Published in final edited form as:

Gastrointest Endosc. 2009 December ; 70(6): 1238–1240. doi:10.1016/j.gie.2009.07.009.

Thinking outside the box: autotransplantation into GI sphincters

Peter J. Kahrilas, MD

Northwestern University, Feinberg School of Medicine, Division of Gastroenterology, Department of Medicine, Chicago, Illinois, USA

Of all the attributes of sphincters, one can not help but marvel at how much we depend on so little. The anal sphincter, the external urethral sphincter, the pylorus, and the lower esophageal sphincter (LES) are all quite small, but their dysfunction can be a life-altering event. It would be nice if we could replace (or repair) them; such is the hope raised by the observations of Pashricha et al¹ in this issue of *Gastrointestinal Endoscopy* in that skeletal muscle-derived cells (MDCs) can be harvested, cultured, and transplanted into the pylorus or LES in animal models with resultant functional augmentation. True, the observations are preliminary, but they are nonetheless intriguing. The experiments represent an innovative and logical extension from the field of urology in which analogous human trials are currently underway using autologous multipotent MDCs to treat stress urinary incontinence.²

The key observations made by Pashricha et al¹ were that MDCs injected into the pylorus of rats or the LES of dogs and then allowed to grow for 4 weeks could be shown to differentiate into mature skeletal muscle in both sphincters. The post-transplant rat pylorus exhibited increased contractility in response to acetylcholine compared to saline solution-injected sham controls. In the three dogs, the transplanted MDCs integrated well into the tissue, particularly into the muscularis mucosa, and resulted in increasing the LES pressure from a mean of 13 mm Hg pre-transplant to 25 mm Hg post-transplant. Bravo pH monitoring studies were also done pre-transplant and post-transplant, and one dog went from 26% esophageal acid exposure time pre-transplant to 1.5% post-transplant. The other two dogs had negligible esophageal acid exposure both pre-transplant and post-transplant. Notably, there were no controls in the dog experiments, and it is not clear that the Bravo study, exhibiting 26% acid exposure pre-transplant, was not the result of premature capsule detachment. No test is described to verify capsule attachment at the end of the study, and the pH tracing is not shown. It would be very unusual for a dog to have this degree of reflux without prior surgical manipulation. The authors conclude that transplanted MDCs may have potential for the treatment of a variety of conditions, including GERD.

The challenges of repairing defective GI sphincters are many, and nowhere are the challenges as evident as they are at the esophagogastric junction. Similar to the case of the external urethral sphincter in childbirth injury, which leads to hypermobility of the sphincter and stress incontinence, esophagogastric junction dysfunction results from the interplay between structural deformity of the esophagogastric junction from repetitive mechanical stress and dysfunction of intrinsic muscular elements. This is not simply a matter of LES

There remains a substantial void in current GERD management strategies between anti-secretory drug therapy at one end and Nissen fundoplication at the other.

hypotension, but also dilatation of the hiatus and laxity of the phreno-esophageal ligament, often associated with a sliding hiatal hernia. The amount that each structural element contributes to dysfunction varies with the individual case, which is an important point because it underscores the heterogeneity of GERD patients. Just because lately we have been treating them all in the same manner does not mean that they are all the same. Just as patients exhibit considerable variability with respect to specific GERD symptoms, so, too, are they heterogeneous with respect to pathophysiology; in some cases the dysfunction is dominated by hiatus hernia, in others sphincter hypotension, and in others by heightened sensitivity.

So, what is the place for a “bulking therapy” in GERD therapeutics? Certainly, this has been a path well traveled for endoscopic GERD therapies. The concept is that by restricting the opening dimensions of the LES, the flow rate of refluxate will be diminished. Consequently, there will be a lesser volume of refluxate, less esophageal distension consequent from reflux, and a more restricted distribution of refluxate within the esophagus. This would hold regardless of the circumstances of LES opening: swallow, transient LES relaxation, or abdominal strain. Prior methods of achieving “sphincter bulking” have included injection of Plexiglass microspheres,³ Gatekeeper hydrogel implants,⁴ injection of Enteryx polymer,⁵ and most recently the injection of Durasphere graphite (Carbon Medical Technologies, St. Paul, MN).⁶ Of these, Durasphere has found some success in the treatment of urinary⁷ and fecal incontinence,⁸ but robust trials with respect to GERD are still awaited. The remainder of these therapies has been withdrawn from the market because of lack of efficacy, safety concerns, or both.⁹ Will injections of MDCs improve for this situation? Certainly, being autologous tissue, thereby avoiding problems of rejection, and having transplanted MDCs mature to exhibit physiological function are attractive advantages. This would not just be “bulking” the LES, but this would be akin to a sphincter on steroids.

