

Electrical bioimpedance and other techniques for gastric emptying and motility evaluation

María Raquel Huerta-Franco, Miguel Vargas-Luna, Juana Berenice Montes-Frausto, Corina Flores-Hernández, Ismael Morales-Mata

María Raquel Huerta-Franco, Corina Flores-Hernández, Ismael Morales-Mata, Health Science Division, Department of Applied Sciences to Work, University of Guanajuato, Av Eugenio Garza Sada 572, Lomas del Campestre, 37150 León, Guanajuato, México

Miguel Vargas-Luna, Juana Berenice Montes-Frausto, Science and Engineering Division, Department of Physical Engineering, University of Guanajuato, Loma del Bosque 103, Lomas del Campestre, 37150 León, Guanajuato, México

Author contributions: Huerta-Franco MR, Vargas-Luna M designed and conducted the study and wrote the manuscript; Morales-Mata I performed the data acquisition and instrumentation review; Montes-Frausto JB and Flores-Hernández C contributed to the data collection, reviewed the literature and provided analytical input.

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Correspondence to: María Raquel Huerta-Franco, PhD, Health Science Division, Department of Applied Sciences to Work, University of Guanajuato, Av Eugenio Garza Sada 572, Lomas del Campestre, 37150 León, Guanajuato, México. mrhuertafranco@ugto.mx

Telephone: +52-477-2569688 Fax: +52- 477-7885100

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Abstract

The aim of this article is to identify non-invasive, inexpensive, highly sensitive and accurate techniques for evaluating and diagnosing gastric diseases. In the case of the stomach, there are highly sensitive and specific methods for assessing gastric motility and emptying (GME). However, these methods are invasive, expensive and/or not technically feasible for all clinicians and patients. We present a summary of the most relevant international information on non-invasive methods and techniques for clinically evaluating GME. We particularly emphasize the potential of gastric electrical bioimpedance (EBI). EBI was initially used mainly in gas-

tric emptying studies and was essentially abandoned in favor of techniques such as electrogastrography and the gold standard, scintigraphy. The current research evaluating the utility of gastric EBI either combines this technique with other frequently used techniques or uses new methods for gastric EBI signal analysis. In this context, we discuss our results and those of other researchers who have worked with gastric EBI. In this review article, we present the following topics: (1) a description of the oldest methods and procedures for evaluating GME; (2) an explanation of the methods currently used to evaluate gastric activity; and (3) a perspective on the newest trends and techniques in clinical and research GME methods. We conclude that gastric EBI is a highly effective non-invasive, easy to use and inexpensive technique for assessing GME.

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Peer reviewer: Shi Liu, Professor, Department of Gastroenterology, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Road, Wuhan 430022, Hubei Province, China

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A HISTORICAL PERSPECTIVE ON ASSESSING GASTRIC FUNCTION

The study of gastric anatomy, physiology and pathol-

ogy has been a subject of scientific interest since ancient times^[1-3]. Early physicians based their clinical diagnoses solely on patient symptoms. One of the first attempts to look inside a living human body occurred at the beginning of the nineteenth century, when a rudimentary endoscope was invented to assess the interior of the urinary tract^[4]. This instrument was also used to study other body cavities, such as the rectum and the pharynx, and it marked the beginning of modern endoscopy^[5,6]. Endoscopy was further developed in the middle of the nineteenth century with the invention of the gastroscope, a specific apparatus for visually inspecting the stomach. The esophagoscope was invented in 1871 and esophageal manometry was introduced in 1885^[7]. After these inventions, the first modern instruments for assessing the interior of the gastric cavity were developed^[8]. Rudolph Schindler^[9] described many important diseases of the human digestive system and, together with Georg Wolf, developed a semiflexible gastroscope^[10,11]. Thereafter, the number of developed and improved techniques and apparatuses greatly increased, enabling additional applications, and there has been great scientific activity on this topic ever since.

