Pathophysiological aspects of diverticular disease of colon and role of large bowel motility

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Abstract

Colonic diverticular disease (diverticulosis) is one of the most common gastrointestinal disorders in Western countries. This disorder is strictly related to aging and fibre intake, and still bears a discrete amount of morbidity. Numerous etiological co-factors have to date been implicated in the pathogenesis of the disease, yet the supporting evidence is still far from absolute. The present review considers the pathophysiology of colonic diverticular disease, with a special emphasis on factors related to abnormal colonic motility.

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INTRODUCTION

Diverticular disease of the colon (diverticulosis) is the most common disease affecting the large bowel in the Western world^[1]. This disease is correlated with the aging process and a low-fiber diet and bears a considerable amount of morbidity^[2]. The continuous aging process of the population also leads to an increase of this disease.

It is commonly thought that an altered motility of the large bowel may have a major pathophysiological role, even though it is probable that multiple factors (anatomic features intrinsic to the colon, alterations in colonic wall with aging, dietary fiber, motor dysfunction, abnormal intraluminal pressures, and possibly genetic influences) interact in ill-defined relationships to play a greater or lesser role in the genesis of colonic diverticul^[3,4].

This article will review the pathogenetic factors of colonic diverticular disease (diverticulosis), with an emphasis on those related to large bowel motility.

ANATOMIC FACTORS

Diverticula are usually found in the left (sigmoid, descending) colon on either mesenteric side of the antimesenteric teniae in Western countries^[5], and occur at weak points in the circular muscle layer, where the blood vessels supply the mucosa^[6], suggesting that increased intraluminal pressure might play a role in their formation. The presence of right-sided diverticula is conversely more frequently seen in Eastern populations^[7]. An impaired structure of the colonic wall has been described in patients with diverticular disease. In fact, both *in vitro*^[8] and *in vivo*^[9] studies showed that these patients displayed an increased colonic compliance in the affected segments. This

might be due to a pathological accentuation of the physiological differences among colonic segments^[10], that has been ascribed to qualitative than quantitative changes in collagen^[11], since the content of the latter remained unaltered, with respect to controls, in the entire colonic wall^[12] and in the muscle layers^[13]. However, the available studies measured colonic compliance by means of latex balloons that constitute a suboptimal method for this measurement. More precise studies with up to date systems (i.e., polyethylene bags, which intrinsic compliance is negligible) are needed. Colonic diverticula were also prevalent in young patients with connective tissue disease^[14,15].

Previous studies showed that a consistent anatomic finding in colonic diverticular disease was the presence of thickening of the bowel wall muscle layers^[16,17]. However, no evidence of hyperplasia or hypertrophy of the muscle cells has been found (although this finding has been challenged^[18]). There is an enormous increase in elastin deposition in the teniae, that leads to shortening of this layer with thickening of the circular muscle layer and produces the concertina-like folds in the inner muscle layer^[12,19]. This deformity (also called myochosis) would narrow the lumen, allowing muscle contractions to obliterate the lumen and divide the bowel into isolated segments^[4].

Unfortunately, available neurophysiopathological data are remarkably few in colonic diverticulosis. A study investigating the myenteric plexus in such patients was unable to demonstrate any morphological abnormality^[20]. Another more recent study showed that cholinergic nerves were dominant in the left-sided diverticular colon, and that a decreased action of non-adrenergic non-cholinergic nerves by nitric oxide might be related to the high intracolonic pressures by colonic segmentation observed in such portions of the viscus^[21]. Moreover, *in vitro* cholinergic stimulation of colons of patients with diverticular disease yielded increased low frequency and uncoordinated smooth muscle contractions in response to acetylcholine, compared with controls^[22].

AGING

Colonic diverticular disease showed a striking correlation with advancing age^[23], and it was estimated that 50 % of the Western population approximately 70 years of age were affected^[24], an important consequence of aging was that the properties of the colon wall changed with a decrease of the tensile strength^[25]. The reason of this decrease is unknown, but it might be related to an increased cross-linking of collagen fibrils with age, which also became smaller, more numerous and more tightly packed in the left colon^[9]. These changes seemed to be accentuated in diverticular disease^[26]. Moreover, since elastin deposition continued throughout life in all layers of the colonic wall^[27] (with predominance in the teniae in diverticular disease), the fibers lost some mechanical properties and became more distensible in diverticulosis^[28].

DIET

There is substantial evidences that colonic diverticulosis was related to civilization, industrialization, and a Western lifestyle and diet^[29]. Dietary factors, and in particular low fiber intake,

have been considered as main pathogenic factors^[30,31], as also shown by the observations that populations moving from rural to urban environments displayed an increased prevalence of the disease^[32], and that vegetarians had a lower incidence of diverticular disease of the colon^[33]. In addition, an interesting observation in rats showed that the animals whose mothers were fed on a fiber-deficient diet had an increased incidence of colonic diverticulosis^[34].

