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A physiological model for the investigation of esophageal motility in healthy and pathologic conditions

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Abstract

Recent technological advances in esophageal manometry allowed the definition of new classification methods for the diagnosis of disorders of esophageal motility and the implementation of innovative computational tools for the autonomic, reliable and unbiased detection of different disorders. Computational models can be developed aiming to interpret the mechanical behavior and functionality of the gastrointestinal tract and to summarize the results from clinical measurements, as high-resolution manometry pressure plots, into model parameters. A physiological model was here developed to interpret data from esophageal high-resolution manometry. Such model accounts for parameters related to specific physiological properties of the biological structures involved in the peristaltic mechanism. The identification of model parameters was performed by minimizing the discrepancy between clinical data from high-resolution manometry and model results. Clinical data were collected from both healthy volunteers ($n = 35$) and patients with different motor disorders, such as achalasia patterns 1 ($n = 13$), 2 ($n = 20$) and 3 ($n = 5$), distal esophageal spasm ($n = 69$), esophago-gastric junction outflow obstruction ($n = 25$), nutcracker esophagus ($n = 11$) and normal motility ($n = 42$). The physiological model that was formulated in this work can properly explain high-resolution manometry data, as confirmed by the evaluation of the coefficient of determination $R^2 = 0.83 - 0.96$. The study finally led to identify the statistical distributions of model parameters for each healthy or pathologic conditions considered, addressing the applicability of the achieved results for the implementation of autonomic diagnosis procedures to support the medical staff during the traditional diagnostic process.

Keywords

Esophageal motility, high-resolution manometry, model, diagnosis, autonomic procedure

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Introduction

In healthy conditions, peristalsis consists in a coordinated contraction of circumferential and longitudinal muscle fibers of the esophageal body that propels intraluminal contents from the oral cavity to the stomach. A disruption of this highly integrated muscular motion limits delivery of food and fluids, causing sense of dysphagia and chest pain.[1] Pathologies and degenerative phenomena may affect the proper esophageal motility as a relevant social-health problem.[2,3]

Peristaltic waves are usually described by the temporal evolution of the pressure field that muscular contractions determine within lumen. Such pressure field can be experimentally measured from pharynx to stomach by means of manometric techniques, which are widely used as diagnostic procedures in esophageal disease.[4,5] During esophageal high-resolution manometry (HRM), a special probe is placed within the patient's esophagus. The probe is equipped with several pressure sensors for a continuous monitoring of the intraluminal pressure. During an HRM test, a patient is asked to

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perform a series of 10 deglutitions of 5 mL water each in a supine posture.[5–8] Many techniques and criteria have been proposed to interpret the results and data from HRM, aiming to define and diagnose pathologies.[6–14] The principal lack of nowadays methodologies pertains to the requirement of highly specialized interpreters of HRM data. Different studies report about inter-observer variability and dependence of the diagnosis on the interpreter accuracy and consistency.[15–17] Further efforts are mandatory to better interpret the physical phenomena pertaining to esophageal motility, aiming to provide objective parameters for the identification of normal and pathologic situations.

Esophageal motility, as well as gastrointestinal motility, remains a highly unpredictable activity in comparison to other areas of physiology, because of the complexity of the biological and physical processes. The peristaltic transport of the material is a neuromuscular function affected by a number of factors.[18] This reflects an intrinsic difficulty in classifying the different motility disorders, thus defining an appropriate treatment. A number of models have been proposed to interpret gastrointestinal motility,[19–24] but they often failed because they did not account for the complex conformation of the esophageal structures and the heterogeneous distribution of mechanical and physiological properties along the duct. Furthermore, further efforts were necessary to identify relationships between model parameters and physio-mechanical properties of the esophageal structures. Finally, model parameters' identification has been usually performed accounting for limited sets of experimental data. The investigation proposed here aimed at providing a model to interpret the results from esophageal HRM and a procedure for the reliable identification of the corresponding model parameters. The model accounts for the distribution of physiological properties along the esophagus, and the model parameters were introduced accounting for specific physio-mechanical properties of esophageal tissues and structures. A procedure was developed to post-process clinical data from HRM and to identify the corresponding model parameters. The identification was performed accounting for measurements developed on a large set of healthy volunteers and pathologic subjects, providing a statistically relevant description of parameters for both healthy and pathologic situations. The action aimed at providing relationships between model parameters and pathologies, leading to the definition of objective criteria for the diagnostic activities.