GASTROINTESTINAL FUNCTION

To appreciate the existing techniques for evaluating gastrointestinal (GIT) function, it is important to have a basic understanding of the physiology and pathology of GIT motility and emptying. Like almost every other organ system, the number of basic physiological processes that occur in the GIT is immense; the major functions of the GIT include swallowing, motility, emptying (of every section), assimilation and elimination. When a piece of food is eaten, the person controls the food as it passes from the mouth to the esophagus, but involuntary functions control the digestive process beyond that point. The GIT cavity includes the mouth, pharynx, esophagus, stomach, small intestine, large intestine, sigmoid, rectum and anus. Among the functions listed above, motility is one of the cornerstones of GIT function. Motility enables swallowing, transit, emptying and elimination and is essential for proper assimilation^[12]. Beginning with swallowing and ending with elimination, motility in different parts of the GIT tract is required for GIT function^[13,14]. Two variables related to GIT motility are particularly important: (1) peristalsis, which is a function of the frequency and magnitude of the gastric contractions that are generated by the pacemaker area; and (2) gastric emptying, which is a measure of the average time that the stomach takes to empty half of its luminal content. The autonomic nervous system regulates GIT motility, controlling peristaltic activity through the myenteric system^[15,16]. Motility defects in any segment of the GIT tract can lead to pathologies that are then manifested as clinical symptoms or complications, such as type 1 and 2 diabetes^[17,18], or as sequelae to GIT surgery^[19,21] or anesthesia^[22,23]. In fact, alterations in GIT motility are

frequently viewed as signs of neuropathy of the myenteric plexus or other pathologies of neuropathic origin. One of the most common GIT motility alterations is reduced transit time (emptying time)^[24,25]. Abnormal gastric emptying is considered to be a clinical marker for a gastric or intestinal motility disorder^[26,27]. Therefore, GIT motility and emptying parameters are important for diagnosis and clinical evaluation. Clinically, this problem can be summarized as the need to better understand the relationship between clinical symptoms and gastric emptying disorders^[28,29]. In a review published in 2004, Quigley^[30] described the difficulties of correlating delayed gastric emptying with pathogenesis. The author found a relationship between delayed gastric emptying and female sex, low body weight, postprandial fullness, vomiting and stress^[31,32]. We and other authors have also found variations associated with the menstrual cycle^[33-36] and even with the anatomical position of the stomach^[37]. All of these studies are limited by the high sensitivity of gastric emptying (in humans) to external factors (the “confusion factor”). In our experience, accurately evaluating gastric function requires standardizing all of the factors that may affect gastric motility and emptying, such as: (1) the duration of the fasting state^[38,39]; (2) control of the patient’s stress and anxiety^[40,41]; (3) the venipuncture^[42,43]; (4) abstinence from smoking and the use of stimulants, such as coffee and certain drugs^[44,45]; (5) the phase of the menstrual cycle in females^[46]; (6) carbohydrate content of the meal^[47]; and (7) body posture^[47,48]. The gastric emptying rate provides only a rough representation of a complex phenomenon that integrates gastric and intestinal function, and its measured values are affected by the methodology employed, in addition to the external factors mentioned above^[48,49]. Functional dyspepsia, gastroparesis, irritable bowel syndrome and chronic constipation are some of the major GIT problems discussed in the literature that are related to gastric motility alterations. However, the relevance of delayed gastric emptying in diseases such as dyspepsia remains unclear^[50,51]. Gastric motility also seems to be a good clinical indication of gastro-esophageal reflux disease because fundoplication tends to accelerate gastric emptying^[52]. In fact, a delay in gastric emptying is common in almost all functional GIT disorders^[53].

TECHNIQUES AND PROCEDURES FOR MONITORING GASTRIC MOTILITY AND EMPTYING

When we consider gastric emptying solely as a consequence of motility, the gold standard technique for evaluating and diagnosing GIT motility defects is scintigraphy^[28,54]. This technique is essentially used to measure gastric emptying. However, scintigraphy provides information in a visual manner and requires the use of ionizing radiation^[55], with all of the associated disadvantages. Besides scintigraphy, many techniques, methods and

procedures for evaluating gastric motility and emptying have been developed in the last century^[28]. To date, none of these techniques has been recognized to be as precise and sensitive as scintigraphy, but some less invasive or less expensive techniques are reasonable alternatives. Invasive techniques for the clinical evaluation of gastric emptying include: (1) monitoring the intubation and absorption kinetics of orally-administered solutes; (2) radiological techniques; (3) scintigraphy; (4) manometry; (5) biomagnetic techniques; (6) breath tests; and (7) endoscopy. Non-invasive techniques include: (1) ultrasonography; (2) magnetic resonance imaging; (3) stethoscope method; (4) electrogastrigraphy (EGG); and (5) electrical bioimpedance and applied potential tomography. All of these techniques have significant literature discussing their application to and use in evaluating disease and comparing different techniques (mainly to scintigraphy). Below, we divide the techniques into invasive and non-invasive and present a brief description of how each is used to assess gastric motility and emptying.

