Minireview

Gastrointestinal ischemia monitoring through impedance spectroscopy as a tool for the management of the critically ill

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Abstract

Impedance spectroscopy (IS) has been proposed as a tool for monitoring mucosal tissue ischemia and damage in the gut of critically ill patients resulting from shock and hypoperfusion. A specific device and system have been developed and tested for this specific application over the past 12 years by our research group. This paper reviews previously published studies as well as unpublished experimental results, and puts the whole in context and perspective to help understand this technology. Results presented include summaries of gastric reactance measurement understanding, *in vivo* measurements in animal models, clinical significance of the measurement, and future perspectives of clinical use of this technology. All of the experimental work done to date has been designed to determine the evolving device prototypes' performance and limitations from an instrumentation point of view. Although there are still questions to be answered with regard to the IS measurement, we conclude that we have reached enough confidence in the measurement and the device's performance and safety to begin clinically oriented research to learn how this technology may be useful in the diagnosis and management of different populations of the critically ill.

Keywords: Impedance spectroscopy, gastric impedance, gastrointestinal ischemia

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Introduction

Splanchnic hypoperfusion and ischemia in the critically ill

Gastrointestinal hypoperfusion in critically ill patients is common, probably underestimated, and associated with a poor prognosis.[1] An association between abnormal gastrointestinal perfusion and critical illness has been suggested for many years.[2] An important objective in the care of critically ill patients is to ensure the adequacy of tissue oxygenation, since tissue ischemia may result in anaerobic metabolism, cellular acidosis, and death.[3] However, at present, there is no clinically useful method to directly monitor the level of gastrointestinal tissue ischemic injury, which may be present well before shock and systemic hypoperfusion becomes evident.

Inadequately oxygenated, the splanchnic tissues may become prone to ischemia-related complications.[4] Clinical monitoring of splanchnic organs has been proposed to be a specific indicator of shock and sepsis.[5–7] Ischemic damage of the gastrointestinal tissue is characterized by alterations in cellular function and energy metabolism, which are caused by an inadequate supply and limited consumption of oxygen, insufficient membrane permeability, and a reduction of extracellular volume. Cellular acidosis due to ischemia is caused by the accumulation of lactic and carbonic acids that produce an increase of hydrogen ions and intracellular osmolality, followed by cellular edema and phospholipids synthesis inhibition, which cause cellular membrane damage.[8] After a certain period of ischemia, the gastrointestinal tissue becomes vulnerable to damage due to reperfusion, in which restored oxygen supply produces free radical species, which lead to further tissue injury.[9] The mucosal injury increases as ischemia persists.[10] For an effective and correctly timed therapy, it may be useful to know ischemic level and tissue damage in a continuous and simple manner.[11] A variety of methods are available for assessment of gastrointestinal perfusion. Some techniques include arterial flow sensors (electromagnetic, Doppler flowmetry, ultrasonic and laser Doppler), analysis methods of tissular perfusion (radioactive markers, fluorescence, etc), gas composition methods (PO_2, PCO_2, and pH needle electrodes), and imaging (arterioscopy, microvascular angioscopy). All these methods have great disadvantages for continuous clinical monitoring either because they are greatly invasive or because they only give instant measurements and are not practical enough for being repeated periodically in critically ill patients.

