The esophagiome: integrated anatomical, mechanical, and physiological analysis of the esophago-gastric segment

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The Esophagiome: the Value of Anatomical, Mechanical and Physiological Data

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Abstract:

Esophageal diseases are highly prevalent and carry significant socioeconomic burden. Despite the apparently simple function of the esophagus, we still struggle to understand the physiology and pathophysiology. There is increasing recognition that alternative approaches must be pursued. High-resolution data assessment and application of multiscale mathematical organ models have gained attention as part of the Physiome Project. This was long recognized in cardiology but only recently gained attention for gastrointestinal tract. The term “Esophagiome” implies a holistic assessment of esophageal function from cellular and muscle physiology to the mechanical responses that transport and mix fluid contents. These anatomical, mechanical and physiological models underlie development of a “virtual esophagus” modeling framework to characterize and analyze function and disease. Functional models incorporate anatomical details with sensory–motor responses, especially related to biomechanical functions such as bolus transport. This review builds on top of previous reviews following the Esophagiome Congress held by OESO in 2015. The focus is on assessment of detailed anatomical and geometric data with advanced imaging technology for evaluation of gastro-esophageal reflux disease, and on esophageal mechanophysiology assessed with distension technology. Esophageal models will ultimately be validated using high-resolution data and provide predictions of novel endoscopic, surgical, and pharmaceutical treatment options.

Key words: Esophagiome; Esophago-Gastric Junction (EGJ); Gastro-Esophageal Reflux Disease (GERD); Imaging technology; Mechanosensation; Modeling

Introduction

The esophagus and the esophago-gastric junction (EGJ) constitute a sophisticated organ for transportation of swallowed fluids and food to the stomach, while preventing reflux of excessive gastric contents into the esophagus. Reflux can cause symptoms of gastro-esophageal reflux disease (GERD). Esophageal diseases are highly prevalent and carry significant socioeconomic burden worldwide[1]. Despite the apparently simple function of the esophagus, we still struggle to understand the physiology and pathophysiology. This is especially true when it comes to GERD. The functions of the esophagus, the EGJ and the upper esophageal sphincter (UES) are underpinned by coordination between anatomical, neurological, and myogenic factors, which require investigations that take into consideration these physiological functions across multiple spatiotemporal scales. There is increasing recognition that alternative approaches that include biomedical engineering, mathematics and computer science must be pursued. One must consider not only the mechanical function of the esophagus but the mechanisms involved in painful conditions, disease states and the generation of other symptoms. Studying pain mechanism in humans is truly complex and require advanced technology and stimulations. For this, it is well known that it requires a stimulus that can be controlled and delivered repeatedly and that responses can be assessed quantitatively with psychophysical and/or neurophysiological methods. However, it also requires that we can model the data using advanced models while taking complex mechanical and sensory aspects into consideration. Peripheral as well as central mechanisms and conditions mimicking pathological pain must be studied.

Assessment of high-resolution data sets and application of multiscale mathematical organ models have gained attention as part of the Physiome. The Physiome project is an effort to gain insight into the neurophysiology and function of the organs of the human body [2]. The term is derived from “physio” (the physiology of the body) and “-ome” (as a whole). The Physiome is the quantitative description of the functioning organism in normal physiological and pathophysiological states using mathematical and computer modeling. The Physiome project is an effort to explain how component in the body, from the molecular scale up to organ systems and beyond, works within the integrated whole. It is a multicenter integrated program to design, develop, implement, test, document, archive, and disseminate quantitative data and integrative models of the functional behavior of the human body [2] (Hunter 2004). Development of multiscale mathematical models capable of predictive investigations of biological function is receiving attention in a number of disciplines in the Physiome project [2, 3].

