The Pressure's on: Finding the Cause of Diverticula Formation

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Diverticular disease of the colon is a common clinical condition affecting up to one-third of the population in developed countries, with the number of associated clinic visits and hospital admissions increasing. Symptomatic diverticulosis significantly reduces quality of life; furthermore, complications of diverticulitis are associated with a high mortality rate [1]. Among gastrointestinal diseases, diverticular disease consumes a large proportion of healthcare expenditures.

In order to prevent and effectively manage diverticular disease, it is important to find the cause of diverticula formation. A carefully executed and nicely illustrated study by Jaung et al. in this issue of *Digestive Diseases and Sciences* focussed on the contribution of excessive intraluminal pressure toward diverticulum formation [2]. High-resolution colonic manometry was executed in nine patients with asymptomatic diverticulosis. Emphasis was placed on the meal-induced low-frequency (2–6 cpm) cyclic motor pattern that usually has an amplitude of 10–30 mmHg [3]. The pressure waves within the cyclic motor pattern propagate over 8–27 cm [3], likely not in the order of 5–20 mm as indicated by Jaung et al. [2]. Jaung et al. did not find evidence for increased manometric pressures or increased colonic activity in the patients and concluded that pressure generated by the cyclic motor pattern was not contributing to diverticulum formation [2]. This appears to contrast with a study by Bassotti et al. who showed that this cyclic motor pattern was present more frequently in patients with diverticulosis, although this was measured in symptomatic patients [4]. Similar to the study by Jaung et al. [2] in the study by Bassotti et al., the amplitude of the pressure waves was low, 25–29 mmHg, also not different from controls [4].

One could question whether such propagating low-amplitude cyclic motor patterns are generating enough local pressure to evoke diverticula formation. The highest pressures

in the human colon are generated by high-amplitude propagating pressure waves (HAPWs or HAPCs) [5]. In the 4-h manometry study by Jaung et al., they were not observed in baseline conditions nor in response to a meal [2] in asymptomatic patients. This contrasts with a 24-h study by Bassotti et al. who found that patients with diverticular disease had on average twice as many HAPWs per 24 h compared to controls [4]. Bassotti et al. [4] found that the pressure amplitudes in patients were not different from controls, but some HAPWs propagated in orad direction which is unusual, suggested to be due to natural obstruction in the distal colon by “accentuation of segmentary contractions” [6]. Another contributing factor to retrograde propulsion was suggested to be abnormal pacemaker activity [6], which was later corroborated as a decrease in the density of the interstitial cells of Cajal (ICC) [4]. Future studies to evaluate the generation of HAPWs may employ bisacodyl to evoke HAPWs. Although bisacodyl is not an endogenous stimulus, the response to the drug is indistinguishable from naturally occurring HAPWs; hence, the mechanism by which bisacodyl generates HAPWs is most likely similar to that of naturally occurring HAPWs except for the initial stimulation [5]. This provocative stimulus is analogous to the testing of the deep tendon reflexes involving the spinal cord with a reflex hammer. Though the stimulus is not endogenous, important information is provided about reflex physiology or pathophysiology. The importance of testing for activity evoked by stimuli is that in patients with diverticulosis, baseline activities can be normal, as shown by Juang et al. [2] and Painter et al. [7], but when stimulated, the activity is exaggerated [7], consistent with the hypothesis of local hypersensitivity.

Although HAPWs generate high pressures, in adults, almost all HAPWs end orad to the sigmoid colon [5], a preferred site of diverticula formation. Myogenic control mechanisms dominate the orchestration of sigmoid colon activity. The ICC of the deep muscular plexus generate the rhythmic activity that is responsible for the low-frequency cyclic motor pattern that can be restricted to a single haustrum. Chen et al. showed haustral activity with persistent ICC-orchestrated rhythmicity associated with propulsive