Materials and methods

Diagnostic measurements

HRM measurements have been performed by a specific trans-esophageal catheter, as a 36-channel probe (ManoScan HRM; Given Imaging Ltd, Israel), according to standard procedures.[10] The adopted measuring device allows mapping the distribution of intraluminal pressure along the overall esophageal structures, from the pharynx to the stomach, with a single placement of the catheter. The probe is equipped with solid-state circumferential pressure transducers, which are equally spaced 10 mm apart along the catheter length. Pressure data are detected and transmitted to a data recorder by means of a solid-state interface. Each pressure sensor provides data about the local evolution of pressure with time.

Diagnostic measurements were performed on different groups of healthy and pathologic patients (Table 1) referred to the Department of Surgical, Oncological and Gastroenterological Sciences at University of Padova, Italy. Activities on both healthy volunteers and pathologic subjects were previously approved by the local human research ethics committee and all subjects provided written informed consent. Typical pathologies of esophageal motility[25,26] were investigated, as achalasia (divided in patterns 1, 2 and 3), distal esophageal spasm (DES), esophago-gastric junction (EGJ) outflow obstruction and nutcracker esophagus. Transnasal catheter placement was performed on subjects in supine position. Once the catheter was placed, each subject was first required to rest for about 10 s in order to identify the actual conformation of the esophagus, as the position of upper esophageal sphincter (UES) and lower esophageal sphincter (LES), and to evaluate the basal pressure distribution. Subsequently, the subject was asked to swallow 5 mL of water for 10 consecutive times, while pressure data were continuously stored. Typical measurement results are reported in Figure 1.

Pressure data were analyzed by specific software. The preliminary analysis was performed by ManoView™ (Given Imaging Ltd) and the actual healthy or pathological situation was evaluated by highly experienced clinicians, according to standard criteria.[8–10,27] Data were subsequently exported from ManoView in ASCII format, imported in MATLAB™ (MathWorks Inc., Natick, MA, USA) and post-processed by specific routines. For each subject, different swallows were autonomously recognized and overlapped, in order to provide a "mean swallow" data set (Figure 2). The averaging action allowed to account for the results from all the swallows at the same time and to minimize the influence of unrelated phenomena, as breathing movement, heartbeat and body movement artifacts, which may affect the pressure measurement.

Physiological model

A physiological model was provided to interpret the distribution of pressure p along the overall length of the esophagus, from UES to LES, during the propagation of the peristaltic wave of normal swallowing. The pressure wave travels along the esophagus in time and can be mathematically described by wave propagation models.[19,21] The specific shape of the pressure wave was

Table 1. Age and weight distribution of healthy volunteers and pathologic subjects.

		Healthy	Achalasia pattern 1	Achalasia pattern 2	Achalasia pattern 3	EGJ outflow obstruction	Nutcracker esophagus	Distal esophageal spasm
Males	Subjects no.	37	11	16	3	6	5	2
	Age (years)	43.2 ± 17.5	57.7 ± 18.1	48.7 ± 15.6	70.0 ± 7.5	52.8 ± 23.1	54.8 ± 10.5	55.5 ± 17.7
	Body weight (kg)	75.7 ± 12.7	75.1 ± 17.0	70.8 ± 15.6	75.7 ± 6.5	78.7 ± 9.9	74.0 ± 9.1	78.25 ± 20.9
Females	Subjects no.	40	2	4	2	19	6	4
	Age (years)	48.8 ± 18.1	61.5 ± 3.5	53.5 ± 19.1	72.5 ± 2.12	57.1 ± 11.9	56.6 ± 8.6	53.2 ± 22.3
	Body weight (kg)	64.2 ± 15.0	51.5 ± 9.2	67.3 ± 22.5	55.9 ± 11.5	62.4 ± 9.2	59.0 ± 4.7	60.5 ± 11.1
Males and females	Subjects no.	77	13	20	5	25	11	6
	Age (years)	46.2 ± 17.9	58.3 ± 16.6	49.7 ± 15.9	70.0 ± 7.5	56.1 ± 14.8	55.8 ± 8.9	54.0 ± 19.0
	Body weight (kg)	69.4 ± 15.1	71.5 ± 18.0	70.1 ± 16.6	75.7 ± 6.5	66.7 ± 11.7	65.7 ± 10.2	66.4 ± 15.6