The Physiome concept has for decades been recognized in cardiology and orthopedics but only recently gained attention for the gastrointestinal (GI) tract. An effort related to the GI tract was first described in 2006 as the GIOME [4] and work has been presented in a series of papers from different groups related to the virtual stomach and intestines [5-9]. The term “Esophagiome” imply a holistic, multiscale treatment of esophageal function from cellular and muscle physiology to the mechanical responses that transport and mix fluid contents. Anatomical, mechanical and electrophysiological models underlie development of a “virtual esophagus” modeling framework to characterize and analyze function and disease. Functional models incorporate

anatomical details with sensory–motor properties and functional responses, especially related to biomechanical functions such as bolus transport. Papers have recently been published on the “virtual esophagus” [10-15]. The term “Esophagiome” gained attention as the overriding theme at the 13th OESO Congress in 2015 (www.OESO.org). A great deal of research has been carried out specific to esophageal mechanics and physiology using mathematical and computer modeling. Significant research in this regard has been published by many interdisciplinary groups 10-13, 15-39. However, much of this research has not yet been integrated into clinical sciences in gastroenterology, where the greatest potential impact might be realized.

This review builds on top of previous reviews following the Esophagiome Congress in 2015 [6, 40]. Those reviews focused on computer modeling and implementation of multi-scale models. Computer models need validation using experimental data. Mechanical data are dependent on anatomical and geometric data, and the primary function of the esophagus is mechanical. Therefore, the focus of the present review is on assessment of detailed anatomical and geometric data with advanced imaging technology and on esophageal mechanophysiology assessed with distension technology in the normal esophagus as well as in GERD. Esophageal models will ultimately be validated using high-resolution big data and provide predictions of novel endoscopic, surgical, and pharmaceutical treatment options.

Structure and Function of the EGJ

The EGJ is the major defense against reflux of gastric contents into the esophagus; however, normal EGJ function is crucial also for normal esophageal swallowing and

venting of air (belching). These represent opposing demands and the complex structure and function of the EGJ reflects this need to allow bolus passage whilst preventing excessive reflux of gastric contents [41]. It follows that EGJ pathology, for example the presence of hiatus hernia, will either impair the passage of food and fluid from the esophagus into the stomach or increase the risk of gastroesophageal reflux. This section reviews the structure and function of the EGJ in health and how this is disrupted in patients with GERD.

EGJ Anatomy

The EGJ comprises an intrinsic component made up by smooth muscles of the lower esophageal sphincter (LES) with the gastric cardia, plus an extrinsic component formed by the crural diaphragm [42-47]. These two components are brought together into a functional unit by the phreno-esophageal ligament that anchors the LES to the crural diaphragm.

In health, LES is 3-4cm long extending from just above the squamo-columnar junction (Z-line) into the proximal stomach with distinct upper and lower sections. The upper section comprises relatively thick, tonically contracted esophageal smooth muscle fibers and the lower section comprises the sling and clasp muscle fibers of the gastric cardia [43, 47]. The acute angle of insertion of the esophagus into the stomach ("angle of His") creates an additional level of protection against reflux at this level. The function of the intrinsic sphincter is modulated by vagal tone such that LES pressure is higher in expiration than inspiration. The striated muscle of the crural diaphragm, which forms the esophageal hiatus, encircles the proximal 2cm of the LES; an anatomical arrangement

that increases EGJ pressure during inspiration, coughing and abdominal straining [42, 46]. Thus, the intrinsic and extrinsic components of the EGJ have complimentary effects that provide effective reflux protection throughout the respiratory cycle and during physical exertion.

EGJ Function

On pharyngeal swallowing a vagal reflex is triggered that results in “deglutitive” relaxation of the esophagus and LES to allow bolus transit from the mouth to the stomach. Repetitive swallowing results in complete relaxation of the intrinsic LES and the extrinsic crural diaphragm to facilitate rapid intake of food and fluid. During this process, relaxation of the proximal stomach (“gastric accommodation”) ensures that the stomach can be filled without an important increase in intra-gastric pressure.

