowel. Our explanatory model could also be extended to diverticula formation in areas outside of the bowel such as the urinary tract, biliary tract (choledochoceles), and bladder. We are not aware of any histologic, biochemical, or anatomic investigation examining vagal dysfunction in these types of diverticular diseases, leaving open the possibility that vagal attrition may play a role in these situations as well. Corroborating empirical evidence is needed to validate the notion that vagal attrition plays a role in these conditions.

In the case of periampullary duodenal diverticula (PAD), also called juxtapapillary duodenal diverticula, a physiologic argument could be made to support the notion that vagal dysfunction plays a role. PADs are thought to occur due to weakening of intestinal smooth muscle during aging, but the mechanism for the impaired smooth muscle function has not been explained [15]. Furthermore, a high correlation between sphincter of Oddi insufficiency and PAD has long been known but an explanation for this association has been elusive [16,17]. Proposed theories for the association include compression of the biliary tract by the diverticulum [18].

Based on our vagal attrition framework, we propose that aging-related vagal withdrawal may be the common upstream dysfunction that induces both sphincter insufficiency and smooth muscle

abnormalities in the adjacent duodenal wall leading to PAD formation. Vagal innervation is crucial for normal functioning of the sphincter of Oddi [19–21]. Furthermore, the duodenum and sphincter of Oddi have been shown to be regulated by a common neural circuit, and it is thought that this common pathway regulates both duodenal motility and sphincter of Oddi function [22]. The epidemiologic evidence suggests that PAD is indeed an under-recognized disease of aging. PAD is rare before age 40 and increases in prevalence with age [15]. Prevalence rates as high as 27% have been reported in patients undergoing gastrointestinal procedures and an autopsy series noted a prevalence rate of 23% [15]. Thus, PAD and the associated sphincter of Oddi dysfunction may represent yet another local example of a condition that arises as a result of global attrition of autonomic innervation during aging [5].

The model of aging-related vagal withdrawal accompanied by end-organ sympathetic bias and cholinergic hypersensitivity may have important implications for understanding diseases of aging outside of the bowel. Indeed, muscarinic hypersensitivity due to increased receptor density has been observed in cardiac autonomic denervation accompanying amyloidosis, a common disease of aging, as well as in pulmonary function following heart–lung transplantation [23,24]. Interestingly, despite the enhanced hypersensitivity of the muscarinic system of the heart following autonomic denervation, the adrenergic system does not become hypersensitive to catecholamines [23]. This dichotomous response to autonomic denervation lends further support to our previously proposed notion that end-organs are intrinsically sympathetic and that their central inhibition by the parasympathetic system can be seen as a form of regulatory hegemony which wanes with age-related vagal withdrawal [5].

Similar to other conditions that manifest abnormal autonomic balance [25,26], we propose that modulation of autonomic function, particularly those that reduce sympatho-vagal ratio through either pharmacologic or electrical means, may help prevent and treat diverticular diseases. Specific embodiments may include electrical modulation of the vagus nerve through medical devices such as pacers or homeopathic methods such as acupuncture. Pharmacologic reduction of end-organ sympathetic bias may be achieved using a wide variety of anti-adrenergic or pro-parasympathetic agents. Many anti-inflammatory, anti-coagulation, and neurohormonal agents may also have anti-adrenergic properties and may help prevent and treat conditions of abnormal autonomic balance such as diverticular diseases [25,26].