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and segmental patterns (Fig. 1) [8]. The cyclic motor pattern is a cluster of propagating pressure waves that can change spontaneously into a segmentation motor pattern (Fig. 1); this likely occurs when the low-frequency cyclic motor pattern interacts with the recently documented high-frequency cyclic motor pattern at ~12 cpm [3, 9]. With the segmentation motor pattern, non-propagating rhythmic contractions can occur for hours [8]. These rhythmic contractions can generate high pressures when the haustrum is isolated by strong haustral boundary contractions at both sides of the haustrum, a phenomenon that Painter et al. observed in patients with sigmoid diverticula [7]. Using a combination of X-rays and colonic manometry (Fig. 1), they observed clusters of strong contractions at ~4 cpm, hence the low-frequency cyclic motor pattern, within the haustra (Fig. 1). After studying patients with diverticulosis using 24-h colonic manometry, Bassotti et al. also suggested that “it is possible that it could originate from a chronic accentuation of the haustral pattern as a result of hypermotility” [6]. Colonic segments harboring diverticula showed a significant increase in 2–3 cycles/min cyclic motor activities associated with pain [4]. Strong local pressures in patients with diverticulosis can also be

deduced from the figures presented in Jaung et al. [2] with amplitudes of ~75 mmHg estimated from the color scale provided.

Basic research has provided evidence of neurogenic impairment in patients with diverticulosis. In vitro studies of the electrical activities of tissues obtained from diverticular disease patients showed that in response to cholinergic stimulation, development of periodic bursts of action potentials normally associated with propulsive activity did not develop, favoring segmental contractile activity associated with low-frequency (average 4.6 cpm) slow-wave activity (Fig. 1) [10]. In addition, the myenteric plexus has been observed to be infiltrated with lymphocytes and eosinophils; a reduction of glial cells was noted as well as hypoganglionosis [4]. Loss of intramuscular ICC (ICC-IM) might reduce nitrergic innervation, and that, together with cholinergic denervation hypersensitivity, might be responsible for local increased excitation [4]. Genome-wide association studies have identified diverticulosis risk loci that contain genes involved in connective tissue integrity and intestinal motility, highlighting the importance of neuromuscular abnormalities in the development of diverticulosis [1]. Patients with connective tissue diseases such as Ehler–Danlos, Marfan’s, and

Fig. 1 Hastral activity in patients with diverticulosis and healthy subjects. **a** X-ray of the rectum (Rec) and sigmoid colon of a patient with diverticulosis. The manometry sensor (Man) was just oral to the rectosigmoid junction. The haustra had diverticula (Div). **b** The haustral boundaries were strongly contracted, isolating haustra where large rhythmic pressures at ~75 mmHg occurred at ~3 cpm. **c** The hypothesis is that high intrahaustral pressures, which develop due to the closed-loop configuration, facilitate the development of diverticula. **d**. Electrical (bar = 1.5 mV) and mechanical (bar = 0.5 mN) activity of a section of the musculature of a diverticular disease patient.

Here, cholinergic excitation caused strong isolated non-propagating activity in contrast to healthy tissue that would generate propulsive contractions. **e–g** Hastral activity in healthy subjects, recorded by high-resolution manometry. **e** Hastral boundary activity at 3 cpm. **f** Intrahaustral segmentation activity at ~4 cpm. **g** In the same subject as **f**, the segmentation activity synchronized into the low-frequency cyclic motor pattern that, when a simultaneous pressure wave occurred, reversed back into a segmentation pattern. Figures **a–c** are reproduced from [7] with permission. Figure **d** is reproduced from [10] and **e–g** from [8] with permission

Williams–Beuren syndrome have an early onset of extensive diverticulosis [1].

The hypothesis that excessive intraluminal pressure is a component of the formation of diverticula has a long history. Whether excessive haustral segmentation is the primary etiology will likely require prospective studies in patients in the period of their life when diverticula formation occurs, a period that may be characterized by excessive stimulation of the sigmoid colon myogenic activities with or without muscle weakness, since basal activities may still be normal as suggested by the studies of Jaung et al. [2] and Painter et al. [7]. We hope that detailed studies of colonic motility will lead to interventions aimed at reducing diverticula formation.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest of any kind.

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