Ingestion of a meal is accompanied by gastric secretion that tends to collect immediately below the LES forming an “acid pocket”. The acid pocket is a supernatant layer of gastric acid overlying an ingested meal immediately below the EGJ. In health, the transition from the acid to alkaline milieu occurs at the EGJ [48]. However, when the barrier is weak or disrupted this transition point can migrate proximally, leading to prolonged acid exposure of the distal esophagus [49-51]. This is observed in patients with mild-moderate GERD with a weak EGJ and is particularly marked in patients with severe GERD in the presence of hiatus hernia. After ingestion of a meal, gastric filling is accompanied by a decrease in LES pressure and an increased frequency of spontaneous, transient LES relaxations (TLESRs) that allow air swallowed during the meal to be released (belching). This is required to avoid gastric bloating. However,

these events represent a major challenge to the EGJ reflux barrier. In addition to belching, a small number of reflux events during TLESRs after meals is normal in healthy individuals. The number of TLESRs is not necessarily higher in patients with mild-moderate GERD. However, the risk of acid reflux events occurring during these relaxations is much higher in this disease. This observation implies that factors other than LES motility and function are involved in reflux protection.

Studies using magnetic resonance imaging combined with high-resolution manometry (HRM) have shown how active contraction of the clasp and sling fibers maintains an acute angle of insertion between the esophagus and the proximal stomach (termed “angle of His” in surgical studies) [52, 53]. Biophysical analysis on 3D models of EGJ anatomy derived from MR images have shown that the presence of an acute angle of insertion allows the proximal stomach to compress the EGJ during gastric filling and that this prevents reflux of gastric contents into the esophagus after meals (Figure 1) [54]. This “flap-valve” effect is much less efficient if the angle of insertion is wide (obtuse) due to ineffective contraction of the clasp and sling fibers or structural disruption of EGJ anatomy, both of which are observed in GERD patients [52]. The importance of smooth muscle function in maintaining the acute angle of insertion was demonstrated in a study that combined HRM and MRI measurements in which patients and controls were investigated after ingestion of baclofen or placebo before and after a large test meal. As expected, the GABA-B agonist inhibited the number of transient LES relaxations and augmented LES pressure. However, baclofen also increased distal LES length and maintained the acute angle of insertion in GERD patients after meal ingestion. These effects on the 'functional anatomy' of the reflux barrier indicate that tonic contraction of

the clasp and sling fibers of the gastric cardia (the distal segment of the EGJ) provide reflux protection by maintaining the aforementioned 'flap valve' mechanism.

Mechanism of Reflux

Large studies have identified several markers that correlate with the severity of reflux defined by the presence of reflux esophagitis or pathological acid exposure on 24hr pH-studies. These include resting LES pressure, intra-abdominal LES length (i.e. distance between PIP and distal LES border. In these studies hiatus hernia is defined by a negative intra-abdominal LES length. Disorders of esophageal motility that impact on clearance function [55-58]. More detailed observations after a test meal identify three main mechanisms that cause individual reflux events [59-62]:

(i) Transient LES Relaxation (TLESR). In health and in patients with mild-moderate GERD most reflux occurs during TLESRs characterized by a period of complete, prolonged (10-60 seconds) relaxation of the LES and crural diaphragm that is not caused by swallowing [62-64]. Gastric distention, laryngeal or pharyngeal stimulation provide the afferent stimulus for the TLESR reflex, which is mediated by a series of events from the dorsal vagal nucleus and nucleus ambiguous via vagal efferent fibers [42].

(ii) Swallow-induced LES relaxations. In health about 5-10% of reflux episodes occur during swallow-induced LES relaxations [65]. The relatively low risk of reflux events during swallow-induced LES relaxations compared to TLESRs is due to incomplete and shorter relaxation of the crural diaphragm during swallowing and immediate clearance of reflux by oncoming peristalsis [65, 66].

(iii) Very low or absent LES pressure is an uncommon cause of reflux in health [60, 61]. However, it occurs frequently in the absence of a mechanically sufficient reflux barrier in patients with a hiatus hernia and severe GERD [62].

High-Resolution Manometry (HRM) can identify TLESRs and other potential causes of reflux more accurately than previous methods [64]. Moreover, the presence of "common cavity pressure" (i.e. equilibration of pressure) between the stomach and the esophagus indicates the occurrence of a reflux event. The introduction of combined high-resolution impedance manometry (HRiM) supports this observation by direct detection of retrograde flow of gastric contents (i.e. reflux) during TLESRs (Figure 2) [64, 67]. It is also possible to discriminate between reflux of air (belching) and gastric secretions based on impedance profiles [64, 67].

