Surgery Open Science 13 (2023)

Contents lists available at ScienceDirect

Surgery Open Science

journal homepage: https://www.journals.elsevier.com/surgery-open-science

Review article

Mechanobiological considerations in colorectal stapling: Implications for technology development

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ARTICLE INFO

Article history:
Received 17 February 2023
Received in revised form 7 April 2023
Accepted 8 April 2023
Available online 16 April 2023

Keywords:
Surgical stapling
Colorectum
Tissue mechanics
Mechanotransduction
Anastomosis
Wound healing

ABSTRACT

Technological advancements in minimally invasive surgery have led to significant improvements in patient outcomes. One such technology is surgical stapling, which has evolved into a key component of many operating rooms by facilitating ease and efficacy in resection and repair of diseased or otherwise compromised tissue. Despite such advancements, adverse post-operative outcomes such as anastomotic leak remain a persistent problem in surgical stapling and its correlates (i.e., hand-sewing), most notably in low colorectal or coloanal procedures. Many factors may drive anastomotic leaks, including tissue perfusion, microbiome composition, and patient factors such as pre-existing disease. Surgical intervention induces complex acute and chronic changes to the mechanical environment of the tissue; however, roles of mechanical forces in post-operative healing remain poorly characterized. It is well known that cells sense and respond to their local mechanical environment and that dysfunction of this "mechanosensing" phenomenon contributes to a myriad of diseases. Mechanosensing has been investigated in wound healing contexts such as dermal incisional and excisional wounds and development of pressure ulcers; however, reports investigating roles of mechanical forces in adverse post-operative gastrointestinal wound healing are lacking. To understand this relationship well, it is critical to understand: 1) the intraoperative material responses of tissue to surgical intervention, and 2) the post-operative mechanobiological response of the tissue to surgically imposed forces. In this review, we summarize the state of the field in each of these contexts while highlighting areas of opportunity for discovery and innovation which can positively impact patient outcomes in minimally invasive surgery.

Contents

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https://doi.org/10.1016/j.sopen.2023.04.004

Introduction

Surgical techniques and associated technology have made significant progress in the last 50 years, most notably with the advancement of minimally invasive surgery (MIS). Surgical stapling is a significant component of MIS and is implemented in a variety of interventions. These advancements have resulted in improvements to clinical outcomes such as faster recovery and shorter length of hospital stay [1]. Despite these advancements, adverse clinical outcomes such as anastomotic leak and stricture remain a persisting problem in challenging stapling applications. Etiologies for these adverse outcomes are multifactorial and are thought to include malnutrition, immunosuppression, diabetes mellitus, radiation or oral anti-inflammatory treatments, and microbiome composition [2–4]. One potential factor that remains poorly understood is the relationship between the local mechanical environment and maladaptive tissue remodeling. Surgical stapling is principally a mechanical intervention that imposes a complex combination of mechanical loads on tissue. To properly understand roles of mechanics in downstream clinical outcomes, it is critical to first understand: 1) the material properties of the target tissue, including effects of age, sex, ethnicity, disease state, etc., 2) the loads applied to the target tissue during intervention, and 3) the temporal post-operative changes to the structure-function relationship of the tissue in response to surgically applied loads.

Roles of the local mechanical environment in disease progression and tissue remodeling are well established in many contexts [5]. Mechanical homeostasis is maintained at three levels: 1) proper regulation of the mechanical properties of the extracellular matrix, 2) proper cell-matrix adhesion and interaction via transmembrane proteins (e.g., integrins via "inside-out signaling"), and 3) proper intracellular signaling in response to cell-matrix interactions (termed "mechanosensing" via "outside-in signaling") (Fig. 1). Clinical pathologies can arise from disruption at any of these levels, e.g., cells may properly adhere and respond to a dysfunctional matrix, or dysfunctional adhesion proteins may inhibit proper binding of the cell to a functional matrix. In this review we aim to summarize current evidence and relevant knowledge gaps in colorectal tissue which details tissue material properties (i.e., load-bearing properties of the extracellular matrix), magnitudes and types of surgically imposed forces, and cellular responses to loading under normal and pathological settings. Proper understanding of these topics will shed light on potential mechanobiological mechanisms driving adverse clinical outcomes in colorectal surgical stapling.

Stapling overview

Surgical stapling is performed to remove diseased or damaged tissue (i.e., resection) or to repair a defect (i.e., anastomosis). In either case, the phases of the stapling process remain the same: 1) grasping of tissue, 2) compression of tissue in locations where staples are to be deployed, 3) delivery of staples to join apposing layers of tissue and maintain adequate compression, and 4) transection to remove undesired tissue. Regardless of the target outcome (i.e., resection or repair) or tissue of interest, optimal tissue compression should be sufficiently high to achieve adequate hemostasis and prevent luminal content leakage into the adjacent space; conversely, tissue compression should be sufficiently low to promote adequate blood flow and wound healing at the site of transection. Given the variety of biological structures and physiological demands that exist across surgical stapling applications, medical device manufacturers have incorporated various design features in staplers to promote an optimal compression profile in as many applications as possible.

Stapling design features. Broadly, staplers are typically designed in linear platforms for resection and circular platforms for anastomotic repair and can be implemented in open or laparoscopic applications. Design considerations in each of these platforms are based on a variety of technical, usability, and cost demands; however, targeting optimal compression drives certain design considerations across all manufacturers and device platforms. Most notably, all major manufacturers offer multiple sizes of staplers which compress to differing final thicknesses to provide surgeons the opportunity to tailor delivery of staples based on the tissue geometry and material properties. The ranges of final thicknesses are driven by the "closed height" of the staples after the staples have been delivered to the tissue. Final form of staple delivery differs by manufacturer with some offering 2 vs. 3 rows of staples on either side of the transection line, varied vs. uniform height staples, and 2-D vs. 3-D staple formation [6].