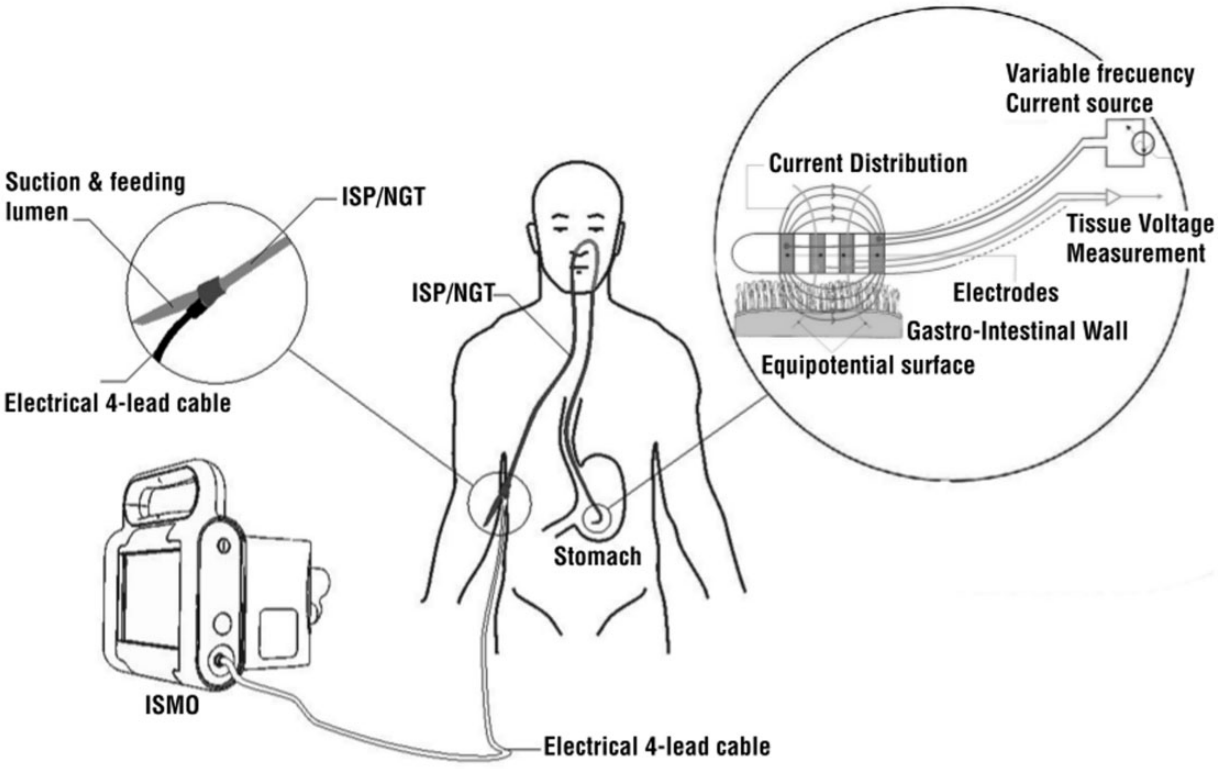

Figure 1 Impedance spectrometer, impedance spectrometry probe, and nasogastric tube (ISP/NGT) setup for the measurement of gastric impedance spectra. The current source produces a constant sinusoidal excitation through the two external electrodes. The two internal electrodes measure the potential generated by the tissue. ISP/NGT has an electric connection to spectrometer for impedance measurements

The only practical technique for assessing gastrointestinal perfusion that has entered clinical practice is gastric tonometry.[3,6,11,12] However, the development of gastric tonometry as a practical clinical technique has been limited by methodological drawbacks and problems of interpretation.[13] Sublingual capnometry[14] requires periodic calibrations, making it cumbersome for continuous monitoring applications, and due to other methodological problems, is no longer commercially available. Orthogonal polarization spectral (OPS) imaging can only be used in tissues with a thin epithelial layer. The obtained data using OPS imaging and its correct analysis are limited by movement artifact, observer-related bias, and even inadequate sedation.[15]

Impedance spectroscopy (IS) of biological tissues

The most used method for impedance measurement in living tissues is the four-electrode method (see Figure 1). The two external electrodes are connected to a constant current source of varying frequency. The two internal electrodes are used for measuring the differential potential generated by the current passing through the tissue. The so-called *mutual impedance* is calculated as the ratio between the measured voltage and the injected current. Electric impedance measurements in biological tissues have been used for decades in a wide variety of applications.[16] IS is the study of the passive electrical properties of biological tissues as a function of frequency. Impedance results from the interaction of an electrical current with the tissue at cellular and molecular levels.