After a reflux episode occurs, the refluxate is cleared most often by a primary peristaltic contraction that also neutralizes acid by bringing saliva from the mouth [68]. In GERD patients with ineffective esophageal motility (IEM) impaired esophageal clearance further prolongs acid exposure and other complications [58, 69, 70]. This is especially common in patients with more severe disease with reflux esophagitis [58, 69, 70]. This group is characterized by an absence of "contractile reserve" in which the esophagus fails to respond to the physiologic challenge of multiple repeated or solid swallows.

Factors that impact on EGJ structure and function

Age and male sex are associated with a an increased risk of GERD due to multiple factors including increased prevalence of abdominal obesity, hiatus hernia and impaired

esophageal motility [55]. A high body mass index (BMI) and, especially, a high waist circumference is associated with an increased risk of GERD in a “dose-response” manner [71]. Obesity has effects on EGJ structure and function that increase the risk of reflux by all the mechanisms discussed above [71-74]. The mechanical hypothesis proposes that obesity results in increased mechanical stress at the EGJ due to increased intra-gastric pressures and disruption of EGJ morphology (i.e. increased separation of the LES and crural diaphragm) which favors reflux [75]. Other hypotheses include the release of metabolic and humoral mediators from visceral adipose tissue that have effects on vagal activity and impact on the frequency of TLESRs [76-78].

In patients with a small hiatus hernia, separation of the LES and crural diaphragm results in a 2-fold increase in reflux events [51] and the risk of GERD increases with the size of the hiatus hernia [55, 79, 80]. The presence of a hiatus hernia has multiple effects on EGJ structure and function that increase the risk of GERD. First, the wide esophageal hiatus impairs the ability of the crural diaphragm to contribute to reflux protection [81]. Indeed, in HRM studies, reduced augmentation of EGJ pressure during inspiration is an independent risk factor for GERD [82]. Second, contraction of the crural diaphragm can trap gastric contents in the hiatal sac that can then pass into the esophagus through the (weak) LES due to negative thoracic pressure during inspiration [81]. Third, the frequency of reflux events of all kinds is increased in patients with hiatus hernia [79, 80] due to mechanical effects on EGJ and proximal gastric function. Whilst TLESR remains an important cause of reflux events in this patient group, other mechanisms appear to be more important in the presence of a hiatus hernia [83]. Additionally, once reflux has occurred, ineffective esophageal motility and impaired

esophageal clearance are common in patients with a large hiatus hernia [84, 85]. Together, these effects result in prolonged exposure of the distal esophagus with acid gastric secretions that cause reflux esophagitis, Barrett esophagus and other complications in GERD.

EGJ structure and function, and GERD

GERD is a complex condition that is defined by the presence of mucosal disease and / or symptoms associated with the retrograde flow of gastric contents into the esophagus [86]. As such, no one measurement of EGJ structure and function provides a definitive GERD diagnosis (although a robustly normal value may rule GERD out) [87]. Notwithstanding this fact, typical GERD patients often have reduced resting EGJ tone and / or disruption of the EGJ barrier (i.e. hiatus hernia). Abnormalities of EGJ structure and function can coexist, and both can contribute to a pathological reflux burden. It is clear that pharmacological therapy does not correct this underlying pathology; whereas, anti-reflux surgery does prevents reflux by (i) restoring the position of the EGJ by reduction of a hiatal hernia and repair of the hiatal orifice and (ii) reducing distensibility of the EGJ and the number of TLESRs associated with reflux by formation of a fundoplication wrap that limits EGJ opening [88, 89]. This surgery reduces the number of reflux events and acid exposure more effectively than other treatments.

It is evident from the review above that GERD is a complex disease where anatomical, geometric, muscle function as well as sensory factors play a role. Due to this complexity, measurements by any one technology (e.g. manometry, imaging) do not fully describe the complex pathophysiology of this condition. For example both

anatomic and pressure data must be integrated to assess factors such as mechanical stress that cannot be measured directly but have to be computed using constitutive equations. The Esophagiome offers a structured approach to such complex problems.