Given the importance of the underlying tissue properties in achieving optimal staple formation, many have sought to provide greater control of applied compression prior to deployment of staples, with some offering manually adjustable compression within a defined range [7] and others monitoring the clamping pressure on tissue to ensure adequate compression [8]. In other contexts where compression is not a regulated variable, loading information can still be leveraged to regulate the rate of staple deployment and tissue transection to account for differences in tissue properties to improve staple formation [9,10]. While these design features constitute a significant step forward in stapling,

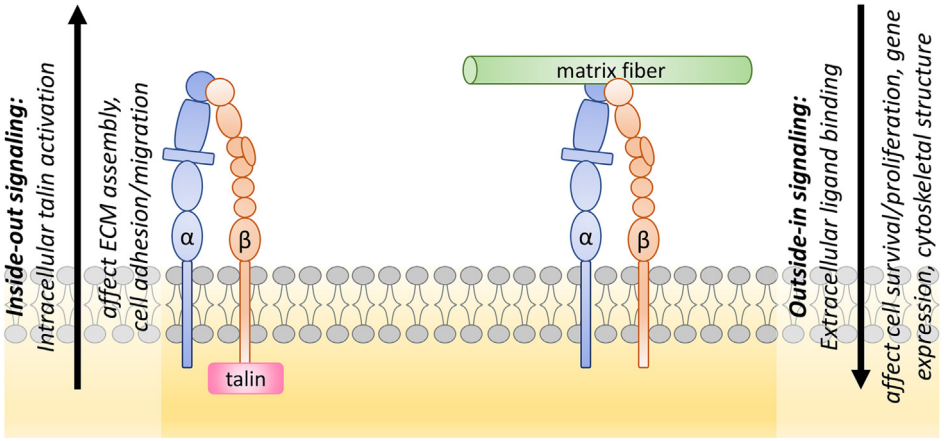

Fig. 1. Graphical depiction of extracellular and intracellular mechanosensing mechanisms. Intracellular signaling activity can activate integrin-mediated extracellular matrix (ECM) assembly, cell adhesion, and migration ("inside-out" signaling). In contrast, integrin binding to varying ECM fibers activate cellular responses such as cell survival and proliferation, gene expression, and changes to the cytoskeletal structure.

there remains little data to suggest what the optimal compression should be and how such values might differ based on tissue type and/or patient demographics and medical history.

Stapling in colorectal applications. Colorectal surgery is used to treat a variety of diseases including colorectal cancer, Crohn's Disease, and ulcerative colitis. In the US alone, there were more than 150,000 new cases of colorectal cancer in 2022, and inflammatory bowel diseases were estimated to affect more than 3 million adults in 2015 [11,12]. Many of these cases are treated with partial or total surgical resection, in which diseased or compromised tissue is isolated and removed. Following resection, the defect is repaired through creation of a colostomy or an intestinal anastomosis.

During the repair process, extension of the bowel segments increases the global longitudinal stress on the tissue, the degree to which depends on the amount of tissue resected and the distance remaining between the open segments. To successfully accomplish the repair, tissue must be compressed to facilitate ease of staple delivery and hemostasis after resection. This action locally increases the radial stress on the tissue, the degree to which depends on the magnitude of compression, which is determined by the material geometry and properties as well as the choice of stapler cartridge (Fig. 2). Many reports consider only the material geometry (e.g., tissue thickness) when discussing applied loads in stapling and neglect the material properties altogether. However, two tissues of identical geometry with different material properties may develop markedly different radial stresses during compression due to differences in material stiffness. Lastly, staples are deployed radially through the tissue to secure the ends of the tissue together, and a circular knife is advanced to remove unwanted tissue obstructing the colonic lumen, at which point radial stress is applied only by the remaining staples rather than by the stapler cartridge and anvil. The radial stress applied by the staples serves to maintain tissue apposition which inhibits bowel content leakage into the peritoneal space, maintains hemostasis at the site of transection, and affects wound healing via regulation of local perfusion and (presumably) via mechanosensitive cellular pathways.

Many post-operative complications can arise following the creation of an intestinal anastomosis, the most serious of which are anastomotic leaks. Leak rates differ depending on the anatomical location of the anastomosis, with enteroenteric anastomoses having the lowest rates of 1–2 % and colorectal/coloanal anastomoses having rates as high as 19 % [4]. Many pre-operative factors may predispose to anastomotic leaks including sex, health status (e.g., diabetic), and lifestyle as well as intraoperative factors such as duration of surgery, antibiotic administration, and surgical technique [2,13]. Still, the clinical effects of tissue compression on anastomotic leak remain unknown as intraoperative and postoperative data on tissue properties and/or loads applied to the site of anastomosis are difficult or impossible to obtain. Though differences in tissue material properties *per se* are not risk factors for anastomotic leaks, many preoperative risk factors are associated with changes to tissue properties in colorectal and/or other contexts, including diabetes [14,15], diet [16,17], and radiotherapy [18], suggesting a clear role of tissue material properties in informing surgical technique.

Risk factors for anastomotic leak may be further stratified by the postoperative day on which the leak occurs, supporting the need to understand pre- and intraoperative factors which drive differential downstream responses (i.e., mechanobiological responses). Early anastomotic leaks before postoperative day 3 are driven primarily by intraoperative factors, namely, surgical technique, whereas late anastomotic leaks after postoperative day 20 are driven primarily by patient-related factors [19]. It remains unclear how surgical technique and/or patient-related factors should drive determination of the optimal compression profile in surgical stapling.

Colorectal tissue mechanics

Efficient and efficacious design of surgical staplers requires a detailed understanding of the material behavior of the tissue subjected to stapling procedures. Further, to properly investigate mechanobiological responses of the tissue to surgical stapling procedures, it is first critical to understand and accurately predict the mechanical forces which are applied during resection and repair. This understanding comes from experimental data in tissue subjected to various loading conditions, but insight may be further derived from analytical and computational techniques that provide the capacity to predict material responses to a given applied load or deformation. Much work exists in the field of colorectal tissue mechanics [20,21], with emphases placed on relationships between mechanics and visceral pain sensation, disease diagnosis, and model development. We will here review advancements in material characterization and modeling of colon with a focus on data which are relevant to surgical stapling (Table 1). We also highlight areas in the