INVASIVE TECHNIQUES FOR EVALUATING GASTRIC MOTILITY AND EMPTYING

Intubation technique

In this technique, the remaining gastric volume is evaluated by liquid aspiration. This technique is not widely used because it is invasive and because it can only measure liquid. However, this technique is frequently used as a complement to absorption kinetic measurements for orally-administered solutes^[56], typically acetaminophen, paracetamol, ethanol, glucose or other substances. This technique estimates gastric emptying by measuring the solute concentrations in the patient's blood, at various times to determine the peak concentration, time to reach maximum concentration, and area under the solute curve^[57,58].

Radiological techniques

This technique consists of radiologically detecting radio-opaque material in the GIT cavity and observing the emptying patterns^[59,60]. Alternatively, in scintigraphy, a radionuclide-labeled meal is ingested and the emitted radiation is detected for image processing^[60,61]. Scintigraphy is strongly preferred to using radio-opaque markers^[62].

Scintigraphy

Scintigraphy is the gold standard for gastric emptying in clinical research and in clinical practice. It shows both the gastric emptying of liquids or solids over time and the intra-gastric distribution of the meal components. As mentioned above, this technique requires the patient to consume a radionuclide-labeled meal. Currently, this technique uses gamma-emitting liquid markers in a non-absorbable chelated form, such as [99Tc]-, [113In]- or [111In]-DTPA (P-Diethylene Triamine Pentaacetic Acid).

Digestible solid markers with a high labeling efficiency are also available (e.g., 99mTc)^[63]. To date, scintigraphy remains the most reliable method for measuring gastric emptying. In fact, this is the technique that is specified for use by formal procedural guidelines for measuring gastric emptying^[64].

Manometry

Manometry is another common technique for measuring gastric motility in many GIT regions (esophagus, small intestine and anus-rectum). In esophageal manometry, a thin, pressure-sensitive tube is passed by swallowing through the subject's mouth or nose and into the stomach. The pressure of the muscle contractions is then measured along several sections of the tube^[65]. A similar technique, antro-duodenal manometry, is used to measure the contractile activity of the distal stomach and duodenum. The changes in the intra-luminal pressure of the stomach and duodenum are measured by solid-state transducers incorporated into a catheter that is positioned under fluoroscopic guidance. Recordings may last for several hours and can be conducted while the patient is ambulatory (24 h)^[66].

Biomagnetism

Biomagnetic techniques can be used to evaluate gastric motility^[67,68], either by monitoring the misalignment of magnetic traces previously aligned in a strongly pulsed magnetic field or by a single small magnetic marker travelling through the GIT^[69]. In both cases, the magnetic field fluctuations are monitored on the surface of the skin and provide information about gastric motility^[70,71].

The breath test

This test uses [14C] octanoic acid as a marker for measuring solid gastric emptying. This isotope is stable and is used to avoid patient radiation exposure^[72,73]. The premise of the breath test is that 13/14C-labeled octanoic acid is retained in the solid phase of a test meal during mixing and grinding in the stomach, rapidly absorbed from the chyme upon entering the duodenum and quickly and completely oxidized in the liver to labeled CO₂, which is rapidly exhaled in the breath^[74].

Endoscopy

Endoscopy is considered to be the preferred technique for internally evaluating gastric anatomy and physiology. It has also been proposed as a technique for assessing gastric emptying. However, its utility for evaluating gastric emptying and quantifying ingested food has not yet been validated^[75].

NON-INVASIVE TECHNIQUES FOR EVALUATING GASTRIC MOTILITY AND EMPTYING

Ultrasonography

Using ultrasonography, it is possible to assess antropyloro-

roduodenal motility and the flow of stomach contents. However, only the gastric antrum can be visualized using ultrasonic techniques; it is not possible to visualize the fundus and corpus of the stomach. The greatest disadvantage of this non-invasive technique is that it is time-consuming and requires an experienced and skilled operator^[76,77].

Magnetic resonance technique

This technique provides detailed visual images of the GIT tract; therefore, its advantage is the possibility of simultaneously measuring gastric emptying and the total volume of the gastric contents. Its main disadvantage is its high cost^[78].