Assuming that the preliminary findings of Pashricha et al¹ can be extended to autologous MDC transplantation into the LES in humans, whom would this treatment potentially benefit? The observation that the 3 dogs exhibited almost a 100% increase in LES pressure post-MDC transplant argues that a defining feature should be LES hypotension. Of course, this is only a minority of GERD patients, but nevertheless an important one. Such individuals usually have severe disease, are often subject to positional reflux, and currently have few attractive treatment options. Targeting LES hypotension is also appealing because it is a readily defined measurement and changes in sphincter function attributable to treatment could be assessed experimentally. Then there is also the fascinating question of how such a sphincter would behave physiologically? Would an LES enhanced by transplantation of striated muscle cells still exhibit deglutitive (or transient) relaxation? In the smooth muscle sphincter, this is a function of nitrergic inhibitory nerves that would not be expected to be operative. Would the enhanced LES exhibit tonic contraction during sleep or would it only contract with ongoing cholinergic input, akin to the upper esophageal sphincter (UES)?¹⁰ Addressing these questions would be logical extensions of the current work prior to human studies. Fortunately, they can be addressed in the chronic dog model, which has proven to be quite robust in testing pharmacological LES therapies.¹¹

In conclusion, these are intriguing experiments that open the door to many possibilities not limited to GERD therapeutics. Certainly, there remains a substantial void in current GERD management strategies between anti-secretory drug therapy at one end and Nissen fundoplication at the other. After all, to be critical of these strategies, anti-secretory drugs only compensate for the physiological dysfunction in GERD, and fundoplication over-corrects the dysfunction.^{12,13} The concept of culturing your own tissue and then re-implanting it to patch up some weak spots really represents thinking outside the box. However, it must also be emphasized just how preliminary these experiments are currently. They demonstrate the feasibility of MDC transplantation with subsequent maturation to striated muscle and survival

of the implanted tissue for 4 weeks. Many hurdles remain to be traversed before that demonstration of feasibility translates into a viable durable therapy. Personally, I am skeptical that transplanted MDCs will find broad application in GERD therapeutics, but I do applaud the ingenuity of the concept and leave the possibility open that a therapeutic niche might exist to be filled by this approach.

Acknowledgments

Supported by grant no. RO1 DC00646 (PJK) from the Public Health Service.

Abbreviations

LES	lower esophageal sphincter
MDCs	muscle-derived cells

REFERENCES

1. Pashricha PJ, Ahmed I, Jankowski PJ, et al. Endoscopic injection of skeletal muscle-derived cells augment gut smooth muscle sphincteric function-implications for a novel therapeutic approach. *Gastrointest Endosc* 2009;70:1231–7. [PubMed: 19647239]
2. Furuta A, Jankowski RJ, Pruchnic R, et al. The potential of muscle-derived stem cells for stress urinary incontinence. *Expert Opin Biol Ther* 2007;7:1483–6. [PubMed: 17916041]
3. Feretis C, Benakins P, Dimopoulos C, et al. Endoscopic implantation of Plexiglas (PMMA) microsphere for the treatment of GERD. *Gastrointest Endosc* 2001;53:423–6. [PubMed: 11275880]
4. Fockens P, Bruno MJ, Gabbrielli A, et al. Endoscopic augmentation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease: multicenter study of the Gatekeeper Reflux Repair System. *Endoscopy* 2004;36:682–9. [PubMed: 15280972]
5. Cohen LB, Johnson DA, Ganz RA, et al. Enteryx implantation for GERD: expanded multicenter trial results and interim postapproval follow-up to 24 months. *Gastrointest Endosc* 2005;61:650–9. [PubMed: 15855967]
6. Ganz RA, Fallon E, Wittchow T, et al. A new injectable agent for the treatment of GERD: results of the Durasphere pilot trial. *Gastrointest Endosc* 2009;69:318–23. [PubMed: 19185691]
7. Lightner D, Calvosa C, Anderson R, et al. A new injectable bulking agent for the treatment of stress urinary incontinence: results of a multicenter, randomized, controlled double-blind study of Durasphere. *Urology* 2001;58:12–5. [PubMed: 11445471]
8. Davis K, Kumar D, Poloniecki J. Preliminary evaluation of an injectable anal sphincter bulking agent (Durasphere) in the management of fecal incontinence. *Aliment Pharmacol Ther* 2003;18:237–43. [PubMed: 12869085]
9. Falk G, Fennerty MB, Rothstein R. AGA Institute technical review on the use of endoscopic therapy for gastroesophageal reflux disease. *Gastroenterology* 2006;131:1315–36. [PubMed: 17030199]
10. Kahrilas PJ, Dodds WJ, Dent J, et al. The effect of sleep, spontaneous gastroesophageal reflux and a meal on UES pressure in humans. *Gastroenterology* 1987;92:466–71. [PubMed: 3792782]
11. Lehmann A, Antonsson M, Bremner-Danielsen M, et al. Activation of the GABA(B) receptor inhibits transient lower esophageal sphincter relaxations in dogs. *Gastroenterology* 1999;117:1147–54. [PubMed: 10535878]
12. Finks JF, Wei H, Birkmeyer JD. The rise and fall of antireflux surgery in the United States. *Surg Endosc* 2006;20:1698–701. [PubMed: 16960665]
13. Kahrilas PJ. Laparoscopic antireflux surgery: silver bullet or the Emperor's new clothes (editorial). *Am J Gastroenterol* 1999;94:1721–3. [PubMed: 10406225]