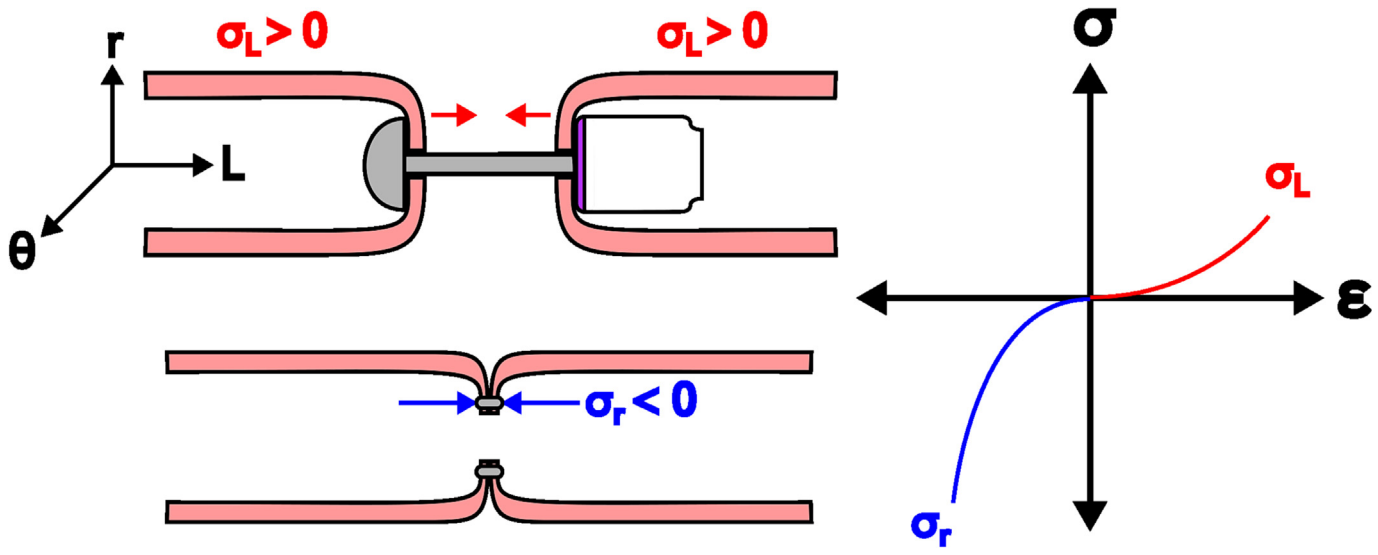

Fig. 2. Mechanical loads applied to colon during surgical resection and repair. Apposition of two ends of colon following surgical resection induces a global longitudinal tensile stress (denoted by σ_L and a positive sign convention for tensile load). The longitudinal stress is developed due to the force required to bring the blind ends together. Following tissue apposition, the tissue is compressed by the staples or suture, inducing a local compressive radial stress (denoted by σ_r and a negative sign convention for compressive load). The compressive stress is developed due to the force applied by the staples or suture.

Table 1
Selected available biomechanical data in colon. Methods: uniaxial and biaxial cylindrical tensile (uniax, biax cyl), uniaxial strip tensile (uniax strip), planar biaxial tensile (planar biax), unconfined uniaxial compression (uniax comp), inflation, indentation, and elastography. Orientations: circumferential (circ), axial (ax), and radial (rad). Regions: ascending (asc), transverse (trans), descending (desc), sigmoid (sig), rectum, spiral (swine only), proximal (prox, rodent/swine only), distal (dist, rodent/swine only). Outputs: stress, strain, pressure-volume, pressure-CSA, elastic or shear modulus, and ultimate tensile strength (UTS).

Species	Condition	Test method	Orientations	Layers?	Regions	Output metric	Experimental variable	Reference
Goat	In vitro	Uniax comp	Rad	N	Unknown	Stress-strain	Loading rate, test condition	Higa et al. [50]
	In vivo	Uniax comp	Rad	N	Unknown	Stress-strain	Loading rate, test condition	Higa et al. [50]
Human	In vitro	Uniax strip	Circ, Ax	N	Asc, trans, desc, sig	Elastic modulus, UTS	Taenia coli	Massalou et al. [42]
		Uniax strip	Circ, Ax	N	Asc, trans, desc, sig	Elastic modulus, UTS	Loading rate, taenia coli	Massalou et al. [40]
		Uniax strip	Ax	N	Asc, trans, desc, sig	Elastic modulus, UTS	Tissue storage, sex, age	Massalou et al. [41]
		Uniax strip	Circ, Ax	N	Unknown	Stress, strain, UTS	Taenia coli	Egorov et al. [39]
		Uniax strip	Circ, Ax	Y	Unknown	Stress, strain, UTS	Tissue storage, taenia coli	Egorov et al. [140]
		Uniax cyl	Circ	N	Asc, trans, desc, sig	UTS, relaxation	Genetic background	Watters et al. [38]
		Uniax strip	Circ, Ax	N	Sig, rectum	UTS, modulus	Species	Christensen et al. [45]
		Indentation	Rad	N	Unknown	Elastic modulus	Inflammation, species	Stewart et al. [44]
		Uniax strip	Circ	Y	Rectum	Length-tension	Contractility	Glavind et al. [143]
		Planar biax	Circ, Ax	N	Asc, trans, desc, sig	Stress-strain	Model development	Howes and Hardy [144]
		Uniax comp	Rad	N	Unknown	Stress-strain, modulus	Colitis, fibrosis	Stidham et al. [37]
	In vivo	Inflation	Circ	N	Asc, desc	Pressure-volume	Loading rate, contractility	Bharucha et al. [33]
		Inflation	Circ	N	Rectum	Pressure-volume	Diverticular disease	Smith et al. [36]
		Inflation	Circ	N	Rectum	Elastic modulus	Model development	Dall et al. [32]
		Inflation	Circ	N	Sig, rectum	Pressure-CSA	Visceral pain	Petersen et al. [34]
		Inflation	Circ	N	Rectum	Pressure-volume	Sex, age, visceral pain	Sloots et al. [35]
		Inflation	Circ	N	Rectum	Pressure-CSA	Visceral pain, contractility	Drewes et al. [137]
		Inflation	Circ	N	Various colon, rectum	Pressure-volume	Diverticular disease	Parks [138]
		Inflation	Circ	N	Rectum	Pressure-volume	Model development	Arhan et al. [136]
		Inflation	Circ	N	Sig, rectum	Pressure-volume	IBS, sensory function	Drewes et al. [139]
		Elastography	Rad	N	Unknown	Elastic modulus	Colitis, fibrosis	Stidham et al. [37]
Mouse	In vitro	Planar biax	Circ, Ax	N	Distal, rectum	Stress-strain	Model development	Siri et al. [56]
		Planar biax	Circ, Ax	Y	Distal, rectum	Stress-strain	Model development	Siri et al. [142]
		Indentation	Rad	N	Unknown	Elastic modulus	Species	Stewart et al. [44]
		Uniax strip	Ax	N	Unknown	Stress-strain, UTS, modulus	Colitis	Gong et al. [145]
		Inflation	Circ, Ax	N	Dist	Stress-strain	Colitis	Yang et al. [146]
Rabbit	In vitro	Inflation	Circ	N	Mid	Stress-strain	Fiber-based diet	Liu et al. [16]
Rat	In vitro	Inflation	Circ, Ax	N	Asc, trans, desc, rectum	Stress-strain	Model development	Gao and Gregersen [147]
		Biax cyl	Circ, Ax	N	Asc, trans, desc, rectum	Stress-strain	Model development	Sokolis et al. [48]
		Biax cyl	Circ, Ax	N	Asc, trans, desc, rectum	Stress-strain	Model development	Sokolis and Sassani [49]
		Inflation	Circ	N	Mid	Stress-strain	Diabetes	Zhao et al. [135]
		Indentation	Rad	N	Prox	Elastic modulus	Hypertension, loading rate	Stewart et al. [148]
		Uniax comp	Rad	N	Prox, dist	Stress-strain, modulus	Colitis, fibrosis	Stidham et al. [37]
		Uniax cyl	Circ	N	Unknown	Stress-strain, UTS, modulus	Sex, age, tissue storage	Watters et al. [149]
		Elastography	Rad	N	Prox, dist	Elastic modulus	Colitis, fibrosis	Stidham et al. [37]
Swine	In vitro	Uniax strip	Circ, Ax	N	Desc (prox, med, dist)	UTS, modulus	Species	Christensen et al. [45]
		Uniax strip, shear	Circ, Ax	N	Unknown	Stress-strain	Model development	Ciarletta et al. [63]
		Biax cyl	Circ, Ax	N	Spiral, desc	Stress-strain	Model development	Patel et al. [53]
		Planar biax	Circ, Ax	N	Spiral (prox, dist), desc	Stress-strain	Model development	Puértolas et al. [47]
		Uniax comp	Rad	N	Unknown	Stress-strain, stress relaxation	Model development	Rosen et al. [51]
		Indentation	Rad	N	Unknown	Elastic modulus	Species	Stewart et al. [44]
		Uniax strip	Circ, Ax	Y	Spiral	Stress-strain	Taenia coli, off-axis, model development	Carniel et al. [46]
		Uniax strip, uniax comp, shear	Circ, Ax, Rad	N	Rectum	Stress-strain, modulus, Poisson's ratio	Model development	Qiao et al. [141]
		Uniax strip	Circ, Ax	N	Spiral	Stress-strain, modulus, Poisson's ratio	Model development	Carniel et al. [62]