Novel bioengineering and clinical tools for studying the EGJ

Geometric Profiling and its Value in the Esophagiome

Geometric profiling is a method to establish the profile of the geometry of the esophagus as an aid to visualizing and measuring the changes in biomechanical and structural function of the lumen in health and disease. Figure 3 identifies traditional diagnostic methods and what they can do to get measurements of esophageal function. None of these methods provide objective measures of the luminal geometry in the esophagus. Geometry has the potential to better represent opening and closing patterns in luminal organs which in turn can help us understand the esophagus structure in health and disease. Used in conjunction with intramural pressure, it can be used to estimate the force of closure of the lumen walls, also known as wall tension [90]. Methods not used widely in clinical practice but in research to estimate tension include endoscopic ultrasound (EUS), Computed Topography (CT) virtual endoscopy, and impedance planimetry that evolved into the Functional Luminal Imaging Probe (FLIP) for distensibility measurements (see later).

EUS has the ability to measure two-dimensional cross-sectional geometry but the radial-scanning probes must be moved longitudinally to obtain three-dimensional information (z axis). This can be painstaking at best and not possible at all when the continuous motor patterns in the normal esophagus are taken into account. For similar

reasons CT is not practical. Endoscopic images are of limited use in this context. It is in effect a 2D representation of a 3D structure and although shape and form in the image provide surface data, we cannot easily make objective measurements of important geometric variables.

Valves do not necessarily have to squeeze tight to be competent. Therefore, manometric studies only provide part of the assessment. Measuring the amount of opening or the opening pattern as cross sectional geometry of a valvular region may be more accurate and provide better diagnostic information [91]. With the introduction of various balloon distension techniques, the concept of distensibility testing as a measurement method has evolved. Distensibility has only been used in recent times in digestive diagnostics. Initially it was used to describe the placement and inflation of an allantoid shaped bag or balloon in the region of the EGJ. These techniques were cumbersome such as the hydrostat by Pandolfino and coworkers [92]. Impedance planimetry was originally developed to study distensibility in luminal organs and evolved into the multi-channel FLIP technology that provided data on luminal geometry. This was further refined to allow the cross-sectional area at the narrowest point in a lumen or valvular region to be plotted against bag or balloon pressure [93]. The first studies placing FLIP in the EGJ demonstrated how it could be used to asses geometry throughout the region [94]. The FLIP system can measure serial cross-sectional areas at high spatial and temporal resolution but cannot provide data on the symmetry of the lumen and on wall thickness. In essence using the FLIP technique, we can inflate a cylindrical bag capable of measuring multiple cross-sectional areas at fixed distances along the lumen of the esophagus. The relation between the narrowest cross section and bag pressure

can be recorded. Figure 4 illustrates this by showing the cross-sectional area measurements through the narrow region (figure 4A) and then a representation of this narrow region in the form of a three-dimensional diagram where the geometric lines represent the cross- sections and the colour change the increase in cross section in mm^2 (figure 4B).

Aspects to distensibility testing have been shown in healthy controls and also to demonstrate different valvular region geometries between healthy controls and patients after anti-reflux surgery [94]. Some investigators found that GERD patients exhibited a two to three fold increase in distensibility at the EGJ [95, 96]. Another group found that they were not able to distinguish between normal controls and GERD patients but a confounding factor may have been that the GERD patients were generally obese [97]. Other examples are demonstration of geometric changes after endoscopic anti-reflux procedures such as Esophyx™ [98]. It has also been used to show geometric changes associated with hiatal hernia where the narrow regions of the lower esophageal sphincter and the crural diaphragm can be clearly observed to be separate [99]. More recently Fynne et al demonstrated that patients with systemic sclerosis have a more flaccid EGJ [100].

