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FRONTIER

Problems with repairing gut sphincters malfunctions

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Abstract

Correcting a gut sphincter malfunction is a difficult problem. Because each sphincter has two opposite functions, that of closure and opening, repairing one there is a risk of damaging the other. Indeed, widening a narrow sphincter, such as lower esophageal sphincter (LES) and anal sphincter, may cause gastroesophageal reflux and fecal incontinence, respectively, whereas narrowing a wide sphincter, may cause a difficult transit. All the corrective treatments for difficult or retrograde transit concerning LES and anal sphincter with their unwanted consequences have been analyzed and discussed. To overcome the drawbacks of sphincter surgical repairs, researchers have devised devices capable of closing and opening the gut lumen, named artificial sphincters (ASs). Their function is based on various mechanisms, *e.g.*, hydraulic, magnetic, mechanical *etc*, operating through many complicated components, such as plastic cuffs, balloons, micropumps, micromotors, connecting tubes and wires, electromechanical clamps, rechargeable batteries, magnetic devices, elastic bands, *etc*. Unfortunately, these structures may facilitate the onset of infections and induce a local fibrotic reaction, which may cause device malfunctioning, whereas the compression of the gut wall to occlude the lumen may give rise to ischemia with erosions and other lesions. Some ASs are already being used in clinical practice, despite their considerable limits, while others are still at the research stage. In view of the adverse events of the ASs mentioned above, we considered applying bioengineering methods to analyze and resolve biomechanical and biological interaction problems with the aim to conceive and build efficient and safe biomimetic ASs.

Key Words: Sphincter; Artificial sphincter; Magnetic sphincter; Gastroesophageal sphincter; Anal sphincter; Gastroesophageal reflux; Fecal incontinence

Core Tip: Gut sphincter corrections are a difficult problem because each sphincter has two opposite functions, that of closure and opening; in repairing one, there is a risk of damaging the other, as demonstrated by the analysis of the literature on interventions for difficult transit concerning the lower esophageal sphincter and anal sphincter, as well as for gastroesophageal reflux and fecal incontinence. Furthermore, artificial sphincters (ASs) capable of closing and opening with various mechanisms, such as hydraulic, magnetic, *etc*, have suffered many complications, limiting their use in practice. Hence, it would be desirable to use computational bioengineering methods to create an efficient and safe AS.

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INTRODUCTION

Gut sphincters are a biological invention consisting of circular bundles of muscular fibers around the gut tube, which, by contracting and relaxing, close and open the lumen, playing an important role in regulating the content flux inside the esophageal-gastrointestinal tube.

There are five gut sphincters, but the ones whose dysfunction creates the highest number of problems, ranging from a straightforward symptom to a more or less severe disease, are lower esophageal sphincter (LES) and anal sphincter.

There are basically two malfunctions that can affect a sphincter: insufficient opening so that the lumen becomes too narrow or remains closed, giving rise to achalasia for LES and difficult evacuation for anal sphincter, and incomplete closure, so that the lumen remains more or less open, giving rise to gastro-esophageal reflux (GER) for LES and to fecal incontinence (FI) for the anal sphincter.

The correction of these disorders seems straightforward enough: widen what is too narrow and tighten what is too wide. This solution seemed like the proverbial egg of Columbus, but it creates structural problems in the sphincter. In fact, each sphincter has two opposite functions: one that allows the content to pass through it by opening its lumen, and the other to block the transit by closing its lumen.

However, it is almost impossible to restore one function without damaging the other, especially with surgical interventions. Furthermore, because all the interventions on one function impair the opposed dysfunction, the correction can never be perfect and, in general, the better the outcome of the correction of one function, the worse the side effect on the other one, and *vice versa*.

In practice, the artificial dilatation of a narrow LES and anal sphincter, both responsible for difficult transit, may lead to GER or FI, respectively. Conversely, the tightening of LES to prevent GER may lead to difficult esophageal transit with dysphagia, and when squeezing the anal canal to repair a FI, a difficult evacuation ensues.

These statements are corroborated by the analysis of the published studies concerning sphincter impairments corrections. However, the research for a solution to this problem has progressed with the creation of devices that replicate the functions of the biological sphincters, named artificial sphincters (ASs). Unfortunately, as will be discussed later, these devices have turned out not to be a definitive solution and, instead, have represented a new source of problems.

To clearly describe the evolution of the problem of repairing sphincter malfunction, this article has been subdivided into three parts: Past, Present and Future (Figure 1). These parts are not rigidly compartmentalized and do not merely reflect a temporal trend but consider the evolution of new ideas to address the problem. The term "Past" does not mean that a procedure or a device has been superseded or is obsolete, but is considered to be based on an old principle, which nonetheless can still be used successfully in some cases.

PART 1 (THE PAST)

The list of malfunctioning sphincters with their respective repairs and unwanted consequences is summarized in Table 1.