EGJ: esophago-gastric junction.

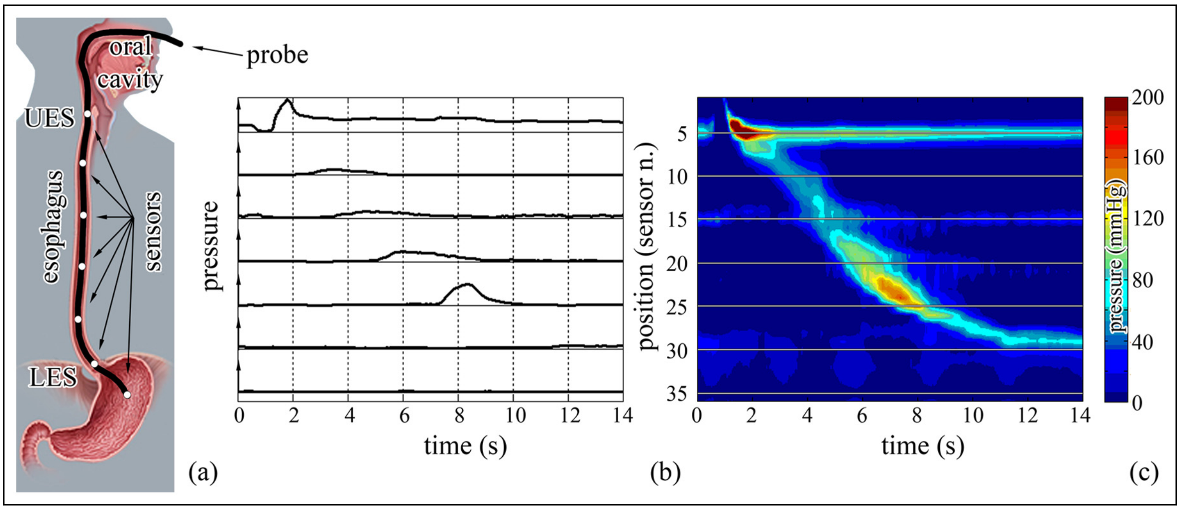

Figure 1. Typical representation of manometric data. (a) Pressure data are measured by transducers along the esophageal structure; only 7 of the 36 measuring positions are reported in the figure. (b) Each transducer measures the local evolution of pressure with time. (c) Data are post-processed to contemporarily show the evolution of pressure with position and time, leading to color gradient representations.