Stethoscope gastric assessment

Acoustically assessing gastric activity through a stethoscope is used clinically but is rarely employed in research to evaluate gastric dysfunction in general^[79,80] or motility in particular^[81].

EKG and electrical bioimpedance

Some of the techniques described above are sensitive to gastric motility *per se*. Two techniques for evaluating gastric motility (EKG and electrical bioimpedance) record the electrical activity resulting from the smooth muscle innervation of the stomach. The first technique, EKG, appeared in 1921^[82]; it measures the electrical activity associated with gastric activity (and possibly activity elsewhere in the GIT) and correlates it with real-time gastric motility^[83].

Electrical bioimpedance

The electrical bio-impedance (EBI) technique for measuring gastric motility and emptying has been investigated only rarely over the past decade. In 1985, McClelland *et al.*^[84] suggested that the EBI technique should be used for evaluating gastric emptying only when using low electrical-conductivity liquids to increase epigastric impedance. These investigators monitored the effects of changing the electrical conductivity of the subject's meals on stomach motility. They also tested the effects of the drug metoclopramide. In this first attempt at gastric impedance evaluation, the subjects were intubated prior to the study and their gastric contents were aspirated after a washout period. The results were encouraging; motility, gastric emptying and the metoclopramide test showed significant results in the expected patterns. Furthermore, the impedance trace showed the correct activity frequency (in the 2-4 cycle/min range). These results and results from other researchers indicated that gastric EBI should be used with one of the following electrical configurations: a one-channel configuration (3 or 4 electrodes) or a multichannel configuration for potential tomography^[85]. For the sake of simplicity, we will only discuss the results of one-channel gastric EBI in this review. In general, the gastric electrical profiles

obtained through EBI are noisier than those obtained through other techniques. In 1992, Kothapalli studied the origin of the gastric electrical bioimpedance changes using a 3D model^[86]. The author demonstrated that the meal resistivity from the epigastric impedance signal is nonlinear, that the impedance signal varies linearly with the circular smooth muscles contractions of the stomach, and that the peristaltic wave changes do not modify the resistivity of the contents. The order of magnitude of the epigastric impedance signal is also a function of the electrode configuration.

Gastric EBI and a liquid meal with low electrical conductivity were used to measure the gastric emptying time^[27]. These investigators recorded the mean stomach impedance continuously for more than two hours. One practical limitation of this method is the need to immobilize the patient for a long period. Therefore, it appears that the change in the mean epigastric EBI magnitude depends strongly on the conductivity of the meal compared to the stomach and surrounding tissues. Typically, a conductive meal has a conductivity of $> 7 \text{ mScm}^{-1}$, a non-conductive meal has a conductivity of $< 2 \text{ mScm}^{-1}$, and a neutral meal has an average conductivity of 4.5 mScm^{-1} . However, Giouvanoudi *et al.*^[87] claimed that the author's half-gastric emptying times (T50s) were shorter than those expected based on scintigraphy. Thus, one of the conclusions from this report was that gastric EBI measurements are mainly influenced by gastric secretion; in other words, the gastric EBI of a neutral meal would be more influenced by gastric acid secretions than by the volume of the meal. It is known that the presence of a meal in the stomach stimulates gastric acid secretion, with a rate that initially increases and subsequently decreases. Gastric function studies using EBI measurements may therefore reflect gastric ionic concentration rather than the volume of the stomach contents. This consideration led to a proposed non-invasive method for continuously recording gastric acid secretions. In 2008, the same authors used gastric EBI to quantitatively determine gastric acidity.

The variations in the gastric EBI signals detected by these researchers, other researchers and our own group can be attributed to several factors: (1) the meal resistivity (lipids, proteins or carbohydrates) in long gastric EBI recordings (emptying studies)^[88,89]; (2) the meal volume; and (3) the contractions of the circular smooth gastric muscles in short gastric EBI recordings (motility studies).

One of the major problems in interpreting gastric EBI patterns (which is also a challenge in EKG) is overlapping signals, movements or impedance changes from other GIT regions. Gastric evaluation generally focuses on the stomach, but the esophagus and much of the large and small intestines are close enough to the gastric region to participate in the signal generation. The effect of this overlap on EKG has been discussed by Amaris *et al.*^[24], who investigated the possibility of overlapping dominant frequencies in cutaneous electrical activity

recorded from the stomach and colon. They concluded that the electrical activity arising from the colon can substantially affect EGG recordings.