Widening a sphincter that is too narrow

LES achalasia: The artificial enlargement of an achalasic and spastic LES obtained with laparoscopic Heller's myotomy (LHM) is followed by dysphagia relief, but also by GER[1]. Therefore, it is necessary to perform an anti-reflux measure such as a partial fundoplication; however, this often does not completely prevent GER[2].

Peroral esophageal myotomy for achalasia seems to be associated with better dysphagia improvement than LHM[3] and pneumatic dilation (PD)[4], but it is followed by a higher postoperative GER, so that at 5-year follow-up, the patients showed reflux esophagitis in 33% of cases *vs* 13% after PD[5]. The latter, on the other hand, is similar to LHM with regard to postoperative GER[6].

The intra-sphincterial injection of botulinum neurotoxin (Botox) to decrease LES pressure in achalasia is associated with low GER, but the improvement of dysphagia is low and only lasts from 6 months to 12 months[7].

The reflux problem does not arise when treating achalasia with nifedipine or isosorbide dinitrate before meals, which temporarily relax the LES[8,9]. In fact, this effect only lasts 1-2 h after meal, after which the sphincter returns to close as previously. The entity of relaxation was similar to that obtained after esophageal PD[10], but this treatment is unsuitable

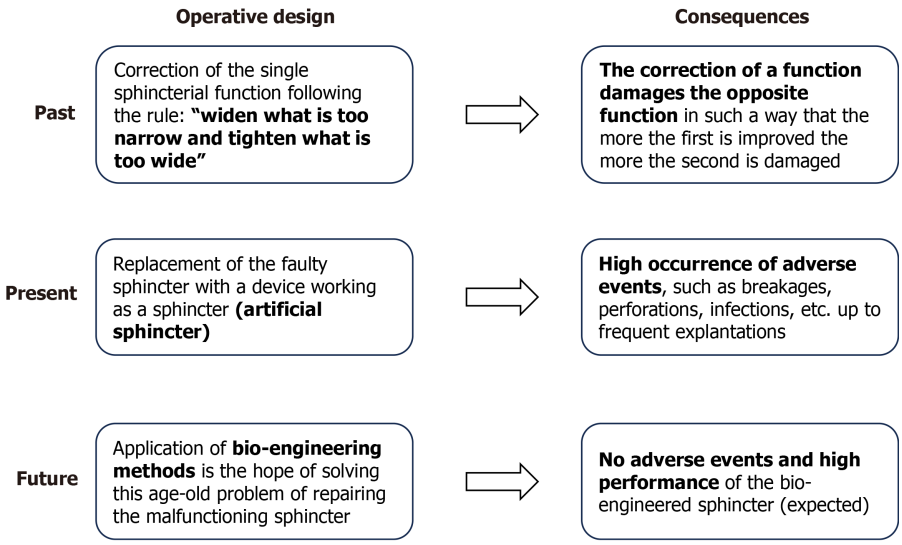

Figure 1 Essential contents of the three parts of the manuscript (Past, Present, and Future) are summarized to explain the evolution of the operative methods utilized to address the problem of the faulty sphincter performance. The investigators started by repairing only one sphincterial function, but the consequences not always positive pushed them to the creation of artificial sphincters, which turned out to be a source of further problems, thus arriving to the conclusion that only the bioengineering methods represent the hope to create in the future safe and efficient sphincters.

for prolonged time and is not proper for everyone[11].

Anal sphincter opening impairment: Regarding the outlet obstruction due to an achalasic, overactive or spastic anal sphincter, which plays a central role in the pathogenesis of anal fissure, anal pain and constipation, the surgical treatment with internal sphincterotomy[12] can be associated with a more or less high rate of FI[13], unlike non-surgical treatments [14]. However, topical glyceryl trinitrate, or calcium channel antagonists, and botulinum toxin injection[15,16] are less effective on anal transit. Nevertheless, also the use of botulinum toxin in patients with difficult anal transit for internal sphincter achalasia[17] may be followed by mild FI[18,19].

Tightening a sphincter that stays open

Gastroesophageal reflux: The surgical treatment of GER essentially consists of narrowing the distal esophageal lumen to limit the retrograde flux from the stomach to the esophagus by means of various procedures. Among the latest ones, laparoscopic and endoscopic fundoplications stand out, followed by the gastro-esophageal junction (GEJ) cicatricial stenosis, GEJ band ligation and deployment of bulking agents at LES level.

Laparoscopic Nissen fundoplication (LNF) with a 360° wrap compressing the abdominal esophagus is considered the gold standard of GER surgical treatments, being highly effective in preventing GER with an 80% success rate at 20-year follow-up[20]. However, it is burdened by difficult esophago-gastric transit, causing more or less severe dysphagia. Consequently, two partial fundoplications have been devised: posterior and anterior. The posterior fundoplication by Toupet[21] obtained a significant decrease in postoperative dysphagia with respect to LNF, testified by faster scintigraphic bolus propagation[22] with no significant worsening in esophageal acid exposure, while also the anterior fundoplication by Dor[23] obtained similar results.