The “protective” action of dietary fiber would make the stools bulkier, thereby increasing the colon size and decreasing intraluminal pressures (since according to Laplace’s law, the pressure required to distend the wall is the greatest where the radius is small)^[35], and reducing colonic transit time^[36]. These hypotheses have been indirectly confirmed by the observations that typical African diets yielded rapid colonic transit times, bulkier stools and no need to strain^[37], whereas those of Europeans resulted in almost double colonic transit times^[38] and firmer and more viscous stools that increased intraluminal pressures and the need to strain. Of course, other dietary factors are likely to play a role in this area, as shown by the fact that a Western-type diet was implicated in the increased proline intake from the gut, that led to elastosis of the sigmoid colon^[39], and that the prevalence of right-sided diverticular disease displayed a strongly positive association with past meat consumption frequency^[40].

COLONIC MOTILITY

Abnormal intraluminal pressure and disordered colonic motility have been implicated as pathogenic factors in diverticulosis. The evidence for this belief (as discussed below) is far from absolute, however, there are several data suggesting that abnormal colonic motility may be considered as an important pathophysiological mechanism. It is worth noting that most studies on colonic motility and myoelectrical activity were biased by poor patient selection, small numbers of patients recruited, heterogeneity of clinical conditions, recording techniques (only the rectosigmoid or even rectal motor activity was often obtained) and duration of recording periods (at best, less than two hours, whereas colonic motility displayed wide and important fluctuations around-the-clock^[41]).

Concerning right-sided colonic diverticular disease, there is paucity of studies facing the motor aspects. Two investigations, featuring very brief recording periods, reported that patients with diverticulosis displayed higher motility indices with respect to controls, both basally and after pharmacologic stimulation^[42, 43]. An increased motor activity was also observed in the segment with diverticula with respect to the non affected sigmoid colon.

Looking at studies in patients with “traditional” diverticulosis, most manometric investigations, as already stated, were carried out in the rectum and (at best) very distal sigmoid area. Therefore, it was possible that the portion of the viscus harboring diverticula might have not been studied at all. This might justify the fact that increased pressures were documented^[44-47] or not found^[48-51] with respect to controls and in response to pharmacological stimulation. Similar contrasting results were reported from myoelectrical studies of the rectosigmoid area^[52, 53]. However, more recent studies, carried out in the true sigmoid and descending colon (and, therefore, investigating colonic segments actually bearing diverticula) are available, which showed an increased motor activity in such patients (both symptomatic and asymptomatic) with respect to controls^[54, 55]. This abnormal motility was reduced following surgery^[56]. More recently, we investigated colonic motility in patients with symptomatic uncomplicated diverticular disease, by means of a 24-hour manometric technique that allows studying most of the viscus, its daily

fluctuations^[57], and detection of the motor equivalents of mass movements, the so-called high-amplitude propagated contractions (HAPC)^[58]. With respect to controls, patients with diverticulosis displayed a significantly overall increase of daily motor activity, except in the transverse colon (the segment not involved by diverticula), and of propulsive activity^[59]. Interestingly, patients had several retropropagated HAPC (never observed in controls), and the motor activity of the affected segments, especially the sigmoid, was significantly higher than that of the unaffected ones (the transverse).

All the above observations seem to support a discrete role of colonic motility (with the probable concurrence of other factors) as a pathophysiological mechanism in diverticular disease. Colonic motility is influenced by the aging process, as shown by the decrease of HAPC frequency with age, whereas segmental contractile activity increases^[60]. Anatomical studies in experimental animal models showed that these changes might be related to aging of colonic smooth muscle^[61].

The muscle thickening observed in affected bowel segments was thought to be obstructive, and to contribute to the delayed transit of feces^[18]. Studies with intracolonic displacement tools suggested that an accentuation of segmentary motor activity (as observed in diverticular disease) might abolish oro-aboral progression of contents^[62], thereby facilitating retropropulsion and drying of the semiliquid fecal matter. Moreover, reverse peristalsis, as observed in animal studies, might be a general response to distal obstruction associated with a narrowed terminal colon segment^[63]. We have shown that a similar mechanism is present in diverticulosis, and this might have some pathophysiological relevance (for instance, a local nondominant pacemaker might take over in the “spastic” region, initiating an oral spreading of contractions along the less active proximal colonic segments).

CONCLUSIONS

Although many evidences suggest that colonic diverticular disease is related to low-residue diet, the scarce effectiveness of dietary manipulations^[64] and the complex relationships with other factors, among which abnormal colonic motility might play an important role, still make this disease a fascinating pathophysiological puzzle. Further studies are needed to understand the intrinsic mechanisms better and possibly, to give us useful insights for a better and more targeted therapeutic approach.

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