IS, in particular, provides good information about tissue structure.[16] Complex IS also provides phase information, allowing a separation of resistive and reactive tissue components. Electrical resistance reflects electrolytes conducting properties, cell membranes act as dielectrics adding a reactive element. The overall impedance reflects the interaction of resistance and reactance within a complex tissue structure. Changes in extra- and intracellular volume, membrane ion permeability, ion pump dysfunction, and/or membrane disruption all directly affect the complex impedance of the tissue at different frequencies. Figure 2 shows the effect of an electrical field in normal (a) and ischemic (b) tissues. In an electric field, normal tissues will store a charge as in a battery. The overall capacitance is limited by ion channels and pumps that leak the charge across the membrane and by interstitial fluid that shortcircuits the cells and discharges them. Under ischemia, cells swell, ion permeability is lower as ion channels, and pumps close. The reduced interstitial space means less effective shortcircuits. The net effect is that tissues can store a greater electrical charge, increasing reactance.

The complete impedance spectrum of a biological tissue provides a distinctive fingerprint of its structure. Some pathologies like ischemia, infarct, or necrosis cause cellular alterations that are reflected as impedance changes.[17]

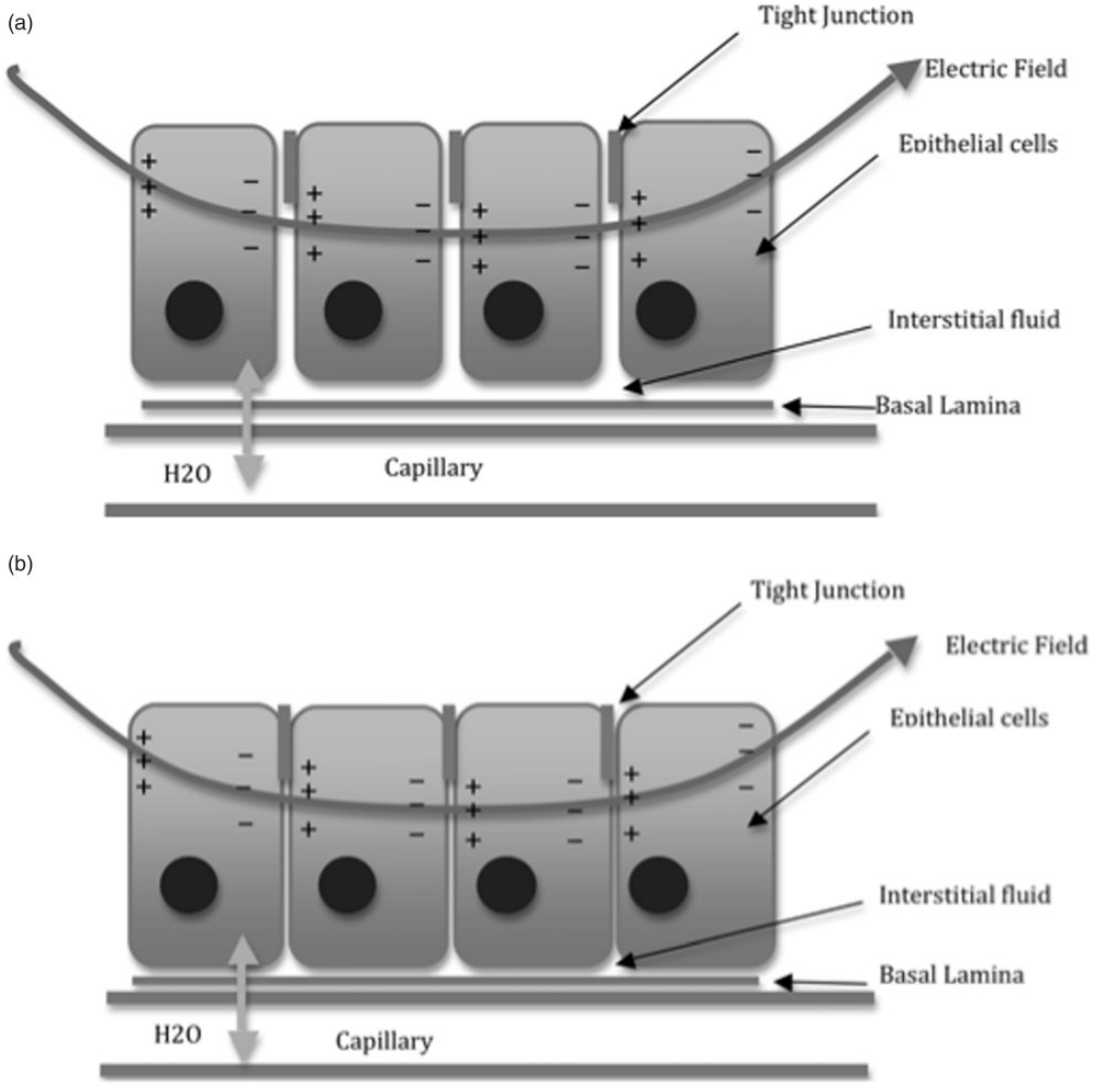

Figure 2 Tissues in a oscillating eletric field. They will store a charge as in a battery. (a) In normal conditions, the overall capacitance is limited by ion channels and pumps that leak the charge across the membrane and by interstitial fluid that shortcircuits the cells and discharges them, (b) under ischemia, cells swell. Ion permeability is lower as ion channels and pumps close. The reduced interstitial space means less effective shortcircuits. The net effect is that tissues can store a greater electrical charge, increasing reactance

IS was reported as a method for tissue ischemia monitoring by Kun and Peura.[18] It has been described as a technique capable of characterizing *in vivo* tissues, and the evolution of ischemia.[19] Gersing[20] reported the ability of this method to provide information about tissue structure, to assess levels of tissue damage in different organs, and the possibility to be applied intraoperatively, continuously, or intermittently with no harm to the tissue. As ischemic injury progresses, inflammatory mediators affect membrane permeability, the balance of intra- and extracellular volume changes, and metabolic waste begins to accumulate. Eventually, metabolic processes cease, ion pumps fail, followed by membrane disruption and cell death. Each of these processes causes characteristic changes in the electrical properties of tissue.

Our research group has been working on the development of an IS device for the past 12 years in collaboration with several other groups (listed in the Acknowledgements section). Our research group reported a relationship between bioimpedance changes with tissular damage level generated by ischemia by means of confocal endomicroscopy and light microscopy[21]; also two animal models of shock were made, one to monitor ischemic injury of the intestinal mucosa in a hemorrhagic shock model in rabbits,[22] other to show that combined splanchnic tissue indicators have the potential of been used as complementary tools for guiding a treatment in septic shock.[23]

