Mechanistic modeling of gastro-esophageal function: A model-based measurement of muscle tone in reflux disease

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Objectives: Gastroesophageal reflux disease (GERD) is a complex disease influenced by a number of biomechanical variables. The manifestation of the disease depends on factors such as the transient relaxations of the lower esophageal sphincter (TLESRs). These TLESRs allow stomach content to reflux into the esophagus and the exposure of the esophageal mucosa to acidic refluxate produces erosive damage. The objective of this modeling exercise is to develop a computer-based model that describes the biomechanical processes involved in the onset of TLESRs. The model will simulate differences between normal versus disease physiology which can produce TLESRs. Consequently, after further experimental validation, the model will help in identifying and quantifying parameters that are involved in the disease. In particular the model in combination with experimental measures can be used to quantitatively obtain a measure of the stretch-tension at the stomach wall. The stretch-tension which is a measure of the smooth muscle tone is important in determining the frequency of TLESRs. One prevalent hypothesis is that the mechanoreceptors which transduce signals that lead to TLESRs do not respond directly to changes in pressure or volume, but rather to changes in tension or strain (Gregersen 1999).

Methods: The model developed combines two representations. The first representation is a 2-dimensional axi-symmetric mechanical model of the stomach and describes the geometry and boundary constraints on the stomach. The model integrates several mechanical and fluid dynamic variables including intragastric pressure, intraabdominal pressure and extraabdominal pressure. The second representation is a 3-dimensional fluid mechanical model which models the transport of gastric contents. The fluid dynamics model explains the relationship between antral pump and pressure pump and the effect of drugs on the intragastric pressure. The complete model described starting with an empty stomach and observe the mechanical changes that occurs over the period when the stomach is filling. With the measured pressure in the stomach and with the known geometry in an empty and a filled state, the model will be able to compute the stretch tension in the stomach wall [1].

Results: The model has been qualified with experimental results [2] which assess the role of tension receptors in gastric perception during proximal isovolumetric gastric distensions. These experiments have used erythromycin which induces gastric contraction or glucagon which induces gastric relaxation. The simulations can reproduce these results and importantly quantify the impact on stresses and strains in the stomach wall. The model therefore can be used with the appropriate experimental inputs to compare healthy and disease states. The experimental inputs are 1) MRI to estimate the shape and volumes of the empty stomach and the filled stomach and 2) the measurement of intragastric pressure in the gastric fundus. Using these two sets of model that can estimate the stresses and strains in the stomach muscle.

Conclusions: The term pharmacometrics in a very literal sense is derived from measurement and pharmacology. In this work, we present a methodology whereby the measurement of a key variable in the pharmacology of a complex disease is enabled through a model-based analysis of experimental results. This variable, the stretch tension of the stomach muscle, is believed to be one critical part of the difference between healthy and disease physiology. There is no direct way to measure this quantity, so an indirect use of a computer model provides a valuable option to clinical research.

References:

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