## References

- [1] Eastwood M. Colonic diverticula. *Proc Nutr Soc* 2003;62(1):31–6.
- [2] Mimura T, Emanuel A, Kamm MA. Pathophysiology of diverticular disease. *Best Pract Res Clin Gastroenterol* 2002;16(4):563–76.
- [3] Stollman N, Raskin JB. Diverticular disease of the colon. *Lancet* 2004;363(9409):631–9.
- [4] Golder M, Burleigh DE, Belai A et al. Smooth muscle cholinergic denervation hypersensitivity in diverticular disease. *Lancet* 2003;361(9373):1945–51.
- [5] Lee PY, Yun AJ, Bazar KA. Conditions of aging as manifestations of sympathetic bias unmasked by loss of parasympathetic function. *Med Hypotheses* 2004;62(6):868–70.
- [6] Li JC, Mi KH, Zhou JL, Busch LC, Kuhnel W. The development of colon innervation in trisomy 16 mice and hirschsprung's disease. *World J Gastroenterol* 2001;7:16–21.
- [7] Lin WM, Hsieh ST, Huang IT, Griffin JW, Chen WP. Ultrastructural localization and regulation of protein gene product 9.5. *Neuroreport* 1997;8:2999–3004.
- [8] Tomita R, Tanjoh K, Fujisaki S, Fukuzawa M. Physiological studies on nitric oxide in the right side of the colon of patients with diverticular disease. *Hepatogastroenterology* 1999;46:2839–44.
- [9] Smith AN. Colonic muscle in diverticular disease. *Clin Gastroenterol* 1986;15:917–35.
- [10] Chelimsky G, Chelimsky TC. Evaluation and treatment of autonomic disorders of the gastrointestinal tract. *Semin Neurol* 2003;23(4):453–8.
- [11] Otte JJ, Larsen L, Andersen JR. Irritable bowel syndrome and symptomatic diverticular disease: different diseases?. *Am J Gastroenterol* 1986;81:529–31.
- [12] Young-Fadok TM, Farrugia G. Cholinergic denervation in diverticular disease. *Lancet* 2003;361(373):1923–4.
- [13] Miura S, Kodaira S, Shatari T, Nishioka M, Hosoda Y, Hisa TK. Recent trends in diverticulosis of the right colon in Japan: retrospective review in a regional hospital. *Dis Colon Rectum* 2000;43(10):1383–9.
- [14] Yap I, Hoe J. A radiological survey of diverticulosis in Singapore. *Singapore Med J* 1991;32:218–20.
- [15] Lobo DN, Balfour TW, Iftikhar SY, Rowlands BJ. Periampullary diverticula and pancreaticobiliary disease. *Br J Surg* 1991;86(5):588–97.
- [16] Viceconte G, Viceconte GW, Bogliolo G. Endoscopic manometry of the sphincter of Oddi in patients with and without juxtaepapillary duodenal diverticula. *Scand J Gastroenterol* 1984;19(3):329–33.
- [17] Sugiyama M, Atomi Y. Periampullary diverticula cause pancreatobiliary reflux. *Scand J Gastroenterol* 2001;36(9):994–7.
- [18] Miyazaki S, Sakamoto T, Miyata M, Yamasaki Y, Yamasaki H, Kuwata K. Function of the sphincter of Oddi in patients with juxtaepapillary duodenal diverticula: evaluation by intraoperative biliary manometry under a duodenal pressure load. *World J Surg* 1995;19(2):307–12.
- [19] Talmage EK, Hillsley K, Kennedy AL, Mawe GM. Identification of the cholinergic neurons in guinea-pig sphincter of Odd ganglia. *J Auton Nerv Syst* 1997;64(1):12–8.
- [20] Harada T, Katsuragi T, Furukawa T. Release of acetylcholine mediated by cholecystokinin receptor from the guinea-pig sphincter of Oddi. *J Pharmacol Exp Ther* 1986;239(2):554–8.
- [21] Sarles JC, Awad R. Role of the autonomic nervous system in the rabbit sphincter of Oddi. *Surg Gastroenterol* 1984;3(2):41–6.

- [22] Kennedy AL, Saccone GT, Mawe GM. Direct neuronal interactions between the duodenum and the sphincter of Oddi. *Curr Gastroenterol Rep* 2000;2(2):104–11.
- [23] Delahaye N, Le Guludec D, Dinanian S et al. Myocardial receptor upregulation and normal response to isoproterenol in denervated hearts by familial amyloid polyneuropathy. *Circulation* 2001;104:2911–6.
- [24] Stretton CD, Mak JC, Belvisi MG, Yacoub MH, Barnes PJ. Cholinergic control of human airways in vitro following extrinsic denervation of the human respiratory tract by heart lung transplant. *Am Rev Respir Dis* 1990;142:1030–3.
- [25] Yun AJ, Lee PY, Bazar KA. Many diseases may reflect dysfunctions of autonomic balance attributable to evolutionary displacement. *Med Hypotheses* 2004;62(6): 847–51.
- [26] Yun AJ, Lee PY, Bazar KA. Modulation of autonomic balance by tumors and viruses. *Med Hypotheses* 2004;63(2): 344–51

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