It has been reported that small intestine peristalsis has frequencies above 7 cpm and that the large intestine has frequencies from 8 cpm to 12 cpm. In fact, peristalsis over the gross structure of the small intestine (duodenum, jejunum and ileum) ranges from 11-12 cpm in the duodenum (the highest frequency) to 8 cpm in the terminal ileum (the lowest frequency)^[90]. Because gastric movements are in the range of 2 cpm to 4 cpm, they are relatively easy to discriminate when measured by EBI. For short-term evaluations, EBI is more sensitive to gastric movements than to meal resistivity or gastric acid concentrations.

In recent years, EBI has been used in combination with other complementary techniques; it has also been used to search for new methodologies for analyzing and interpreting gastric signals. Combined synchronous EGG and gastric EBI has been studied by Zhangyong *et al.*^[91-93]. These researchers collected both surface signals (gastric EBI and EGG). They decomposed the signals by multiresolution analysis and by energy- and frequency-spectrum analysis. The signals were classified according to the dominant power and dominant frequency, and several variables were calculated: (1) the EGG and gastric EBI rhythms; (2) the signal power spectrum and dynamic spectrum; (3) the normal EGG rhythm and power rates; and (4) the gastric IBE. In 2007, they estimated either the gastric emptying time or gastric motility over long periods (30 to 60 min recordings) in healthy adults. Their results demonstrated that the gastric EBI signal and the synchronous EGG exhibit similar features in both the time and frequency domains. However, the gastric motility did not correlate with the synchronous EGG measurements, especially in cases of gastric disease; therefore, the EGG signal could not be directly correlated to the EBI signal. Nevertheless, these authors suggested that the gastric EBI and synchronous EGG signals should be analyzed together^[92]. These authors also evaluated volunteers with functional dyspepsia and a control group using the same signal analysis protocol. They observed significant differences in the time and frequency domains of the gastric signal between the two groups. They considered the main power frequency (position and dispersion), percentage of normal frequency, frequency instability coefficient, percentage of normal power and power instability coefficient. The authors found that patients with functional dyspepsia had abnormal motility, as measured by EBI and EGG. After one week of treatment, the patients showed normal EGG signals but abnormal gastric EBI. After three weeks of treatment, however, both the EBI and EGG signals were normal. One conclusion suggested by these results is that the EGG and gastric EBI signals are not directly correlated. The EGG technique measures gastric electrical activity, while EBI measures the electrical impedance

of the gastric region that is sensitive to internal gastric movements in short-term recordings. Normal gastric electrical activity does not imply normal gastric motility, which is directly detected by gastric EBI^[94]. Similar comparisons of EEG and antroduodenal manometry were discussed by Abid and Lindberg in 2007^[95].

Another approach is to analyze the frequency domain of the gastric EBI signal and consider alternative parameters with their corresponding interpretations. Moreover, it has been suggested that short evaluations are more useful for outpatient techniques that can be used in clinics or medical offices. In 2007, we suggested that electrical impedance could be used to assess gastric motility^[94]. Our principal aim was to use the global characteristics of the gastric EBI Fourier spectrum; we evaluated healthy subjects in the fasting state and after ingesting a meal. For the statistical analysis, we used the median of the area under the frequency spectrum in the region from 1 cpm to 6 cpm. The area from 2 cpm to 4 cpm corresponds to the gastric region rather than the complete region, which includes the intestines (assuming respiration is unaffected). Therefore, an analysis of the 1-6 cpm region should provide some insight into the relative activity changes of the stomach.