The problem of GER resistant to PPI seemed to have been solved, but driven by the intention to avoid surgery, endoscopists strove to realize the fundoplication endoscopically using special sewing machines. The endoscopic incisionless fundoplication (TIF)[24] was conceived with the aim of restoring the integrity of the angle of His, miming a Toupet fundoplication by means of an endoscopic sewing machine. This can place multiple stitches connecting the lower esophageal wall with that of the opposite gastric fundus. However, compared to LNF, the results showed a higher probability of increasing the percent time at pH < 4 in the distal esophagus, while dysphagia was still present, albeit less severe and frequent[25].

The same intervention realized with the EsophyX device was significantly less effective in reducing acid reflux parameters than LNF[26], but the postoperative dysphagia was greatly improved[27]. Similarly, other esophageal fundoplications, obtained with different endoscopic devices such as Ultrasonic surgical endostapler Medigus[28,29], Plicator instrument[30], NDO plicator[31], GERDx device[32] and Endocinch[33], showed limited effectiveness in reducing acid reflux parameters, associated with an unexpectedly high improvement in reflux symptom score with scarce dysphagia[34-38].

The Stretta® system[39], an esophageal anti-reflux treatment based on non-ablative radiofrequency application on LES, improved the acid symptom score, despite a not proportioned improvement in esophageal acid exposure[40] without inducing dysphagia. This improvement in reflux symptoms, even with persistence of GER, could be due to decreased visceral sensitivity[41].

Perhaps the discrepancy between occurrence of GER and symptoms described after the endoscopic fundoplications could be caused by the same phenomenon of esophageal hyposensitivity. It would be interesting to perform the Bernstein

Table 1 List of malfunctions of sphincters with their respective repairing interventions followed by positive results and negative consequences; The table proves the correctness of the statement that repairing one function of a sphincter , the other remains more or less damaged

Sphincter malfunction	Repair of sphincter malfunction	Function improvement[1]	Damage of the opposite function[1]
		Dysphagia	Gastro-esophageal reflux
LES achalasia	LHM[1,2]	++++	++++
	POEM[3]	++++	+++
	Pneumatic dilation[5]	+++	+++
	Botox[7]	++	++
	Nifedipine and isosorbide dinitrate	+++ (transitory)	/
		Transit improvement	Fecal incontinence
Anal sphincter opening impairment	Internal sphincterotomy[12]	++++	++/+++
	GTN and calcium channel antagonists (topical)[15]	++	+
	Botulinum toxin injection[16]	++	+
		Ger prevention	Dysphagia
Gastro-esophageal reflux	LNF[20]	++++	++++
	PF, by Toupet[21]	++++	+++
	AF by Dor[23]	++++	+++
	TIF[24] (Esophyx[26], MUSE[28,29], Plicator instrument[30], NDO Plicator[31], GERDx device [32] and Endocinch[33])	++	+/++
	Stretta® system[39]	++	+
	Mucosal resection[42,43]	+++	+++
	Mucosal ablation[44]	+++	+++
	Band ligation[45] and clip-band ligation[46]	+++	+++
		FI prevention	Transit impairment
Fecal incontinence	Anal sphincter encirclement with meshes[47,48]	+	+
	Infiltrations with bio-compatible materials[49]	+	+
	Sphinkeeper[50]	+++	+++
	Gracilis muscle transplant[51,52]	+++	+++

[1]The level of improvement and that of damage vary from ++++ (high) to + (low). AF: Anterior fundoplication; Botox: Botulinum neurotoxin; FI: Fecal incontinence; GTN: Glyceryl trinitrate; LES: Lower esophageal sphincter; LHM: Laparoscopic Heller's myotomy; LNF: Laparoscopic Nissen fundoplication; MUSE: Ultrasonic surgical endostapler Medigus; PF: Posterior fundoplication; POEM: Peroral esophageal myotomy; TIF: Endoscopic incisionless fundoplication.

acid perfusion test in these cases.

The persistence of GER after these operations may be due to the fact that these esophageal fundoplications offer a scarce obstacle through the GEJ, which on the one hand, decreases the occurrence of dysphagia, but on the other, does not hinder the retrograde flux of acid in a sufficiently efficacious manner.

Furthermore, some investigators, always in search of new esophageal anti-reflux solutions, excogitated interventions aimed at blocking the retrograde gastro-esophageal flux of acid by narrowing the distal esophageal lumen. They create a cicatricial stenosis in the distal esophagus by performing a mucosal resection[42,43] or mucosal ablation[44]. This procedure has obtained good results regarding GER, but, as could be expected, was followed by dysphagia that sometimes requires balloon dilation.

Band ligation[45] and clip-band ligation[46] techniques, which consist of placing one or more rubber bands at GEJ level, also aim to reduce the width of the GEJ lumen for decreasing GER. However, they are followed by dysphagia in 25% of cases.