field which require further development to provide greater insight into the local mechanical environment of the tissue during surgical stapling procedures.

Anatomy and microstructure. In humans, the colon can be divided into the ascending, transverse, descending, and sigmoid colon followed by the rectum. Folds within the colon known as haustra arise due to contraction of longitudinally oriented fibers of smooth muscle called taenia coli which support diameter reduction during contraction [22]. These folds exist along the entire length of the colon except for the rectum, at which point the taenia coli expand from longitudinal fibers to an entire layer.

Because of the extensive use of animal models in material characterization of colon as well as medical device testing, it is important also to understand differences between the human colon and animal models of interest. The anatomical features of the colon in various animals have some similarity to humans, though none are exactly alike [23]. Porcine colon is much longer and lacks the regional differentiation of human colon, instead being oriented in a spiral formation from the cecum to the descending colon [24]. The canine colon more closely resembles the human colon in its regional differentiation, though it lacks a clear sigmoid region prior to the rectum. The canine colon also lacks the visible haustra of the human and porcine colon [23], though haustra in porcine colon are limited to the spiral region and not the distal region. The rodent colon, though helpful for high-throughput and mechanistic investigations, has significant limitations with regards to its anatomical and physiological similarity to humans. For instance, rat colon does not contain haustra and has a relatively shorter length than that of humans.

Histologically, the colon is divided into five distinct layers: the mucosa – the inner layer of the tissue consisting of epithelial cells and smooth muscle cells, the submucosa – a fibrous layer and primary contributor to the tissue's tensile strength, the muscularis externa – two layers of smooth muscle cells oriented circumferentially (inner layer) and longitudinally (outer layer), and the serosa – the outermost layer of the tissue consisting of mesothelial cells which secrete fluid for lubrication. The rectum alone contains an additional layer of muscle where the taenia coli expand from fibers to an entire layer and contains squamous rather than columnar epithelial cells.

The predominant component of the submucosa tissue matrix is collagen, most of which is collagen I (68 %), followed by collagen III (20 %) and collagen V (12 %) [25]. The degradation of the matrix is regulated by matrix metalloproteinases (MMPs), a broad class of proteases that selectively catabolize various structural proteins. In turn, MMP activity is inhibited by tissue inhibitors of metalloproteinases (TIMPs). Together, MMPs and TIMPs regulate the composition and mechanical integrity of the tissue matrix [26]. Viscoelastic and biphasic properties of the tissue are regulated through relatively low but significant levels of elastin and proteoglycans [27,28]. These proteins additionally play biological roles through their sequestration of growth factor cytokines [29,30]. Clinically, lower collagen I/III ratio and higher MMP- 1, 2, and 9 levels are associated with anastomotic leaks [31]. Thus, the underlying biological causes and mechanical consequences of these aberrations should be further investigated as a potential target for intervention.

Material testing and characterization. Clinical evaluation of normal and pathophysiologic function of the colon relies in part on understanding the structural properties of the tissue; namely, distensibility calculations via impedance planimetry or ultrasound. Impedance planimetry is a technique leveraging balloon distension to provide simultaneous measurements of luminal cross-sectional area and pressure, providing the basis for characterization of structural mechanical parameters such as distensibility or stiffness. Its utility is not limited to passive structural parameters as pressure changes can be detected during colonic peristalsis, thus aiding in characterization of colonic motility. Balloon distension and impedance planimetry have been implemented widely in colon and other tissues to characterize *in vivo* mechanical properties of the tissue including baseline studies [32–34,136] and investigations of age [35], sex [35], and disease state [36,137–139] on colonic compliance. Similarly, other modalities have been implemented for characterization of structural stiffness, including ultrasound elastography imaging [37]. Though helpful for diagnostics, these *in vivo* data relate primarily to circumferential properties of the tissue and provide little insight into the longitudinal and radial stresses developed during colorectal resection and repair (Fig. 2). To address this, *ex vivo* testing must be implemented.