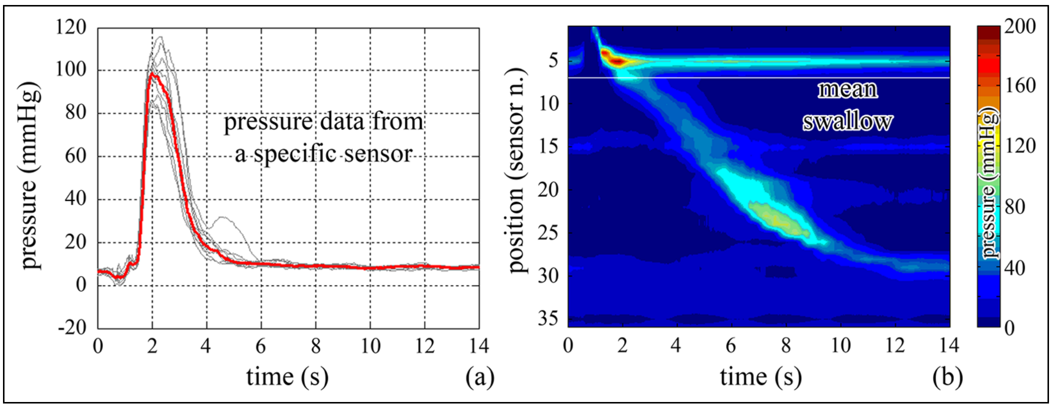

Figure 2. Averaging of pressure data from the different swallows. With regard to each sensor, (a) pressure versus time data from the different swallows were averaged (b) providing a manometric average image of the specific subject.

already described by means of hyperbolic functions.[23] In detail, the following formulation was adopted

$$p(x, t) = s(x, t) + \delta(x, t) \tag{1}$$

with

$$s(x, t) = p_0(x) + [p_{max}(x) - p_0(x)] \operatorname{sech}\left\{\frac{\beta(x)}{L}[x - \eta(x)t]\right\} \tag{2}$$

$$\delta(x, t) = \frac{5}{4}\Delta(x) \left\{\tanh\left[\frac{2}{\phi(x)}\left(t - \frac{x}{\eta(x)}\right)\right] - \frac{1}{5}\tanh\left[\frac{2}{5\phi(x)}\left(t - \frac{x}{\eta(x)}\right)\right]\right\} \tag{3}$$

where t is the time and x specifies the position along the esophageal axis, as the longitudinal distance from the UES. With regard to the bell-shaped function $s(x, t)$, L is the esophageal length, as the distance between UES and LES, $p_0(x)$ evaluates the local value of basal pressure, while $p_{max}(x)$ is the maximum pressure the esophageal muscular tissue provides at position x during the overall swallowing process, referred to $p_0(x)$. $\eta(x)$ is related to the local propagation speed of the pressure wave. In detail, the pressure reaches the maximum value p_{max} at location x at a specific time t_{max} that is related to η by the following formulation

$$t_{max}(x) = \frac{x}{\eta(x)} \tag{4}$$

Finally, $\beta(x)$ is related to the local value of the full width $\phi(x)$ of the pressure wave at the half maximum of the pressure wave itself,[28] as

$$\beta(x) = \frac{2L \cdot \operatorname{arsech}(1/2)}{\phi(x)\eta(x)} \tag{5}$$

The S-shaped function $\delta(x, t)$ is introduced to account for the different pressure conditions before and after the local transit of the peristaltic wave, which is a phenomenon that mostly occurs at the sphincteric regions of the esophagus. In detail, low-pressure conditions are required before the wave propagation to allow the bolus transit, while higher pressure conditions are mandatory to avoid reflux phenomena after the peristaltic propagation. Such pressure variation is specifically defined by the parameter $\Delta(x)$. A graphical representation is proposed in Figure 3(a) to better explain the model and the parameters.