Finally, we developed some human studies to evaluate the clinical significance of the impedance measurements: in healthy volunteers,[24] in elective cardiovascular surgery patients,[25–27] and the last one in general critically ill patients.[28] This document attempts to summarize our work to date, showing the importance of gastric ischemia monitoring and main animal and human results.

The measurement of gastric reactance

Proposed technology. The proposed IS system consists of three elements: the IS probe and nasogastric tube (ISP/NGT), the impedance spectrometer monitor (ISMo), and the pattern recognition system.

The ISMo generates an excitation current of 1 mA p-p at 25 different frequencies in a 100 Hz to 1 MHz bandwidth. Four Ag ring electrodes located on the distal tip of the plastic ISP/NGT function as ionic to electronic current transducers, and can be inserted in any hollow viscous organ.[29,30] These electrodes have equal diameter to the catheter, and are placed along the same axis at the distal tip of the catheter. The two outer ring electrodes inject a current into the tissue, and the two inner electrodes measure the resulting voltage (see Figure 1). The electrodes are connected to leads that provide an electrical connection to the other end of the catheter along the wall of the tubing or in the lumen. At the other, proximal end, the leads end in an electrical multichannel connector that can be plugged into the ISMo. The catheter tube may include a second lumen for sampling and feeding like a Levin-type gastric catheter, and/or a third lumen for a vented feeding/sump tube as in a Salem-type gastric catheter.

The impedance spectra are obtained by making discrete measurements of amplitude and phase of the electrical response of the tissue at each frequency relative to a reference electrical resistance. From these measurements, we can calculate the resistance and reactance at each frequency.[30] Although the tissue is only effectively stimulated for a total of 3 s for all 25 frequencies, the entire spectrum takes about 8 s to complete (allowing tissue relaxation and calculations). A complete spectrum is obtained every minute. To reduce the effect of noise and motion artifact, the spectra are averaged every 10 min. In order to calculate the characteristic electrical values that best describe the observed measurements (instead of relying on any one single measurement that may be noisy), a theoretical model based on the Cole equations[31] was fitted for two dispersion regions (low and high frequencies) using a proprietary weighted least means squared algorithm to obtain the coordinates of a circle. Complex impedance (Z) is described by

$$Z = R + jX \tag{1}$$

Using Cole–Cole equation to describe a semicircle, taking frequency into account

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^\alpha} \tag{2}$$

where R = resistance of tissue (real part), X = reactance of tissue (imaginary), R_0 = impedance at zero frequency, R_∞ = impedance at infinite frequency, τ = characteristic time constant, α = measure of the semicircular arc's depression below the real axis, which is a constant between 0 and 1.