Much *ex vivo* data is available which details the material properties of human colon. Watters et al. performed uniaxial cylindrical tensile testing on human colon samples until failure. The authors reported differences in ultimate tensile strength of the tissue as a function of anatomical region, age, and genetic background [38], with the sigmoid colon tending to have lower tensile strength compared to other regions of the tissue, and colons in patients of African descent having higher tensile strength compared with those of European descent. Differences in tensile strength were attributed to thicker tissue, thereby lowering internal stress according to Laplace's Law. This study provides detailed insight into anatomical and patient factors driving circumferential material properties of colonic tissue, but the testing modality inhibits data collection for tissue properties governing longitudinally-oriented material behavior.

Other groups have performed strip uniaxial tensile tests on circumferential and longitudinal sections of human colon without the detailed insight into differences across region, age, or genetics. Egorov et al. report circumferential tensile strength at 826 kPa [39] (compared with ranges from ~800 kPa to 1.4 MPa in Watters et al. depending on region and genetic background). Egorov et al. also tested longitudinal specimens of taenia coli and haustra. Taenia coli exhibit a bimodal axial behavior whereas the haustra exhibit a more monotonic behavior. The authors suggest that this phenomenon may be attributable to layer-specific failure as confirmed by microscopy, with muscular and serosal layers failing first while the mucosa and submucosa remain intact [140]. Massalou et al. report the most robust data set of uniaxial tensile testing in human colon ($n = 336$ samples from 28 donors) and report effects of loading speed on circumferential and axial material behavior with or without taenia coli [40]. A similar biphasic response was observed in both circumferential and longitudinal directions, lending support to the idea of progressive and layer-specific failure as observed by others. Similar data from the same group are reported elsewhere and further detail material differences as a function of age, sex, and anatomical region, though these data are all reported at dynamic loading speeds of 1 m/s [41,42]. Human colon material behavior has been characterized with other modalities including planar biaxial testing at high strain rates [43] and indentation [44]. Notably, indentation experiments alone have been used to quantify differences in material properties between healthy and inflamed colon in humans, showing that inflamed colon exhibits a stiffer response in compression. Similar to *in vivo* methods, these data are helpful for diagnostics, but indentation experiments apply compressive deformations which are significantly lower than those in surgical contexts. Extrapolation of such data to inform design of staplers and other similar devices is therefore tenuous.

Animal models have been utilized to lend further insight into biomechanical structure and function of colon. At least one study reports direct comparisons between material properties of human and porcine sigmoid colon and rectum using uniaxial strip testing and suggests statistically significant differences in ultimate tensile strength and elongation at failure between species [45]. However, medical history of the human specimens is not reported, creating difficulty in interpreting differences as driven by species, disease state, or both. Similar data have been obtained in porcine tissue by other groups [46], while others have implemented more advanced techniques for characterization of colon, including planar biaxial testing [47,142]. Smaller species such as rat and mouse further enable researchers to maintain physiological

configurations through biaxial inflation-extension testing while obtaining robust multiaxial data [48,49]. Tensile data such as these are helpful for characterization but difficult to translate to surgical contexts due to lack of information regarding tensile loads developed during resection and repair. Clinical data reporting length of tissue resected would provide further insight. Data reporting longitudinal forces required to appose tissue following resection would be more helpful; however, such data are markedly more difficult to obtain and may be better suited for preclinical investigation.

Little data exist which report material response of colon under high magnitudes of compression, which is key for understanding the compressive phase of surgical stapling. Higa et al. provide helpful data reporting *in vivo* and *ex vivo* compressive responses of goat colon under different loading rates [50]. Three samples were tested under each loading condition, and the study reported lower *in vivo* stresses compared to *ex vivo* stresses under similar conditions (e.g., 120 vs. 205 kPa at a loading rate of 5 mm/s and compressive strain of 70 %). Similar data have been reported in pigs [51,141] and rats [37]. To properly inform expected loads during colorectal stapling, similar work should be performed in human colon from all relevant clinical contexts, e.g., varying age, sex, BMI, genetic background, and medical history. Doing so will provide a framework to understand load requirements for mechanical design and may also inform investigations of mechanically-mediated colonic healing.

Material modeling and simulation of the colon. While *ex vivo* data can facilitate understanding of native loading conditions and material requirements, limitations persist including technical, sourcing, and financial constraints which increase difficulty in fully characterizing the tissue. Thus, experimental data that give way to constitutive modeling combined with numerical simulations can improve clinical insight and efficiency. Many studies investigating material behavior of the colon also leveraged constitutive modeling to lend insight into the experimental data. These include incorporation of exponential strain energy functions to accurately capture the nonlinearity of the tissue. These strain energy functions can take various forms, ranging from purely phenomenological [48,52] to variants accounting for combinations of isotropic and anisotropic materials [46,47,49,53,54]. Puértolas et al. [47] modeled colonic data from their own planar biaxial testing using five commonly implemented constitutive models and found that the microstructurally-motivated model originally proposed by Baek et al. [55] provided the best predictive capability for the data. Such observations highlight the importance of understanding microstructural content and organization of the tissue to properly inform analytical and numerical simulations.

Constitutive formulations have been utilized to model the colon for multiple purposes. Zhao et al. modeled mouse colorectum using finite element analysis to demonstrate differences in layer-specific and anatomically disparate spatial distribution of stresses in the colon wall [54]. Simulations were validated against experimental findings from the same lab which included planar biaxial testing and inflation-extension testing of whole and layer-dissected mouse colon [56]. Others have performed finite element simulations to inform mechanical parameters which may drive development of diverticulosis using material data from healthy swine colon under inflation-extension testing [57]. These data provide an excellent foundation for simulations which aim to capture detailed spatial information or inform disease progression; however, limitations exist such as the animal model of choice or lack of radial compression data which inhibits application in parametric studies of medical device design.

Others have performed parametric studies of colonic stents for design purposes, but the simulations lack detailed data regarding the material behavior of the tissue and rather focus exclusively on the properties of the stent [58,59]. Indeed, peristaltic contractions are modeled with imposed displacements [59] rather than on interactions between the tissue and device, which have been modeled in other contexts such as esophagus [60]. Investigations of surgical stapler performance have been performed numerically by leveraging compressive material properties of porcine colon, but the material model is purely phenomenological [52]. Notably, these simulations lack consideration of the viscoelastic behavior of the tissue which has been shown experimentally in gastrointestinal tissue and modeled numerically [61–63]. Such a gap highlights the need for experimental, analytical, and computational testing of tissue under clinically relevant loading conditions. For example, tissue testing and modeling should comprise compression speeds which are typically implemented with surgical staplers. Quantifying spatial and temporal changes in stresses imposed by staples after intraoperative deployment will better inform biological responses which may lead to adverse postoperative outcomes such as anastomotic leak. Realization of such experimental data and modeling capabilities will not only support enhanced capacity for parametric studies in device design but also future efforts to implement computational models as diagnostic tools which can inform intraoperative and postoperative decision-making (i.e., the digital twin) [64].