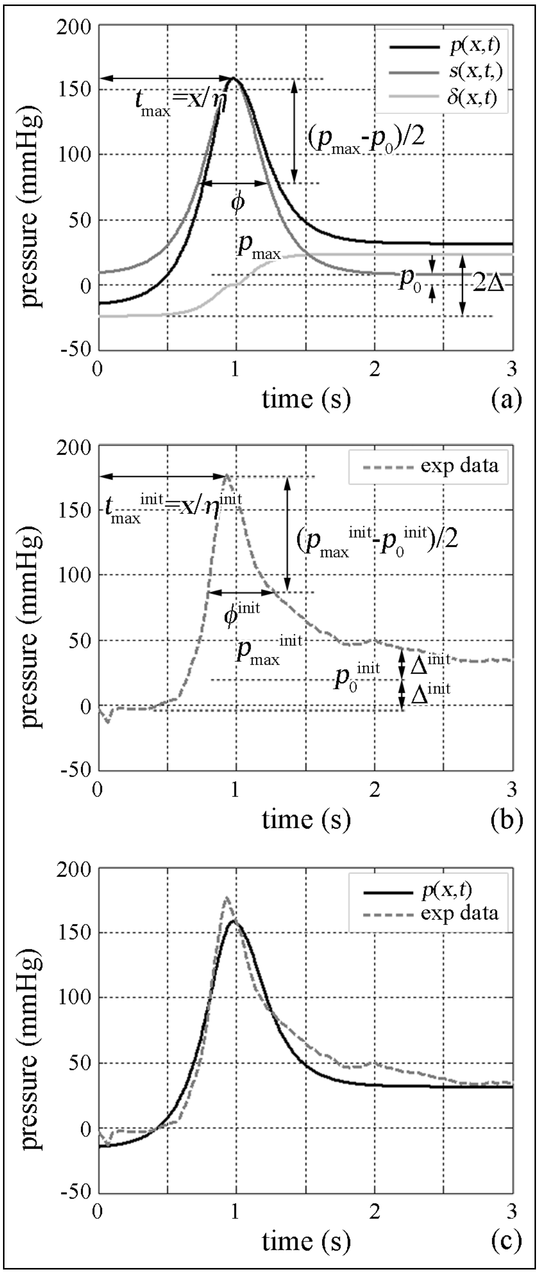

Figure 3. (a) Graphical representation to show the physical meaning of model parameters. (b) Identification of initial values of parameters by processing experimental data. (c) Comparison of model results and experimental data after discrepancy minimization.

Model identification and statistical analysis

With regard to each investigated subject, the model parameters were identified accounting for the mean swallow data. The model identification required to evaluate the trend of the parameters p_0, p_{max}, t_{max}, β and Δ with the position along the esophageal axis x. Pressure measurements were performed within specific points along the esophageal length, according to the specific locations of pressure sensors. Each sensor provided the local evolution of intraluminal pressure in time. The minimization of the discrepancy between experimental pressure and model results (equation (1)) led to the identification of the local values of p_0, p_{max}, t_{max}, β and Δ. Accounting for the non-linearity of the problem, the parameters' identification had to be performed by non-linear optimization techniques.[29,30] The technique required to specify the initial values of the parameters, as the starting point for the parameters' optimization procedure. The initial values were evaluated by processing the experimental pressure versus time data from the

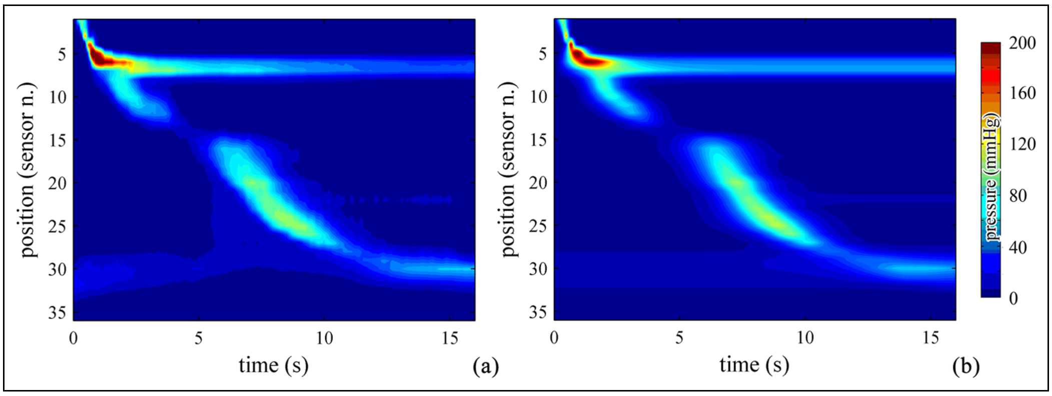

Figure 4. (a) Pressure gradient maps from HRM data and (b) model results with regard to the median deglutition of a healthy subject.

mean swallow data set, as depicted in Figure 3(b). In detail, the basal pressure values, both before and after the wave peak, were averaged, leading to p_0^{init}. The pressure and time at the wave peak were $p_{max}^{\text{init}} = p_{peak} - p_0^{\text{init}}$ and t_{max}^{init}, respectively. β^{init} was evaluated by equation (4), where $\eta^{\text{init}} = x/t_{max}^{\text{init}}$ and ϕ^{init} was the full width of the pressure wave at its half maximum. Δ^{init} was evaluated by computing the difference between the basal pressure values after and before the wave peak. The formulation proposed allowed to well interpret the experimental data, as reported in Figure 3(c).