Other techniques aimed at decreasing the diameter of the GEJ lumen by means of injection or deployment of inert or bulking agents as Enteryx and Gatekeeper are seldom used as they are deemed unsatisfactory, as well as superficial plications of tissue at GEJ, whereas the Angelkich collar has been definitively abandoned. Therefore, it is not worth going into too much depth about them.

Fecal incontinence: FI has been addressed by narrowing the anal canal lumen by means of AS encirclement with meshes [47,48] or infiltrations with biocompatible materials (autologous fat, collagen, silicone, Durasphere or synthetic gel, *etc*) [49]. However, the results have proven unsatisfactory, as they were ineffective or not durable, often requiring subsequent interventions, and were the cause of difficult anal transit.

On the contrary, deployment around the anal sphincter of a series of self-expandable solid implants, named Sphinkeeper, has led to a short-term functional improvement even in severe forms of FI. However, over 25% of patients have complained of obstructed defecation, whereas implant migration was a fairly common occurrence[50].

Finally, the gracilis muscle transplant[51,52], albeit effective and durable, shows evacuation difficulties in 25% of patients, high morbidity, and involves a complicated procedure.

Comment to part 1

There is no perfect solution for repairing sphincter function: All of the attempts that have been made over the years to repair sphincters, with some satisfactory results, have confirmed the initial axiom that when repairing one function of the sphincter, the other inevitably gets damaged.

Some of the interventions described above are still used successfully, especially those for widening a sphincter that is too narrow, such as sphincterotomy of LES and anal sphincter.

With regard to the techniques to prevent GER, patients often prefer endoscopic fundoplications because of the paucity of reflux symptoms and dysphagia and to avoid surgery. The doctors often honor their wishes, even though there is insufficient evidence to determine the safety and efficacy of these endoscopic procedures[34] and no consensus exists in the current clinical guidelines for them[37]. GER prevention by means of greater or lesser tightening of the distal esophagus is followed by a more or less severe dysphagia. Thus, it is necessary to carefully evaluate the functionality of esophageal peristalsis before the intervention to choose the most suitable solution to avoid a subsequent severe dysphagia.

Considering the operations that create a cicatricial stenosis of the distal esophagus, it is peculiar that, to counteract the reflux, someone should resort to a complication of the reflux, which we generally try to avoid with anti-reflux measures.

The interventions of anal canal narrowing for FI are rarely used and only in cases of mild FI, being subjected to the above listed drawbacks. More effective interventions are instead used in severe cases. Sphinkeeper, on the other hand, has been used even in severe FI with short-term functional improvement, despite the frequent occurrence of implant migration and difficult evacuation[50].

PART 2 (THE PRESENT)

Creating an artificial sphincter.

As explained at the beginning, a basic defect of all these simplistic principles of sphincter repairs, defined by the axiom "widen what is too narrow and tighten what is too wide", is the lack of adaptation of the repair to the requirements of the moment. If you close a passage, whether cardial or anal, it stays stably closed and no longer opens, whereas if you open the passage, it always stays open, contrasting the opposite closing function.

The partial failure of these sphincter corrections has pushed investigators to create devices replicating the functions of the biological sphincters, which consist in a continuous closure with opening when required. This kind of device is named artificial sphincter (AS). A list of the operative modes utilized by the ASs is in Table 2.

The occlusion of the sphincter is in general realized with an external compression of its wall in different modalities, unilateral, bilateral (clamping) or circumferential (annular). The means of compression can be different, *i.e.* hydraulic, magnetic, mechanical, exploiting the properties of special materials, *etc* and by means of various expedients.

The opening can be obtained with a mechanism manually activated by the patients alerted by their own sensations or by sensors that inform them of the need to open it, while in other cases the opening may take place automatically, induced by a fixed increase in endoluminal pressure.

The hydraulic way

Sphincter occlusion is obtained and maintained by a system of fluid-filled cuffs that compress the gut at the level of the sphincter or just above it. To obtain the occlusion, the fluid, aspirated from a reservoir balloon, is pushed by a pump, activated by manual squeezing or by an electric micropump, into the compressing cuff, whereas a manual valve or two-way pump decreases the cuff pressure, allowing the lumen to open and the content to transit. This system has been exploited only for preventing FI and has never been applied to LES for preventing GER.

The first hydraulic closing mechanism for the anal canal was experimented by Christiansen and Sparsø[53], who modified the Acticon™ Neosphincter (AMS) 800 artificial urinary sphincter for this purpose. It essentially consisted of three parts: a fluid-filled cuff around the anal canal, a pressure regulating balloon reservoir and a manual pump, placed in the scrotum or in a big lip, used for inflating the cuff, while a valve serves to induce cuff deflation, as required for defecation. This system was implanted in 10 patients and, after 6 months follow-up, showed excellent results in 5, good ones in 3, and acceptable ones in 2, in whom, however, the cuff obstructed defecation. This AS was considered only an

Table 2 List of different operating modes utilized for the artificial sphincters with the indication of the sphincter to replace

