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Feasibility and scalability of spring parameters in distraction enterogenesis in a murine model



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ABSTRACT

Background: Distraction enterogenesis has been investigated as a novel treatment for short bowel syndrome (SBS). With variable intestinal sizes, it is critical to determine safe, translatable spring characteristics in differently sized animal models before clinical use. Nitinol springs have been shown to lengthen intestines in rats and pigs. Here, we show spring-mediated intestinal lengthening is scalable and feasible in a murine model.

Materials and methods: A 10-mm nitinol spring was compressed to 3 mm and placed in a 5-mm intestinal segment isolated from continuity in mice. A noncompressed spring placed in a similar fashion served as a control. Spring parameters were proportionally extrapolated from previous spring parameters to accommodate the smaller size of murine intestines. After 2–3 wk, the intestinal segments were examined for size and histology.

Results: Experimental group with spring constants, $k = 0.2\text{--}1.4$ N/m, showed intestinal lengthening from 5.0 ± 0.6 mm to 9.5 ± 0.8 mm ($P < 0.0001$), whereas control segments lengthened from 5.3 ± 0.5 mm to 6.4 ± 1.0 mm ($P < 0.02$). Diameter increased similarly in both groups. Isolated segment perforation was noted when $k \geq 0.8$ N/m. Histologically, lengthened segments had increased muscularis thickness and crypt depth in comparison to normal intestine.

Conclusions: Nitinol springs with $k \leq 0.4$ N/m can safely yield nearly 2-fold distraction enterogenesis in length and diameter in a scalable mouse model. Not only does this study derive the safe ranges and translatable spring characteristics in a scalable murine model for patients with short bowel syndrome, it also demonstrates the feasibility of spring-mediated intestinal lengthening in a mouse, which can be used to study underlying mechanisms in the future.

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Introduction

Short bowel syndrome (SBS) is a highly morbid disease with a loss of intestinal length leading to nutrient malabsorption.¹ This can be complicated by life-long total parenteral nutrition (TPN), subsequent infections, and liver failure.¹ Etiologies of SBS include midgut volvulus, necrotizing enterocolitis, intestinal atresia, and aganglionosis.² Current surgical therapies include increase in bowel surface area, transit-slowng procedures, or bowel transplantation, but patient selection and long-term benefits are limited.^{2–5} New treatments for SBS are needed.

Multiple modalities for distraction enterogenesis have been studied as a potential treatment for SBS. Mechanical forces act on the intestines to induce lengthening.^{6–13} Self-expanding springs have been shown to lengthen intestines in rats and pigs using size criteria for scalability.^{10,11,14} Given the variability of intestinal sizes, it is critical to determine safe, translatable spring characteristics in differently sized animal models before clinical use. The mechanism for distraction enterogenesis is also currently under investigation, but only one model exists.^{15,16} In this study, we developed a new surgical mouse model to test feasibility and confirm effective method of scalability that can be translated to clinical application as well as set the foundation for future studies of underlying mechanisms.

Materials and methods

The use of animals was approved by the Animal Research Committee (Institutional Review Board Number 2016-098-01).

Spring characteristic extrapolation

Spring constants and size were extrapolated for mice intestines from our previous spring characteristics in rats. In our previous model, rats weighed 300 g with intestinal cross-sectional area of 1.06 mm². Spring constants were 1 N/m and expanded from 10–30 mm. According to Hooke's law (force = spring constant × change in length), the spring force measured 0.02 N.^{11,14}

Adult C57BL/6-Tg mice (Jackson Laboratory, Bar Harbor, ME) have an average preoperative weight of 24 ± 3 g and have intestinal cross-sectional area of 0.1 mm², estimated using the formula for area of an annulus. Mice weight and cross-sectional area was 12× and 10× less in comparison to rats. These factors were used to extrapolate a proportionally decreased spring constant. The targeted spring force was 0.002 N. Using Hooke's law, to obtain a spring expansion from 5–10 mm, the targeted spring constant was 0.4 N/m (Fig. 1).

Spring production

Springs were made by a process called shape setting heat treatment as previously described¹⁰ from biocompatible material called nickel titanium also known as nitinol. Nitinol is used in many medical devices including surgical instruments

Hooke's Law

Force = spring constant * change in length

$$.002 \text{ N} = k * (10 - 5 \text{ mm})$$

$$k = 0.4 \text{ N/m}$$

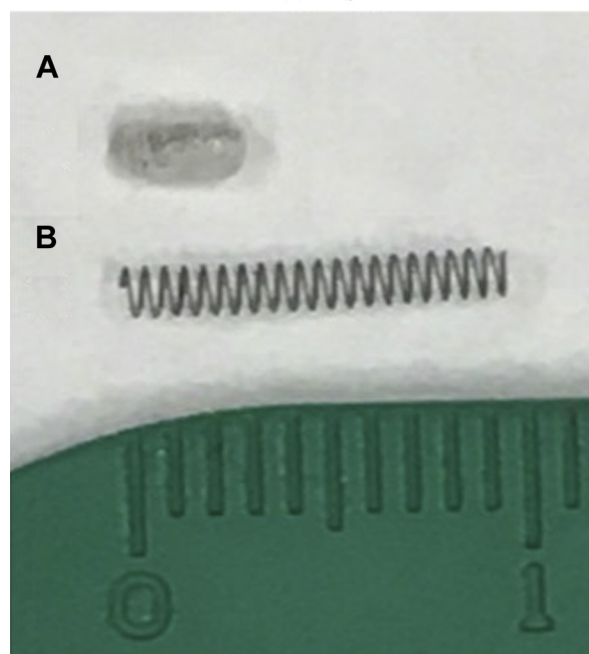


Fig. 1 – Photo of a nitinol spring used in the experimental group with $k = 0.4 \text{ N/m}$ as (A) compressed in gelatin capsule and (B) expanded. Hooke's law is used to extrapolate targeted spring constants. (Color version of figure is available online.)

and vascular stents.¹⁷ It has also been successfully utilized for distraction enterogenesis in rats in previous studies.¹⁰

Spring measurements were 1.5- to 2-mm outer diameter, compressed length of 3 mm, expanded length of 10 mm, and spring constants (k) 0.2–2.2 N/m. The springs were placed into size 9 Gelatin capsules (Torpac, Inc, Fairfield, NJ) and coated three times with cellulose acetate phthalate¹⁸ (Eastman Chemicals, Kingsport, TN) (Fig. 1).

Surgical procedure

Adult mice aged 8 wk ($n = 36$) were anesthetized with inhaled oxygen and vaporized isoflurane. A midline laparotomy and spring placement were performed using light microscopy at 6.5× magnification (Carl Zeiss Microscopy, Jena, Germany). An intestinal segment was isolated on its mesenteric pedicle. The experimental group had a 10-mm nitinol spring compressed to 3 mm placed in a 5-mm isolated intestinal segment ($n = 27$; Fig. 2A). The control group had a noncompressed nitinol spring placed in a 5-mm isolated intestinal segment ($n = 9$). The ends of the isolated segment were sutured with 6-0 Gortex suture (Gore Medical, Flagstaff, AZ). Intestinal continuity was restored by an end-to-end anastomoses of the proximal and distal intestines with interrupted 6-0 Gortex. The bowel was placed back into the abdomen, and the abdominal wall was closed in layers.

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