In 2009, we published new results for gastric motility using EBI techniques and short-term recordings. In that study, we proposed using EBI to evaluate gastric motility through considering the global features of the fast Fourier transform (FFT) spectra, and we mainly considered the median of the area under the FFT spectra. The study was performed in 11 healthy subjects who were evaluated under both fasting and postprandial conditions. The results indicated that the median of the area under the FFT spectrum is informationally equivalent to the main peak of the spectrum for purposes of determining the changes in gastric motility from the fasting to the postprandial state. This finding demonstrates that short EBI recordings are valid for evaluating gastric motility. In the same year, we published another study in which metoclopramide was used to generate physical stress in the gastric tract^[89]. We evaluated the differences in the short-term EBI signal for the gastric region in the fasting state, 60 min after the administration of metoclopramide (a drug that promotes gastric motility and gastric stress) and after food ingestion. We recorded the real component of the EBI signal from the gastric region for 1000 s (approximately 15 min). In that study, we compared the median of the area under the curve, the relative area under the curve at 2-4 cpm and 4-8 cpm and the main peak activity to the usual analysis. The frequency range was divided into four regions: R1 spanned 1-2 cpm, R2 spanned 2-4 cpm, R3 spanned 4-8 cpm, and R4 spanned 8-12 cpm. We found that the median of the area under the curve in the 2-8 cycles per minute (cpm) frequency range decreased from 4.7 cpm in the fasting condition to 4.0 cpm in the medicated state ($P = 0.004$). This result was consistent with the observed change in the relative

area under the FFT curve between 4 cpm and 8 cpm, which decreased from 38.3% to 26.6% ($P = 0.012$). In that study, we also demonstrated that the main peak position in the region from 2 cpm to 8 cpm decreased. The main peak activity was 4.72 cpm in the fasting state and declined to 3.45 cpm in the medicated state ($P = 0.025$). There was also a decrease from the fasting state to the postprandial state at 3.02 cpm ($P = 0.0013$). These results demonstrated that global changes in the GIT tract can be measured using short-term EBI, giving useful information on gastric motility. Therefore, we concluded that short-term EBI can be used to assess gastric motility changes in individuals experiencing gastric stress by analyzing the area medians and relative areas under the FFT curve.

More recently, our group has used the short-term EBI technique to evaluate the physiological changes in gastric activity due to psychological stress using the Stroop and Raven test. Our analysis of the changes in the gastric EBI signal used the methodology described above and indicated a significant decrease in gastric motility during the stress test. These results demonstrated that short-term records of gastric EBI may be useful for evaluating the sympathetic nervous system response to acute psychological stress.

CONCLUSION

This review of a broad spectrum of the literature on assessing gastric function shows that the techniques for evaluating gastric motility and emptying have evolved from invasive to non-invasive and have become more sensitive, inexpensive and easier for general practitioners to use in small clinics and physician's offices. Although scintigraphy has been the gold standard for gastric evaluation, it is an invasive technique. This review has emphasized that electrical bioimpedance is a non-invasive alternative technique for evaluating gastric motility and emptying time. This technique can be implemented using small and inexpensive devices once the frequency and amplitude of the stimulation are known. The similarities between gastric EBI and EGG, both of which record information from cutaneous electrodes, enable simultaneous recordings for complementary signal analysis; one detects gastric electrical activity, while the other is sensitive to internal gastric movements. The relatively simple signal analysis required for gastric EBI could make this technique a good candidate for basic clinical evaluation and even an ambulatory method for assessing gastric motility and emptying. However, several important topics remain to be addressed by researchers: (1) To promote a general protocol for clinically assessing gastric motility and emptying in both healthy subjects and patients with the most common gastric diseases, there should be a summary of the major confounding factors for each technique. Implementing a standard protocol would enable systematic comparisons between groups of researchers, and improvements to specific

methodologies could be directed in a common direction. The limitations and scope of each technique would then be clearer, which would encourage using more than one complementary technique; (2) The need for a standard signal processing protocol is similar, but the number of possible signal analysis approaches is several times larger; (3) Improvements to existing methodologies and efforts to overcome the handicaps of existing techniques must be the main motivation of signal analysis research; and (4) Finally, with the goal of offering a technique for outpatient clinics, medical offices and (possibly) remote recordings, a simple, cheap, reasonably sensitive and compact instrument must be developed; gastric electrical bioimpedance is a good candidate technique for this type of instrument.

In summary, electrical bioimpedance is a non-invasive technique that shares some limitations with EGG but that is sensitive to gastric movement. It uses inexpensive, compact devices, making it a good candidate for potential ambulatory and home monitoring. Signal analysis has recently improved, enabling the detection of gastric changes due to food ingestion, medication and stress, among other factors. Further research should address alternative signal analysis approaches, validation, movement discrimination, limitations, variability factors, the normal range of significant parameters and assessment protocols. For these reasons, this technique has great potential to become a user-friendly methodology for assessing gastric motility and emptying.

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