Colorectal mechanobiology

Extensive data exist regarding mechanosensing and mechanotransduction in the colon relating to visceral sensation and physiological function (e.g., motility). It is not the intent of this review to recapitulate the data available in these spaces, and the interested reader is referred to multiple excellent reviews [65–69]. While these data are helpful in understanding structure and function of the colon, little data exist which demonstrate roles of applied mechanical forces in maladaptive colonic remodeling. Therefore, our aim is to summarize the data that do exist with specific focus on surgical applications and highlight relevant knowledge gaps which require further investigation.

Roles of mechanical forces in growth and remodeling of tissue are well established in a variety of fields. Mechanical loading drives embryological development [70], homeostatic maintenance of tissue structure and function [71,72], and adaptation to endogenous and exogenous stimuli [73–77] through feedback mechanisms between a cell's intracellular tension and the matrix's exerted stiffness to remodel the matrix. In each of these contexts, it is critical to establish relevant loading conditions, microstructural environment, and cell populations of interest. Each cell type in the colon experiences a variety of complex mechanical stimuli which depend on physiological demands, disease states, and exogenous interventions, and virtually all cell types residing in the colon contain subpopulations which act as mechanosensors [66,78]. The predominant cell population in the healthy adult colon is epithelial cells, with smaller levels of endothelial, fibroblast, mesenchymal, B, and T/NK cells; recent advances in spatiotemporal transcriptomics have begun to identify diversity within each of these cell populations that may predict disease formation [79].

Fibroblasts and myofibroblasts are among the most well-studied cell populations known to drive matrix remodeling in a variety of tissues. Fibroblasts respond to their microenvironment stiffness and deposit collagen or secrete MMPs to increase or decrease stiffness, respectively, to achieve homeostasis [80]. Through mechanical stress from ECM stiffness, activation of TGF-1β, and binding to integrin αV, fibroblasts undergo phenotypic transformation to contractile myofibroblasts, through activation of the contractile protein αSMA [81]. Due to their contractile ability, myofibroblasts are ubiquitous in dermal wound closure [82], and have also been found in other contexts to tension the extracellular matrix and repair the tissue [83,84]. However, prolonged presence or chronic dysregulation of these myofibroblasts leads to excessive matrix deposition, crosslinking, and ultimate stiffening, and has been associated in tumor progression and Crohn's disease [85]. Epithelial cells lining the mucosa are responsible for the highly regenerative capacity of the colon lining [86]. However, in cases of chronic inflammation, epithelial cells can lose their regenerative capacity, and instead undergo epidermal differentiation due to increased intracellular

mechanotransduction from the YAP-TAZ/β-catenin pathway [87]. In addition to inflammatory diseases local to the gastrointestinal tract, disease arising from diabetes and obesity also cause systemic chronic inflammation [88], thereby potentially altering the regenerative capacity of the tissue through impaired mechanotransduction.

Fluid shear stress on the colonic epithelium is intermittent due to peristaltic contractions and highly dependent on mucus and fecal properties as well as rate of propulsion [89]. Mechanical stretch of the colonic epithelium drives balance of cell proliferation and apoptosis to maintain homeostasis in epithelial turnover [90]. Similarly, mechanical stretch of colonic smooth muscle stimulates TGFβ1 and α1 collagen expression [91]. The critical role of mechanical loading in maintaining homeostasis is exemplified in a bioreactor of human colonic biopsies, where perfusion-culture maintained microenvironment architecture and cell populations superior to static-culture [92]. These functions and many more contribute to structural and physiological homeostasis of the tissue, and while perturbations to these parameters have been investigated in the context of disease progression, rarely has the relationship between surgically applied forces and postoperative outcomes been evaluated in colorectal contexts.

Mechanics as an input to anastomotic healing. Colorectal surgery necessarily requires transection of tissue to remove diseased tissue as well as combined compression and tension to repair remaining tissue. Consequently, two tissue remodeling cascades may occur simultaneously: 1) mechanically-mediated growth and remodeling of native tissue due to compression and tension, 2) tissue regeneration and repair in response to transection. Though these responses may work simultaneously and synergistically to restore function to the tissue, it is likely that disparate underlying signaling pathways drive these processes, and each process should be understood independently to optimize opportunities to reduce adverse postoperative outcomes.

Many fundamental studies have elucidated roles of mechanics in classic wound healing contexts, namely, following incisional or excisional dermal wounds [93]. *In vitro* and *in vivo* studies together have demonstrated efficacy of tension reduction in promotion of regenerative rather than fibrotic wound healing [94,95]. Interestingly, large animal studies have revealed a key role of classical mechanotransduction pathways in profibrotic wound healing and demonstrate further that disruption of these pathways during normal wound healing can accelerate the healing process toward a regenerative skin phenotype [96]. While these studies and others are helpful in establishing the precedent of mechanically-mediated signaling in wound healing, the results do not necessarily translate to colonic wound healing following surgical intervention due to significant differences in cell populations, extracellular matrix structural content, microbiological environment, and mechanical loading. Indeed, though detailed mechanistic studies of mechanotransduction in colonic wound healing are lacking, a recent study demonstrated a critical role of YAP/TAZ signaling in proper repair of the colonic epithelium in response to colitis-induced injury [97]. This observation appears to contrast with results obtained in mechanically-mediated skin regeneration [96], but the differences may lie not only in physiological differences between colon and skin, but also in animal model of choice (i.e., pig vs. mouse) or wound model of choice (i.e., excisional wound vs. ulceration). Still, the observations highlight the need for additional studies in mechanically-mediated colonic wound healing to better elucidate mechanisms which may promote adverse postoperative outcomes such as anastomotic leak.