Measurements from both healthy and pathologic subjects were processed by the procedure, leading to the identification of sets of curves $p_0(x)$, $p_{max}(x)$, $t_{max}(x)$, $\beta(x)$ and $\Delta(x)$. Furthermore, the actual propagation speed of the pressure wave, as $v(x)$, was computed accounting for the function $t_{max}(x)$ and numerical differentiation techniques.[31] The reliability of the model, defined as its capability to interpret experimental data from esophageal HRM, was statistically assessed by computing the mean coefficient of determination R^2.[32]

The curves from each subject provided data about the functionality of the esophagus of each specific subject. In order to homogenize the information from the different subjects, the axial coordinate x was normalized by the esophageal length L. Thus, the normalized position ranges between 0, as the UES, and 1, as the LES. The continuous trend of the parameters with the normalized position was identified by spline interpolating functions.

Subsequently, the curves from healthy and pathologic subjects were statistically analyzed aiming to identify the distributions of the parameters in health and disease.[33] In detail, with regard to each group, the median parameters and 50% scatter bands were computed. Finally, parameters' distributions of healthy volunteers and patients were compared to evaluate the influence of pathologies on the model parameters.

Results

A huge amount of experimental data were collected from HRM tests. The acquired data provide information about the esophageal motility of several healthy and pathologic subjects, providing a rich data set. A specific physiological model has been developed to interpret the action of esophageal muscles, as the measured pressure, in time and along the axial direction of the esophagus. A procedure for the identification of model parameters was implemented, in order to identify the optimal parameter values to minimize the discrepancy between experimental data and model results. The physiological model is able to properly explain data from HRM, with regard to healthy subjects and the different pathologies investigated. The suitability of the model was first assessed by observing high similarity between every median HRM map and the corresponding physiological model image. As a matter of example, the comparison of the pressure map from the HRMs of a healthy subject and the corresponding model results are reported in Figure 4. The model finally proved to be a reliable tool to interpret HRM data, as the different groups showed the median values of the coefficient of determination R^2 ranging between 0.83 and 0.96, as reported in Table 2 together with the corresponding standard deviations.

Table 2. Evaluation of discrepancy between HRM data and model results by the coefficient of determination R^2 (median values and standard deviations for the different groups).

Pathology	R^2
Healthy subjects	0.959 ± 0.026
Achalasia pattern 1	0.883 ± 0.210
Achalasia pattern 2	0.828 ± 0.180
Achalasia pattern 3	0.886 ± 0.038
Distal esophageal spasm	0.919 ± 0.040
EGJ outflow obstruction	0.956 ± 0.027
Nutcracker esophagus	0.958 ± 0.014

EGJ: esophago-gastric junction.

The model parameters' distributions were statistically analyzed for the different conditions, as reported in Figure 5, for healthy and pathologic subjects. The parameters' distributions of pathologic situations are overlapped to the healthy patients' ones, in order to