Other investigators have assessed geometric data y in the body of the esophagus using FLIP. As this data is quite complex, it can be visualized better using color contour plotting (topography) similar to the technique used for high-resolution manometry except color changes represent cross sectional area changes instead of pressure. Evidence from studies of eosinophilic esophagitis patients show value in using this topographical technique to demonstrate changes in esophageal geometric

parameters related to the disease state [101]. Color contour plotting may also have a role in studying the geometric changes that occur in the upper esophageal sphincter (UES) during swallowing. As these swallow events are very fast causing the UES to open for less than 0.5 sec, the contour plotting may prove ideal for tracing events and identify constricted UES in certain disease groups [102].

These published examples demonstrate how geometric profiling will have a role in future studies in the monitoring and treatment of esophageal diseases. The concept should also provide a better understanding of the esophagus as an organ by providing better objective methods of form and function than existed previously. This in turn will provide better samples and models for the Human Physiome project (http://physiomeproject.org/). Initiative such as the Esophagiome project will in time lead to smarter, more precise and tailored medicine and treatments. Geometric and mechanical models based on FLIP for geometric profiling fits well here. The cross-sectional area measurements have a high spatial and temporal resolution and therefore provide data on function in real-time. If we model the data with some simple assumptions we can predict flow through the luminal region. This could be particularly important in the valvular regions at either end of the esophagus where understanding the flow of ingested food and liquids and reflux of acids and gastric contents are important. Some early studies predicting flow have been conducts but this needs further follow up and investigation [103].

Diffusion tensor magnetic resonance imaging

Diffusion tensor magnetic resonance imaging (DT-MRI) is an extension of conventional MRI with the added capability of tracking and measuring the random motion of water molecules in all three dimensions [104]. Since water diffusion is influenced by the microstructure, architecture, and physical properties of tissues, DT-MRI can provide information about how water diffuses in biological tissues containing a large number of fibers to build complicated 3D tissue architecture. DT-MRI is a promising tool to investigate the complex orientation of tissues especially the muscle architecture in the EGJ region [105, 106] which is important in the Esophagiome project. However, there are limitations due to the long acquisition time.

Technology of DT-MRI and fiber tractography

The basic concept behind DT-MRI is that water molecules diffuse differently along tissue depending on its type, integrity, architecture, and presence of barriers, giving information about its orientation and quantitative anisotropy [107]. Water molecules tends to diffuse predominantly along the long axis of the fibers. The anisotropic nature can reveal the microscopic properties of the anatomy of the fibers in the organs [108]. DT-MRI is sensitive to this anisotropy and is able to characterize it by noninvasively quantifying and assessing the self-diffusion of water *in vivo* or *in vitro*. The information of the local fibers orientation extracted from the water anisotropic diffusion in the organs forms the basis of utilizing DT-MRI to reconstruct fiber pathways and to build connectivity map. DT-MRI characterizes the diffusion behavior on a voxel by voxel basis and for each voxel, the diffusion tensor yields the diffusion coefficient corresponding to any direction in space [109]. The direction of the greatest diffusion can be determined by evaluating the

diffusion tensor in each voxel, which corresponds to the dominant axis of the fiber bundles traversing the voxel. Therefore, the DT-MRI model assumes that, in each voxel, there is a unique orientation of the fibers, the direction of which is represented by the tensor's main eigenvector. This assumption is not valid in case of crossing fibers. Therefore, It is unable to resolve multiple fiber orientations within an MRI voxel [110]. In order to map the structure of fiber crossings, i.e. when the fibers are interdigitating, brushing past each other, curving, bending or diverging, more advanced MR imaging methods such as diffusion spectrum MRI (DS-MRI) may be needed. DS-MRI can describe diffusion in each voxel with a probability density function (PDF) which for each voxel specifies the 3D distribution of microscopic displacements of MR-visible spins that it contains [110].

The information in the DT-MRI data can be exploited to reconstruct the fiber pathways of the organs by fiber tractography (FT). The streamline-based tracking technique is the one most commonly used in FT studies [111] and it appears to give excellent results in many instances if the principal eigenvector field is smooth and the fibers are strongly oriented along a certain direction such as white matter of brain [112]. Streamline deterministic FT has advantages that it is simple, fast and reliable. However, it also has disadvantages such as being sensitive to noise and difficulty to show the crossing fibers inside the voxel [113]. Probabilistic FT can overcome these disadvantages [113]. Furthermore, a variety of methods have been proposed aiming to overcome the limitations of the streamline tracking technique is exposed [114]. These may include diffusion tensor deflection [115], probabilistic monte-carlo method based tracking [116], and diffusion simulation-based fiber tractography [117].