Operative strategies for artificial sphincters function	Sphincter replaced
Hydraulic	
Acticon™ neosphincter[54]	Anal sphincter
Prosthetic anal system[56,57]	Anal sphincter
Artificial anal band, alias soft anal band or AMI artificial anal sphincter[58]	Anal sphincter
German artificial sphincter system[59,60]	Anal sphincter
Magnetic	
Magnetic collar LINX[62]	LES
Magnetic collar FENIX[63]	Anal sphincter
Two-plaques magnetic system[61]	LES
Two-plaques magnetic system	Anal sphincter
A mixed bag of strategies	
Artificial anal sphincter using a shape memory alloy[80,81]	Anal sphincter
Puborectalis-like artificial anal sphincter[84]	Anal sphincter
Internal artificial anal sphincter[86]	Anal sphincter
Artificial anal sphincter based on a novel clamping mechanism[87]	Anal sphincter
Artificial anal sphincter system[88]	Anal sphincter

LES: Lower esophageal sphincter.

alternative to colostomy.

On the contrary, the AMS was tested with a multicenter study by Wong *et al*[54] and showed a long-term successful outcome in 85% of patients and an intention-to-treat success rate of 53%. Like the device by Christiansen and Sparsø[53], it is based on a fluid-filled cuff, which compresses the anal canal annularly with the aid of a manually activated pump, keeping the passage continuously closed, whereas a manual valve can decompress the cuff, enabling fecal transit. However, the implantation procedure is difficult and the device often gives rise to more or less severe complications, requiring surgical revision in 46%-50% of the cases, the majority of which are due to infections (25%-40%), while in 37% of cases it was explanted[55]. For these reasons, it is reserved for the most severe cases.

The prosthetic anal system[56] is composed of a fluid-inflatable linear cuff placed against a gel-filled cuff around the anorectal junction, which, once inflated induces the bending of the latter, closing the transit at a low pressure. Manual deflation of the cuff allows for the passage of feces with a lumen diameter of about 22.5 mm. At a median follow-up of 59 months, 9 of 12 patients with severe FI showed continence, whereas it had been removed in three patients. There was no device-related infection after the initial operation, no device erosion and no clinical or histological evidence of gastrointestinal ischemia, thanks to the low operating pressure due to the bending mechanism[57]. It only caused constipation.

The AMI Artificial Anal Band, also called Soft Anal Band or Artificial Anal Sphincter (AAS)[58] consists of a subcutaneous balloon reservoir that fills the liquid under pressure into the liquid-filled band to close the sphincter when manually squeezed, whereas by pressing a subcutaneous valve, the band is emptied to allow for defecation. This device was tested in 43 patients with a 3-month follow-up and considering the high rates of complications (48.8%), revisions (32.6%) and explantations (21%), the authors[58] concluded that it was the last resort method to avoid a stoma.

The German Artificial Sphincter System (GASS)[59,60] comprises a support ring placed around the anorectal junction, which includes a fluid reservoir on the outer side, and an occlusive cuff on the inner side. The cuffs made in polyurethane are controlled by an integrated bidirectional micropump/valve unit with a remote-controlled rechargeable battery. It has been tested in animals only but yielding promising results, being able to restore continence for liquids and solids.

The magnetic way

An important forward step has been achieved with the exploitation of magnetic force to create a sphincter with some of the characteristics of the biological ones. I conceived this idea by observing the realization of gastrointestinal anastomoses with a couple of small magnetic disks. These disks, once applied face-to-face inside the lumens of two adjacent intestinal loops, attracted each other and caused necrosis of the compressed walls to generate an anastomosis between the two adjacent loops. I thought that a pair of magnets with a less powerful attraction force placed face-to-face outside the opposite walls of a sphincter, could close the sphincter lumen by attracting each other, detaching when the intraluminal pressure exceeds the force of attraction, and adhering again when the intraluminal pressure decreases, closing the lumen again. This pair of magnetic plaques must be considered the first magnetic sphincter (MS). So, in July 2003 I sent a

manuscript to the *Journal of Biomechanics* describing the bench experiment in which the working mechanism of the two magnetic plaques was clearly demonstrated. After various time-consuming vicissitudes, which I could recount on request, the manuscript was finally published in 2006[61].

In the meantime, TORAX Medical, Inc. Share View, MN, United States produced a kind of MS to prevent GER, named: LINX, MS augmentation, commonly called "magnetic collar", which was experimented for the first time in 2008[62]. The same company also produced a MS for the anal canal to prevent FI, named FENIX, a continence restoration system, working with the same mechanism as LINX. The FENIX MS was tested in clinical practice for the first time in 2010[63], but in 2020 the same company suspended its sales and clinical studies. Currently, however, the only kind of MS in production, now made by Ethicon LLC, Somerville, NJ, United States, a part of J & J, is the "magnetic collar" LINX for GER prevention.