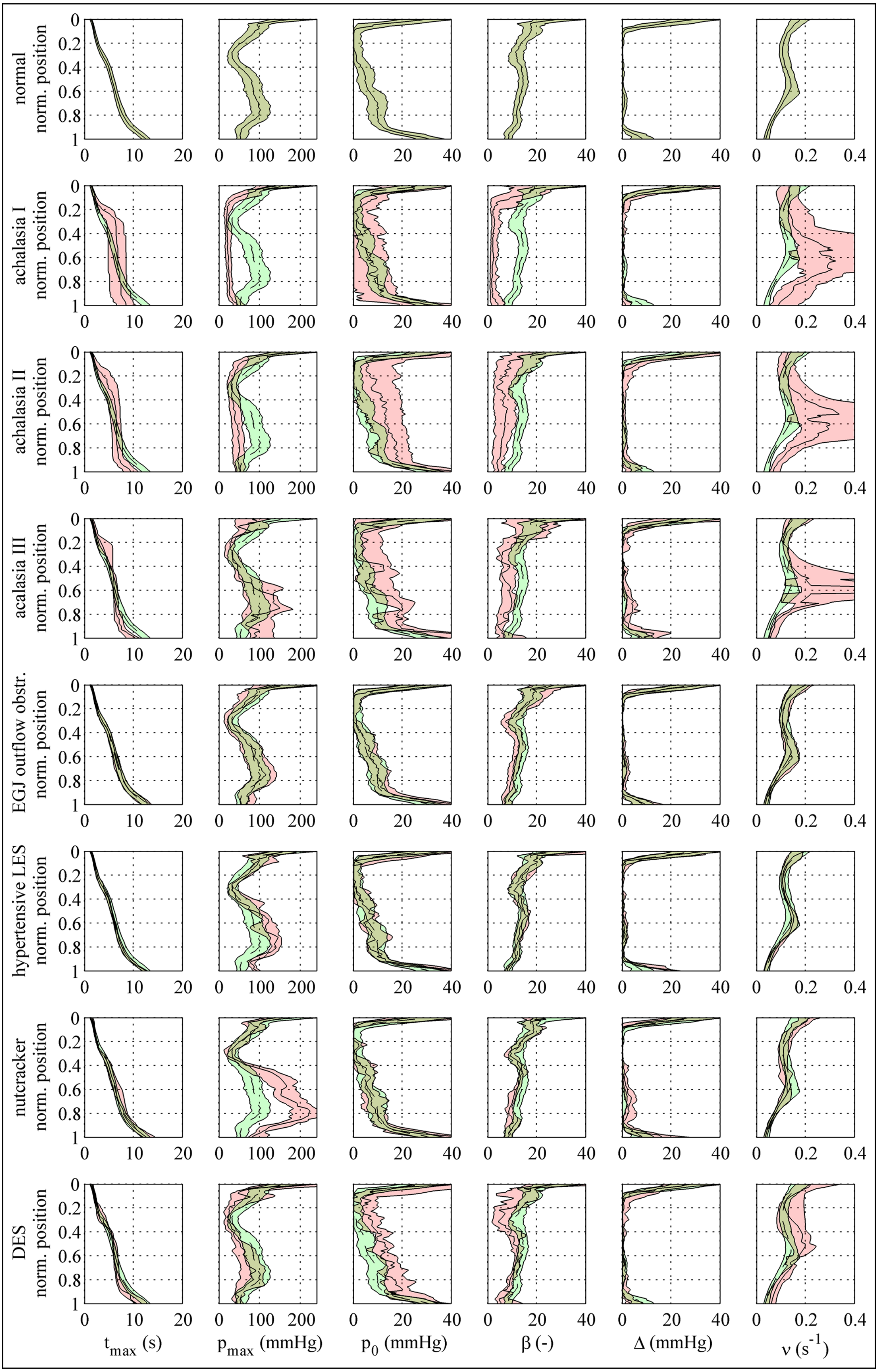

Figure 5. Distribution of physiological model parameters of the entire data sets of healthy (green regions) and pathologic (red regions) subjects, as median data and 50% scatter bands. Parameters of healthy subjects are overlapped to show the different trends of healthy and pathologic situations.

emphasize the influence of pathologies on the parameters. The parameters' distributions, represented by colored areas, showed significant differences in correspondence to the very same regions that are affected by each pathology. The following main differences can be observed between pathological and healthy subjects:

- Achalasia pattern 1 subjects showed significantly lower p_{max} and p_0 along the overall esophagus, because of the absent peristalsis, lower Δ at the lower sphincteric level, because of the LES dysfunction, and higher ν because of the low-amplitude panesophageal contractions.
- Achalasia pattern 2 subjects showed similar parameters' distributions with regard to the achalasia pattern 1 ones, with slightly higher p_{max} and p_0 due to the slightly higher amplitude contractions.
- Achalasia pattern 3 subjects showed lower p_0 along the overall esophagus, with higher ν because of the spastic contractions measured within the overall distal part of the esophagus, but not significantly different p_{max}.
- No significant differences were found between EGJ outflow obstruction subjects and healthy situations.
- Hypertensive LES subjects showed significantly higher p_0 and Δ at the lower sphincteric region, and higher p_{max} at $x \in [0.5, 0.9]$.
- Nutcracker esophagus subjects showed significantly higher p_{max} at $x \in [0.5, 0.9]$, because of the hypertonic peristalsis.
- DES subjects showed significantly higher ν at $x \in [0.7, 0.9]$, because of the spastic contractions of the overall proximal-central part of the esophagus.

Discussion and conclusion

The classification of esophageal motility disorders based on manometric data has been a challenging field in the past decades. Accounting for the limited technologies available at the time, as the perfused stationary manometry, the corresponding classification was inadequate, as different diseases were not well defined and often overlapping each other.[26] The development of HRM allowed the definition of the "Chicago classification," accounting for the parameters that were even unthinkable just few years ago. This classification[9] has seen a major revision in 2012[10] and another major revision is now underway, confirming that the widely used current classification is still far from perfect. The principal lack of such methodologies pertains to the requirement of a highly specialized interpreter of the data, introducing inter- and intra-observer variabilities with regard to the final diagnosis. The lack of a good classification system prevents the application of the best available treatment for a given disease. There is therefore a need for a better classification tool for the motility disorders of the gullet.

Hence, a general framework for processing clinical data from HRM was developed in this article, aiming to provide tools to be applied for the implementation of an autonomic decision support system for the diagnosis of esophageal motility diseases. A physiological model was preliminarily provided to interpret the trend of pressure with time along the esophagus during swallowing, as the typical clinical information provided by HRM. The model accounts for parameters that are related to specific physiological properties of the esophageal structures, providing a description of the distribution of such properties along the esophagus itself, and a procedure was implemented for the fast and reliable identification of such parameters. Clinical data from both healthy volunteers and pathological subjects were processed by MATLAB routines, achieving a good agreement between experimental data and model results. The statistical analysis allowed the evaluation of the influence of pathologies on the parameters, and significant differences have been observed between the conditions investigated in specific regions of the esophagus. In detail, each pathology determines a significant variation in one or more parameters within the very same region of the esophagus where the pathology actually influences the specific physio-mechanical properties associated with such parameters.

The model results give the same clinical information as the corresponding raw data, but only require the storage of six parameters' values for each one of the 36 pressure signals measured, while HRM measurements require the storage of thousands of pressure values, corresponding to each point of the time grid, for each one of the 36 pressure signals acquired. Such a high compression rate suggests the applicability of the model as a tool for compression algorithms for the storage of huge amount of HRM data.

The achieved results suggest the capability of the developed procedure to provide a reliable computational tool for the diagnostic activity. They can be applied to process clinical data of a patient and to identify the corresponding parameters. Subsequently, patient parameters should be compared with a database of parameters identified accounting for clinical data of healthy and pathologic subjects to autonomously identify its healthy or pathologic condition. The reliability of such procedure depends on the quality of the database. A preliminary database was here developed, but it must be largely extended, shared and continuously updated in order to implement a reliable autonomic diagnosis procedure. The identification procedure can be refined as well; even if the averaging process may decrease the influence of unrelated phenomena, it prevents the identification of pathologies on the basis of symptoms that do not characterize all the 10 deglutitions. To improve the identification procedure, a set of parameters should be identified on the basis of the HRM data related to each single deglutition.

Declaration of conflicting interests

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