DT-MRI organ architecture studies.

DT-MRI based fiber tractography has become a popular noninvasive method to track the nerve fibers of the white matter tracts in the brain [118]. In normal brain, DT-MRI based fiber tractography can visualize the characterization of white matter and the complex network of nerve fibers connecting different brain areas [119, 120]. In diseased brain, DT-MRI based tractography has been used to demonstrate different abnormalities in tumor [121], aging [122], malformations [123], Alzheimer's disease [124], multiple sclerosis [125], stroke [126], close head injury [127], alcoholism [128], and HIV infection [129]. DT-MRI has also been used to access pathologies of the spinal cord [130, 131] and peripheral nervous system [132].

Cardiology is another field that use DT-MRI mostly to track muscle fiber orientation [133-137]. The 3D architecture of the left and right ventricular myocardium have been demonstrated by DT-MRI based tractography [133, 134, 138]. Furthermore, cardiac microstructure can be measured by improved DT-MRI [139]. Cardiac DT-MRI has been used to assess tissue mechanical properties [140], cardiac contraction [139, 141], cardiac hypertrophy [142], myocardial infarction [143], ischemic heart disease [144], and myocardial fibrosis [145]. DT-MRI based tractography has been also applied to other organs, which are rich in muscle fibers such as musculoskeletal [146] and tongue [147].

DT-MRI is a promising tool to investigate muscle architecture of EGJ.

DT-MRI-based fiber tractography may be a relevant tool to investigate the complex architecture and orientation of muscle fibers in the EGJ. The 3D anatomy of EGJ was

recently reconstructed by means of histological techniques with extra high-resolution microscopic imaging [12]. However, the 3D smooth muscle fiber orientation could not be obtained from the conventional histology studies. Understanding the anatomical structures to determine the function of EGJ, we require knowledge of myofibers architecture at spatial scales. The individual layers of the normal human esophageal wall has been determined by using DT-MRI-based fiber tractography [105]. They demonstrated that diffusion-tensor MRI based tractography is able to depict eight different layers of the normal esophageal wall in vivo [105]. Furthermore, the same group also demonstrated that DT-MRI-based fiber tractography could evaluate the depth of mural invasion by esophageal carcinomas [148]. Gilbert and coworkers have examined myoarchitecture of bovine esophagus with DS-MRI and tractography [149]. They demonstrated that the esophageal muscular architecture consists of crossing myofibers. Furthermore, the degree of helicity decreases from the proximal esophagus predominated with striated muscle to the distal esophagus composed of smooth muscle fiber [149].

More recently, DT-MRI-based fiber tractography has been applied to quantitatively describe the muscle fiber arrangement in the excised and embedded porcine LES region (Figure 5) [106]. Such detailed structural studies require many hours of acquisition time. The smooth muscle fibers distributed heterogeneously across the LES region wall. In the proximal LES region, the fibers changed from the longitudinal helix crossing fiber structure in the outer longitudinal smooth muscle layer, to the circumferential helix crossing fiber structure in the inner circumferential smooth muscle layer (Figure 6) [106]. In the distal LES region, the muscle fibers transferred direction

gradually, from outer longitudinal fiber with the fiber angles distribution peaking at ±72.5 degrees to the inner oblique fibers with fiber angle distribution peaking at -47.3 degree (Figure 6) [106]. Furthermore, the flap-valve region could be detected where the fibers in this region were primarily circumferentially distributed throughout the wall [106]. DT-MRI provides a non-destructive and high-resolution method for reconstructing the fiber orientation throughout the EGJ. Such information can potentially help to explain the complex interplay of LES contraction and relaxation during food transport in the EGJ. Fully comprehensive mathematical anatomical models need such data to be integrated with mechanical data in a multiscale fashion to advance the Esophagiome field.