This kind of MS[64] works like the one in my experiment, but in a more sophisticated way. It consists of a series of titanium beads with magnetic cores, connected with a flexible titanium wire in the form of a collar, along which they can slide one against the other, being attracted by their magnetic force. This "magnetic collar" is surgically positioned around the abdominal esophagus or the anal canal, which in this manner are circularly compressed and closed. The increase in intraluminal pressure moves the beads away along the wire, widening the collar so that the lumen opens, thus enabling the content transit, after which the endoluminal pressure decreases and the collar tightens again, closing the lumen.

The outcomes of LINX MS are comparable to those of Nissen fundoplication[65], whereas FENIX MS did not show similar-satisfactory results[66]. Both the MSs may be subjected to adverse events: The LINX "magnetic collar" can present dysphagia, recurrence of GER, erosions of the gut wall and protrusion into the visceral lumen, requiring explantation [67], whereas in the period in which it was marketed, the FENIX device presented constipation, fecal obstruction, recurrence of incontinence, erosions, bleeding, penetration into the rectal wall up to explantation or spontaneous expulsion in some cases[68].

The complications are essentially due to the fact that, when designing the device, no account was taken of the biological reactions of the living tissues. The first problem is represented by a fibrotic reaction of the surrounding tissues, which encapsulates the device and might interfere with the back-and-forth movements of the magnetic beads[69,70], possibly causing difficult transit with dysphagia or reflux relapse. Furthermore, the continuous compression, exerted on the biologic tissues of the abdominal esophagus wall by the "magnetic collar", which, being metallic, has a certain weight, and sometimes is too tight, may, in some cases, cause a local ischemia, leading to erosions and even perforations. However, even if the functional block of the collar by fibrosis occurs, its anti-reflux activity could continue whenever the "Angelchik effect" comes into play. The "notorious" Angelchik prosthesis[71] consisted of a silicone collar, placed around the GEJ to prevent GER through its "padding action", due to its weight, against the posterior wall of the abdominal esophagus, which creates a barrier to GER[72] as effective as that of Nissen fundoplication[73]. However, it also caused severe dysphagia[74], erosions and perforations[75] to the extent that it was shelved after more than 10 years. Given the similarity of the two collars, it could be hypothesized that the "magnetic collar" could also exert a "padding action" similar to that of the Angelchick collar.

On the contrary, the "two-plaques magnetic system", directly derived from the experiment described in the first publication[61], presents structural and functional characteristics, suggesting fewer complications and a sphincter capacity better than the magnetic collar.

With regard to GER prevention, the two magnetic plaques applied to the esophageal wall at the LES level on its opposite sides, attracting each other, compress the lumen up to its occlusion, but detach themselves following the arrival of peristalsis pushing the bolus, after which they return to close the lumen, attracting each other again. The plaques may be surgically applied to the LES wall or, preferably, inserted endoscopically under the mucosa[76] or into subadventitial tunnels at the level of LES with the system of Dobashi *et al*[77]. As they are separated by the esophageal lumen, the fibrosis around them cannot impair their movements of attachment and detachment, but can contribute to their fixation to the wall.

With regard to FI prevention, anal canal occlusion may be obtained by inserting the plaques on the opposite sides of the anal canal wall, on the antero-posterior and longitudinal planes, between the external and internal muscle bundles or externally to them, with the opposite polarities face to face to attract each other, thus clamping the anal canal like pliers [78]. The increase of the endoluminal pressure induced by defecation easily detaches the plaques, opening the lumen and allowing the passage of stool, after which they adhere again, closing the lumen. To obtain a stable fixation of the plaques coated with a biocompatible material, the plaques can be fitted with holes for stitches, hooks, *etc* in addition to the fixing effect of the local fibrosis.

This "two-plaques magnetic system", although tested only in animals "*ex vivo*", allows one to envisage many advantages as opposed to the "magnetic collar".

In fact, an analysis on the effectiveness of the occlusion methods performed by Marziale *et al*[79] showed that the clamping method, as that of the two plaques, was up to 35% more efficient than the circumferential one, which is that of the "magnetic collar", using the same sealing pressure.

Furthermore, there is the possibility to choose not only the shape and dimensions of the plaques, but also their magnetic force for an appropriate occlusion pressure. In fact, it would be possible, particularly for the FI, to select magnets with different attraction forces on the basis of a simple measurement of the endoanal pressure by means of a manometric probe, not only prior to, but also during magnet implantation. This allows one to choose an endoluminal pressure suitable to block the transit, which must neither be too low or too high, thus avoiding the risk of incontinence or ischemia of the compressed tissues, respectively. This would be an important step toward a "customization" of the devices, as the thickness of the anal wall between the plaques "*in situ*" is different from one patient to another.

In addition, this system should allow a surgical procedure for implanting the plaques outside the abdominal cavity, thereby avoiding the risk of severe infections.

Finally, the magnetic plaques should be less costly than the "magnetic collar".