Perhaps the most relevant study investigating roles of mechanics in anastomotic healing systematically evaluated differences in suture placement and applied tension to suture on downstream vascularization of anastomotic wounds in rats [98]. The study investigates loads applied to the site of anastomosis by varying uniformity of compression (i.e., short vs. long interrupted sutures, cf. Fig. 3A illustrating distances between sutures) and magnitude of compression (Fig. 3B illustrating qualitative categories of suture tension and subsequent tissue compression). The study found that long interrupted sutures were insufficient for preventing mucosal prolapse regardless of the magnitude of compression, and more uniform compression (i.e., short interrupted suture) promoted better tissue apposition and wound healing with a "moderate" suture tension, pointing to the role of compressive force in optimizing the wound healing cascade. As recently as 2013, a systematic review investigating a variety of variables in colorectal anastomosis technique which may affect postoperative outcomes reports that Waninger et al. remains the only study in which suture tension (and thus applied compressive pressure) is systematically investigated as a variable driving anastomotic healing [99]. Although such studies remain lacking, interest in compression as a mediator of colonic remodeling appears to remain. Indeed, devices for performing compression anastomoses continue to reside in the market and tout better compression profiles in creation of colorectal anastomoses as a driver of better wound healing in preclinical models [100,101].

Still, the "optimal applied force" in colorectal anastomoses remains unknown and an area of interest for many surgeons and manufacturers [102]. While none have quantitatively demonstrated a direct link between tissue compression and anastomotic leak, some studies have systematically investigated the influence of applied compression on tissue damage [103–109]. Various markers are used to quantify tissue damage including apoptosis [104,106,109], necrosis [106,109], inflammation [104,107], matrix damage [110,111], gross structural changes [103,107,108,112], and functional physiological changes (e.g., loss of vasocontractility) [105]. In the few studies directly investigating colon, at least one report details statistically significant changes to muscular cross-sectional area with applied pressures exceeding 96 psi applied for at least 60 s or 222 psi applied for as little as 5 s. The authors do not explicitly identify a "safe" threshold of compression, but others report maximum applied pressures of 87 psi to achieve patent anastomoses, suggesting that pressures need not exceed this value for proper tissue apposition and therefore should not exceed this value to minimize tissue trauma (though tissue trauma is not explicitly investigated in this study) [102]. These numbers follow closely with *ex vivo* evaluations of compression-induced trauma to human colon in which histopathologic scoring revealed a conservative cutoff of 50 psi to minimize tissue trauma [112]. The agreement between compressive loads which induce tissue trauma and those which are sufficient for patent anastomoses highlight a potential relationship between gross tissue trauma and optimal postoperative healing. None of these reports investigate cellular responses to applied forces, and those that do prescribe deformations rather than loads [106,109] or investigate significantly lower maximum pressures (e.g., 1.38 psi in rat arteries [105], 34.8 psi in porcine small bowel, liver, and ureter [104], 7.98 psi in rabbit small bowel [107]). However, a link between acute or subchronic tissue damage and anastomotic leak (or other forms of maladaptive tissue remodeling) has yet to be firmly established.

Importantly, the "optimal" compression profile (i.e., magnitude, rate, and duration of applied compression) must not be a one size fits all value, but rather a tailored value which considers patient factors as well as preoperative and intraoperative data to promote regenerative healing processes in a patient-specific manner. Many investigators are beginning to recognize the opportunity to leverage combined experimental and computational data to identify relevant mechanical parameters in tissue damage [73] and wound healing cascades [113] which open further opportunity to leverage state-of-the-art models toward patient-specific surgery. However, patient-specific surgery can only be achieved by the generation of significant amounts of data to aid in understanding the complex interplay between mechanics, tissue remodeling, and wound healing in clinically relevant disease contexts.

Mechanics as an output of anastomotic healing. While the precise mechanical mechanisms influencing anastomotic healing remain under-characterized, mechanical strength stands as a gold standard in evaluating anastomotic integrity [114,115]. Studies investigating