Perspectives

A key next step for the Esophagiome in modeling of esophageal function is to relate detailed 3D anatomical imaging data and mathematical models to physiological behavior during flow dynamics, esophageal peristalsis, and EGJ relaxations. There is a need to improve the anatomical models by incorporating microstructural detail, such as true muscle fiber orientations and muscle type. Integration of universal modeling standards and simulation environments will also be critical factors in the development of accurate sophisticated models. More specific constitutive laws and neurophysiological models of active tension generation (tone) are needed to increase the accuracy of the simulations. Models of the electrophysiological components associated with peristalsis and innervation will also provide innovative research directions. In addition, there is a need for new experimental methods, such as the development of minimally invasive and

high-resolution sensors to provide the data to both parameterize and validate mathematical models.

Despite the apparently simple transport function of the esophagus, the research briefly reviewed in this paper demonstrated clearly that the Esophagiome requires a multidisciplinary effort in which scientists and clinicians work closely together. It will require a different type of multidisciplinary team work than many in the medical field are used to today. The goals include the development of advanced mathematical and computer models to apply to advance diagnostics of GERD and other esophagus diseases, both through interpretation of mechanophysiological data and through the design of new or improved medical devices and endoscopic and surgical procedures for the benefit of patients suffering from esophageal diseases and symptoms.

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Conflicts of Interest

Jingbo Zhao and Mark Fox declare no conflict of interests. Barry McMahon and Hans Gregersen disclose that they have a royalty and milestone-based agreement with Medtronic on the FLIP technology.

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Figure legends

Figure 1

Left panel: Three-dimensional (3D) reconstruction of the esophagus and proximal portion of the stomach at the EGJ from representative anatomic images in a healthy female volunteer. Right panel: A slicing plane rotating around the esophageal axis at 6° increments is shown schematically allows measurement of the esophago-gastric insertion angle. Schematic of one representative plane through the proximal stomach and distal esophagus shows the definition of the insertion angle for each individual slicing plane.

Figure 2

Each reflux event visualized by magnetic resonance imaging (MRI; upper panel) was associated with “common cavity” intraluminal pressure change in the esophagus and proximal stomach (HR Manometry; lower panel). At t_1 the EGJ is closed, then at t_2 a transient relaxation of the sphincter occurs followed at t_3 by opening with common cavity pressure indicating the occurrence of reflux and finally at t_4 with clearance and EGJ closure. The inset provides direct measurement of EGJ opening (15-19 mm in healthy subjects and 18-21mm in GERD patients).

Figure 3

Standard diagnostic tests for the esophagus listed on the left and on the right brief summary of the information that can be gathered.

Figure 4

A: Demonstrates what the bag-like balloon on the probe would look like straddling a valve region in the esophagus. The red concentric rings demonstrating the cross sectional area measurements. B: The three dimensional profile that can be displayed proving a functional imaging representation of the geometries measured by the probe. Hence, the term function lumen imaging probe.

Figure 5

Diffusion tensor tractographic images of the LES region. The tracks are color coded with the blue color representing tracks parallel to the central axis along the LES region whereas the green color represents tracks that lie predominantly within a transverse plane of the LES region. a: the fiber distribution from a transverse plane, indicating the layered fiber distribution across the LES wall, b: fiber distribution along the longitudinal axis of the LES region.

Figure 6

2D maps of the fiber distribution at the LES region are shown in a1 (longitudinal muscle) and b1 (circumferential muscle). Black line indicated the position of diaphragm. The polar angles of every slice from 0 to 360 degree were used as the x-axis and the length along the LES region was used as the y-axis. The direction of vectors showed the orientation of the projected primary eigenvector. Color changes from blue to red indicates the fiber angle increased from -90 to 90 degree, angle = ±90 degree means the longitudinal direction and angle = ±0 the circumferential direction. The histogram distribution of the fiber are shown in a2 (longitudinal, proximal), a3 (longitudinal, distal), b2 (circumferential, proximal) and b3 (circumferential, distal).