A mixed bag of ways

This is a series of ASs that perform their closing-opening function with disparate operating mechanisms: by exploiting the physical properties of a special alloy, by using a clamping mechanism similar to the continence action of the puborectalis muscle and by other kinds of clamping, activated in different ways. None of these ASs is designed to prevent GER, but only FI.

The AAS using a Shape Memory Alloy (AAS-SMA)[80,81] is based on a metallic alloy that reversibly increases its volume when heated by an electric current. The lumen occlusion is obtained with two stick-shaped plaques glued at their extremities, which sandwich the intestine with a pressure of about 40 mmHg. When heated with an electric current at 55°C, the plaques tend to lengthen, but if they are prevented from elongating, they detach themselves in the center forming an ogival gap, which relieves the pressure on the intestine, thereby allowing transit. However the device may cause burns and infections in animals, where it was experimented[80,81], so it is not ready for clinical practice. Wang *et al* [82,83], however, experimented a novel AAS-SMA on pig intestine with various thicknesses and demonstrated that it may occlude the lumen without excessive pressure, preventing ischemic necrosis of the biologic tissues.

The puborectalis-like AAS (PAAS)[84] clamps and releases the anorectal tract by means of a rotatable arm driven by a micro-motor. The device consists of three rings: the two located above and below are fixed full rings, while the middle one is a rotating half ring controlled by a rechargeable micro-motor. The latter ring continuously clamps the anorectal tract and releases it when a sensor informs the patient of the need to defecate. However, the duration of the device in animals is unsatisfactory for clinical application[85].

The internal AAS (IASS)[86] differs from the above AS only because it has a more reliable sensor technology, as the pressure sensors are located in the inner wall of the rings.

The AAS based on a Novel Clamping Mechanism (AAS-NCM)[87] consists of a closed three-ring unit with two rotating shafts, driven by a micro-motor. Each ring is fixed by a pin at one end, while it is connected to two rotating shafts at the other end. The mini-motor transmits the force to two rotating shafts through a reducer and with a pair of gears that serves to rotate the two shafts. In this way, the clamping unit can perform the actions of clamping and relaxing. The micro-motor is powered by a transcutaneous energy transfer system through a receiving coil with a magnetic core. Preliminary tests have been conducted only "*in vitro*", which have positively verified the safety and reliability of the system[87].

The AAS System (AASS)[88] includes three systems to block and unlock the anal canal: (1) A set of fluid-filled cuffs[89] operated with a micro-pump equipped with a motor gear[88]; (2) A mechanical clamp unit with two hinged metal plates that compress the anal canal controlled by an electromagnet[90]; and (3) An elastic scaling cuff operated by a micro-motor with a remote control and sensors that advise the patient to defecate[91]. This system functions in animals, but for a short time, having been blocked by a fibrous reaction, and has never been trialed in patients.

Moreover, there are new alternative principles for the operations of ASs, which have not yet been exploited, but may be used for designing future ASs: The Electro-thermal actuators[92], the embedded pneumatic networks[93], the ionic electroactive polymers[94], and the dielectric elastomer actuators[95]. In addition, there are the dielectric electro-active polymer actuators, which exhibit a change in size or shape when stimulated by an electric field, displaying interesting versatility, response time, and reaction forces with low energy consumption, which would be very useful for a sensory feed-back, as proposed by Fattorini *et al*[96]. Finally, there is also a new Ferroelectric polymer nanocomposite[97] in the form of soft matter, highly effective in converting electrical energy into mechanical force with very low energy consumption, which would be ideal as an actuator for ASs.

Comment to part 2

Replacing the faulty sphincter with AS sometimes is an even worse attempt than repair: The overview of the above-described ASs is not encouraging in view of the clinical practice. Out of a total of thirteen devices developed only one is clinically available for GER, that is the MS LINX, whereas for FI only three with hydraulic systems, namely the Acticon™ Neosphincter, the Prostetic Anal Sphincter and the Artificial Anal Band are utilizable. The other MS, FENIX, was suspended in its sales and clinical studies by the manufacturer in 2020. The GASS, the AAS-SMA and the PAAS have only been tested in animals "*in vivo*", whereas the Two-plaque magnetic system for GER and FI were only tested in animals "*ex vivo*". The remaining ASs, which are the AASNCM, the IASS and the AASS, have only been tested "*in vitro*" or were simply conceived.

In conclusion, the ASs used in clinical practice for GER are the MS LINX and for FI, those based on hydraulic mechanisms. The latter ones, however, are used in the most severe cases when other less invasive systems and sacral nerve stimulation have failed. In fact, these ASs are affected by many complications, such as infections, postoperative pain, device malfunction and lesions of the surrounding tissues, so that the removal rate of these ASs reached 40% of implants, where 51% of those are due to malfunction and 56% due to infections. However, these values are much lower for MS-LINX for GER[88].