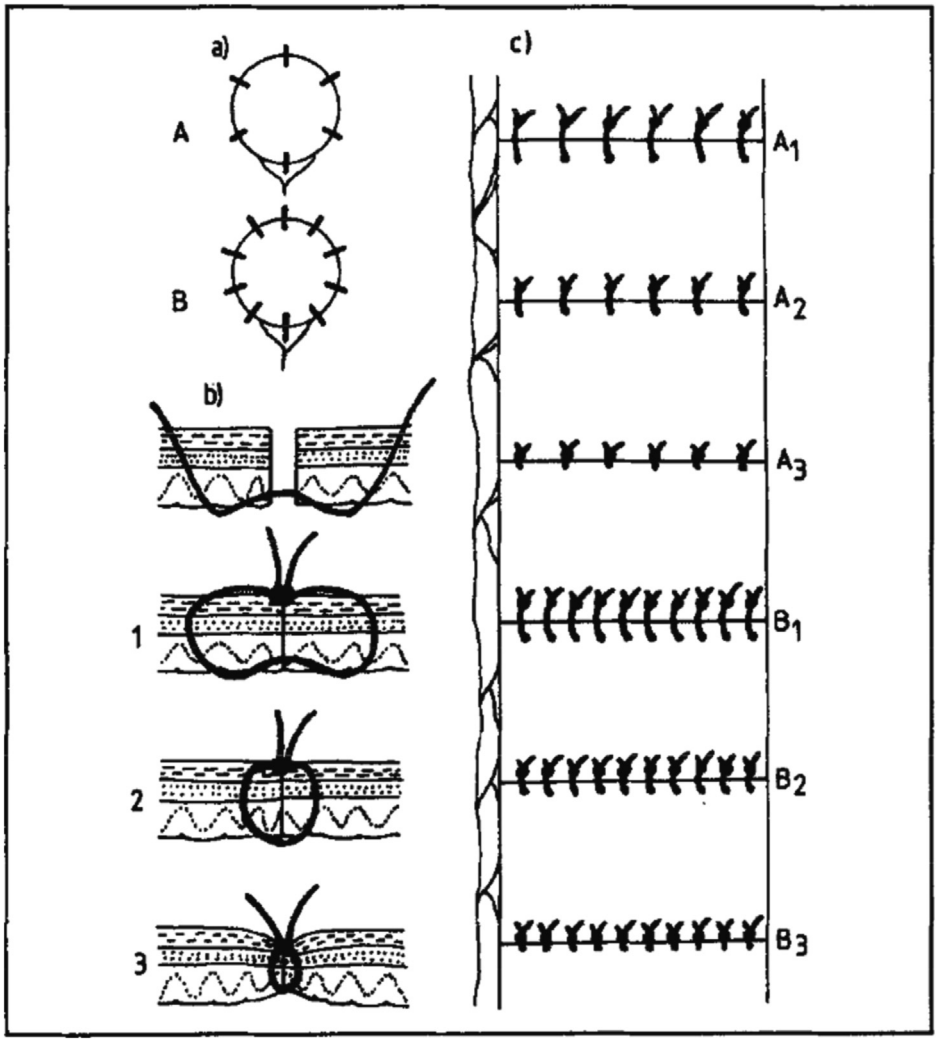

Fig. 3. Summary of suturing conditions implemented in the study by Waninger et al. Experimental groups consisted of low, moderate, and high applied pressure at the site of apposition (denoted by groups 1, 2, and 3, respectively) and high and low suture distance (denoted by groups A and B, respectively). Together, these conditions created six experimental groups which systematically interrogated the effects of compression magnitude and uniformity on the healing of colonic anastomoses in rats.
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various contributors to anastomotic healing abound, and many investigators utilize metrics which directly or indirectly relate to the mechanics of the tissue; namely, burst testing or tensile testing as a metric for anastomotic strength and/or collagen deposition or hydroxyproline expression as a metric for appropriate extracellular matrix remodeling. These metrics and others provide a relatively consistent methodology for evaluating specific variables as mediators of anastomotic wound healing.

Because of the high-throughput nature and greater degree of control in rodent models, most anastomotic healing studies are performed in rats or mice. These most often include sutured anastomoses rather than stapled due to the size limitations of the animals; however, the information obtained from these studies can still translate well to stapling applications. One key area of investigation is the relationship between nutrition, colonic microbial content (i.e., the microbiome), and alteration of tissue mechanical properties via enzymatic degradation of collagen. At least one study demonstrated an increase in tensile strength of colonic anastomoses at postoperative day 21 with proper preoperative feeding compared to malnourished controls [116]. This observation was correlated with increased expression of collagen type I and an increased collagen maturation index. This study did not systematically evaluate dietary content but simply altered the total intake of food for malnourished and preoperative feeding groups. However, others have investigated roles of specific micronutrients in activating enzymatic pathways. Insulin and galacto-oligosaccharides supplemented for 2 weeks prior to surgery increased hydroxyproline content and reduced enzymatic activity of matrix metalloproteinase 9 (MMP-9) at postoperative day 6 in mice [117]. These observations correlated with increased anastomotic healing score defined by enhanced mucosal and muscular continuity and re-epithelialization. Similarly, other groups have shown increased risk of anastomotic leak in mice fed with a high-fat/low-fiber or "western" diet compared with chow-fed controls, an observation that is reversible with a short course of standard chow preoperative feeding for 1 week [118]. Though the study does not explicitly investigate collagen content, the authors report increased content of collagenolytic *E. faecalis*, a bacterial strain which has been shown by the same lab to induce MMP-9 activation, reduce collagen content, and potentiate anastomotic leaks in mice [119].

Other variables have been investigated in the context of anastomotic healing using similar analyses of anastomotic strength. Preoperative treatments and/or conditions which may alter tissue structure and function have been evaluated as an input to anastomotic healing. Preoperative radiotherapy is a significant consideration given its possible association with clinical anastomotic leaks [4]. When leveraging burst strength or collagen content as an indicator for anastomotic healing, preclinical models are conflicting regarding roles of preoperative

radiotherapy, with some suggesting no difference in burst strength [115,120] or similar metrics [121] while others report a decrease in burst strength with radiotherapy [122,123]. Interestingly, while some suggest that radiotherapy alone is not sufficient to induce anastomotic leak, one study suggests that radiotherapy applied in more highly collagenolytic environments significantly predisposes to leak via enhanced MMP activation [121]. Conversely, the single study demonstrating sufficiency of radiotherapy to impair anastomotic wound healing also demonstrates a beneficial effect of soluble fiber administration in reducing MMP-2 activation and improving burst strength [122]. Other studies similarly evaluate variables such as hypoxia in the development of anastomotic leaks with similar disagreement among studies [124–126]. Importantly, the use of rodent models offers the opportunity to evaluate anastomotic healing propensity in the context of clinically relevant diseases such as diabetes [127], colitis [128,129], and other conditions [130].

Though mechanical properties of the tissue are a helpful tool for evaluating these and other variables in anastomotic healing, it is noteworthy that many of these variables may alter the material properties of the tissue prior to surgical intervention and formation of anastomoses. Gamma radiation drives collagen damage and remodeling in rat tail tendon [131], and although this phenomenon has not been reported explicitly in colon, reports detailing changes to proteolytic enzyme activity and edema following irradiation point to possible preoperative changes to tissue properties which may affect the "optimal" compression during creation of intestinal anastomosis [132,133]. Similarly, tissue remodeling in the context of diabetes [14,134,135] combined with altered wound healing capacity suggests a need for tailored treatment of the tissue during creation of anastomosis.

Conclusions and remaining gaps

It is well-established that the tissue's mechanical environment, both from intrinsic, composition-imparted mechanical properties, as well as external mechanical forces, influences the cellular response, and vice versa, through mechanotransduction pathways. However, the optimal mechanical stapling profiles remain unknown due to an incomplete understanding of the full mechanical environment of colon. Experimental characterization of the local mechanical environment will help to understand loads sensed by the intramural cells. The consequences of the mechanical environment on cellular responses and healing following stapling are largely unknown. Principles of wound healing from stapling borrows largely from dermal wound healing, which lacks some of the specialized cell types, structure, and mechanical environment of the colon. Furthermore, there are biological effects from the stapling loads that may activate additional healing cascades. Thus, there is a gap in the understanding of the specific mediators of improved and aberrant healing processes. Here, there is an opportunity for the field to increasingly leverage cellular and molecular biology technologies to evaluate the effects of mechanical loading in colonic wound healing. Taken together, improved characterization and understanding of the interplay between mechanics and biology of the colon can lead to optimal, patient-specific stapling technologies to improve clinical outcomes.

Funding sources

The research and writing for this review were sponsored and funded by Medtronic (Minneapolis, MN, USA) and we thank the company for its support.

Ethical approval statement

Development of this review did not involve author participation in studies with human or animal subjects and therefore did not require institutional ethical review.

CRediT authorship contribution statement

A.W.C. conceived of the manuscript, reviewed all relevant literature topics, and drafted supporting text, figures, and tables. M.C. reviewed tissue mechanics and mechanobiology literature and drafted supporting text and figs. S.J.B. reviewed mechanobiology literature and drafted supporting text. E.M.C. reviewed clinical stapling literature and drafted supporting text.

Conflicts of interest

A.W.C., M.C., S.J.B., and E.M.C. are or were employees of Medtronic PLC when contributing to the development of this report.

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