The central points can be obtained as follows

$$R_c = x_0 \tag{3}$$

$$X_c = y_0 - r \tag{4}$$

The central frequency (F_c) is estimated calculating the average τ over all measured frequencies in the respective frequency range.

Each of these dispersion regions is described by a distinct semicircle in the Cole–Cole plot (resistance vs. reactance plot). A special software developed by this research group, controls the impedance spectrometer operations and data acquisition, storage, and analysis. The fitted model composed of two semicircles can then be described by the coordinates of the top of each semicircle, which we called the central frequency of each dispersion region (see Figure 3). With this process, we can condense the information from 50 measurements to six characteristic parameters: R_L (central resistance at low frequency), R_H (central resistance at high frequency), X_L (central reactance at low frequency), X_H (central reactance at high frequency), f_L (central frequency at low frequency), and f_H (central frequency at high frequency).[24,26]

Of all these measurements, we propose the use of the X_L as the primary measurement to assess the health of the gastric mucosa as it is sensitive to mucosal cell edema and changes in intracellular to extracellular volume ratio (IV/EV), but it is insensitive to changes in gastric contents and the electrode to mucosal interface impedance. Experimental results described below confirmed that X_L is the most descriptive and reliable index of all the other characteristic parameters. (However the current prototype also provides all the other measurements for future research purposes.)

Safety and specificity results

- Electrical safety rat study

Tissue damage caused by electrical stimulation is an energy and frequency function of the stimulus absorbed by the tissue surface area over which it is distributed. Schwan recommended that effectively current density distributed in an electrode applied to biological tissues remains below 1 mA/cm^2 to avoid burns.[32] Most of the published experimental data have been obtained using needle electrodes that concentrate the electrical energy in narrow point. Under the proposed current levels and electrode geometry, the energy density applied to the tissue with our catheter remains within safe levels. As there is no experimental data with surface area stimulation of gastrointestinal mucosa with electrodes, we wanted to validate that the electrical stimulation of our device was safe and determine the threshold current that will cause some tissue injury.

The experiment tested electrode geometry proposed with different currents up to 100 times greater than the 1 mA (current applied for human use) at different frequencies and duration in the small bowel of rats. Damage was assessed by histopathology analysis of intestinal samples.

The catheter was implanted in the small intestine of 30 rats, and tissue was exposed to a train of 15 stimulations separated by 2 s of relaxation. The stimulation was one of all possible combinations of current intensity levels (1 mA; 2.5 mA; 10 mA; and 100 mA), with different duration times, and different frequencies. As the same time of

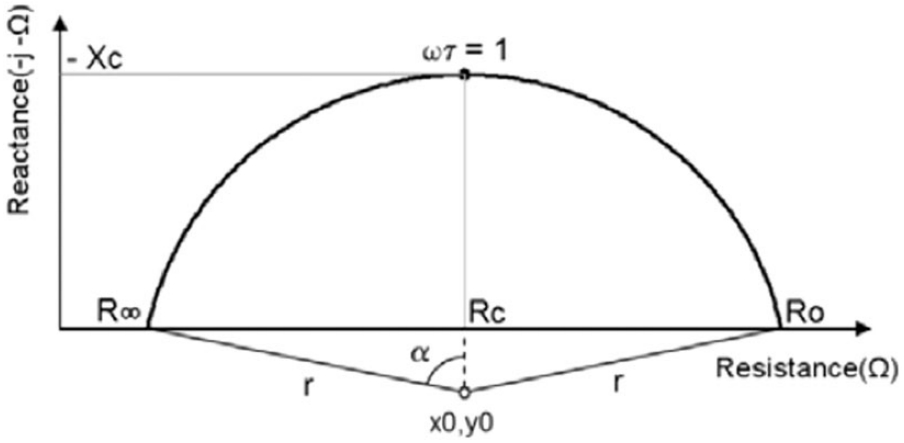

Figure 3 Plot of impedance resembling semi circle in complex domain. x_0 and y_0 are the centre of the semi circle, and r is the radius. We calculated the central parameters *Rc*, *Xc*, and *fc* for each dispersion region of the gastric mucosa