These problems are especially due to the local biological reaction of the organism, which tends to expel or incorporate the AS on par with a foreign body, often causing malfunctioning of moving tools. Also, the continuous and at times excessive compression on the gut wall to obtain an occlusion of the lumen may cause ischemia, erosions and other lesions. Furthermore, the numerous and complex components of these ASs could facilitate the onset of infections in the abdominal cavity. Finally, the fact that ASs with manually controlled systems are mostly used by elderly patients with limited fine motor skills and force generation should also be considered, so that, even when correctly activated, the slow time taken to open and close the AS represents another downside.

At this point fecal incontinence demands for help, being prevented less satisfactorily. Considering the above-described defects of the ASs for FI and waiting for a presumably long time for the next generation of safe and effective ASs, I would like to advocate an old AS previously described: the Two-plaque magnetic system for FI. It potentially possesses most of the requisites of a bio-mimetic sphincter, as previously explained in detail. It closes and opens the anal canal automatically without many components as the other ASs, and it can be custom-tailored in shape, size and force of attraction, as the occlusion pressure can be accurately measured during its insertion to choose the optimal one. This AS is easy enough to insert into the perianal site outside the abdominal cavity, thus avoiding the risk of severe infections in the abdominal cavity itself. Finally, the device should have a comparatively low cost. It has passed the "*ex vivo*" tests and awaits the "*in vivo*" ones, and I hope there are surgeons willing to venture down this new path, which in my opinion should be fruitful.

PART 3 (THE FUTURE)

Bioengineering approach that is"*Spes ultima dea*" - ancient Latin saying, that translates as: "Hope is last goddess" (to pray to).

The large number of various ASs based on the most disparate physical principles, means that a satisfactory solution of an effective, durable and safe AS with all the characteristics of the biological ones, has yet to be found. There are many reasons for this partial failure, which I alluded to earlier, and there are still many problems to resolve: (1) Avoiding the encapsulation of the device by fibrous tissue impairing its components in motion; (2) Finding a way to exert a constant pressure on the gut wall, without damaging it and that rapidly adapts its value on the basis of the needs of the moment; and (3) Finally, the device must be as small as possible, easy to insert in its location with only one surgical incision and not overly complex with many components, to avoid the risk of infections.

The availability of new technologies with new alternative actuators described earlier should have enabled the realization of devices, taking into account what was previously listed as necessary for an effective and safe bio-mimetic AS. However, this did not happen. Considering the poor results obtained so far, the need for another approach to avoid making previous errors appears quite evident.

As suggested by Toniolo *et al*[98], a more rational approach based on the bioengineering methods could be the solution. Computational procedures, considering the interaction of the surrounding biological tissues with the different occlusion methods, may help to minimize tissue damage and realize ASs following the principles listed above. Computational biomechanics by means of structural modeling tools may simulate the mechanical behavior of the anatomical structures interacting with ASs and may help to correctly insert the device in anatomical regions and biological structures and to implement the "sensorization" of ASs. The *in silico* analysis and simulation should allow us to compare the effects of various AS occlusion methods on the surrounding biological structures, to foresee the complications and side-effects, thereby finding the ideal compromise between harms and benefits.

It is also possible to implement the 3Rs approach, which Toniolo *et al*[98] refer to, *i.e.* Replacing, Reducing and Refining the experimentations on human cadavers and animal models. However, a series of "*in vitro*" and "*in vivo*" tests in animals on biocompatibility are still necessary before starting clinical trials. However, even during the experimentation in animals and humans, the pairing of bioengineering methods with surgical practice is of critical importance to provide positive feedback.

Furthermore, computational modeling and advanced imaging techniques with the possibility of analyzing the patient's anatomical configuration may be useful for conducting the surgical planning and for helping the doctor in the choice of the most suitable sphincter characteristics for each patient, making it possible to customize the device.

The future assistance of bioengineering for surgical practice may not only be fruitful for the latter, but also, conversely, its results can be evaluated in practice for possible program modifications.

CONCLUSION

The repair of malfunctioning gut sphincters has always been one of the most puzzling and troublesome problems of gastroenterology. At the beginning of the story, the following axiom was followed by the operators: Widen what is too narrow and tighten what is too wide. However, the consequence was that, by restoring one function, the other was damaged, and the more efficient the correction is, the more severe the damage is, so that, in some cases, it may have been necessary to "correct the correction". However, the clinical results of this procedure have seldom been satisfactory, and investigators have considered creating devices capable of replacing or helping the malfunctioning sphincters. Unfortunately, the new and complicated ASs have turned out to be the source of many more or less serious problems when tested in practice and the problem remains unresolved. It has been suggested to apply the bioengineering methods and resources to help investigators in the conception, design, realization and customization of effective and safe ASs. These new methods should be capable of correctly tuning the occlusion pressure, closing and opening the AS with "sensorization" and preventing tissue damage and device malfunctions. It should realize these goals *via* biomechanics up to biomechatronics, taking into account all the advices and recommendations for a safe AS listed above. I am confident that within a few years creativity, driven by bioengineering methods and AI, will be able to solve this age-old problem of repairing sphincter malfunctions, as has already been achieved for the pathophysiological and clinical problems of other medical disciplines.

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