tissue stimulation, impedance was measured. The stimulated tissue was then removed and chemical fixed using 10% formaldehyde for light microscopy. Small bowel tissue was processed with the conventional histological techniques. The tissue was cut longitudinally and stained using hematoxylin–eosin. A blinded pathology expert scored each sample according to the following scale: level 0 (no damage), level 1 (superficial damage, only epithelial villi cells affected), level 2 (epithelial and connective tissues damage was observed reaching only the tip third of the villi), level 3 (damage reached the mid third of the villi), and level 4 (damage reached the base third of the villi, even affecting basal glands). Figure 4 shows two samples stimulated at different current levels. The total energy absorbed by the mucosa (which is function of tissue impedance), current applied, and stimulus duration was calculated for each sample. The energy threshold to cause some observable damage was found to be 0.172 mJ, almost two orders of magnitude above the energy level at the proposed current level of 1 mA, which is in the order of 0.005 mJ.

Development of a mathematical model of the electric characteristics of the gastric mucosa. A bioelectrical model of the intestinal tissue under IS measurements was developed in order to obtain a current density map, and to establish a relationship between the geometry of the electrodes used for the electric stimulation and its effect in the current distribution model. Finite element analysis techniques were used in an electrical complex model of the gastrointestinal wall for electrical measurements simulation and validation of the estimated current distribution in the tissue. Figure 5 presents the current density and power distribution. The stimulation and distribution effect of the current density is proportional to the size and distance between the electrodes, in this way, the electrode geometry was validated in the final design of the probe, providing an optimal current density that concentrates the excitation current in the gastric mucosa layer, which means a greater sensibility to the structural changes of interest. It was also confirmed theoretically, that the maximum current density is at least two orders of magnitude lower than the minimum current

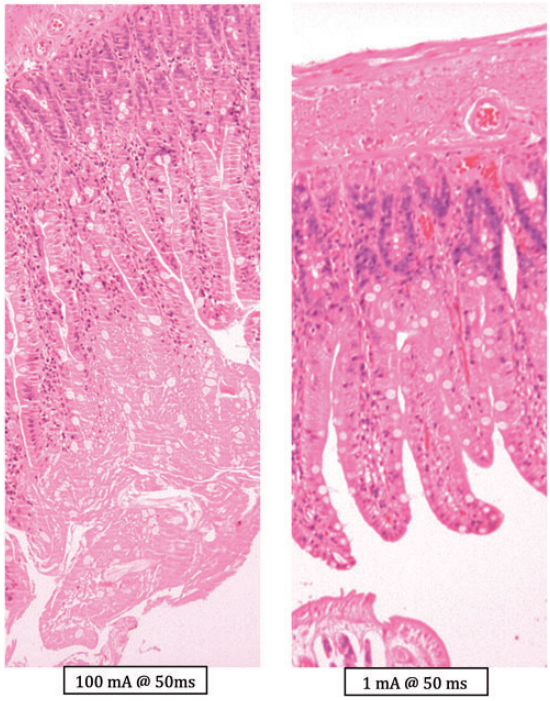

Figure 4 Hematoxylin and eosin-stained histological sections of rat small vowel tissue at different level of current stimulation. On the right, the tissue is intact despite being stimulated with 1 mA/50 ms bursts. On the left, the tissue in the area in contact with the electrode shows disintegration of villi tips and loss of cell nuclei in the damaged region, this photomicrograph was scored as level 3 and corresponds to stimuli of 100 mA/50 ms

density that can cause tissue damage; magnitudes that give us a greater safety margin.

In vivo measurement of gastric reactance

Superior mesenteric artery (SMA) occlusion in animal models

Pig study. The objective was to determine how impedance spectra change over time in ischemia/reperfusion

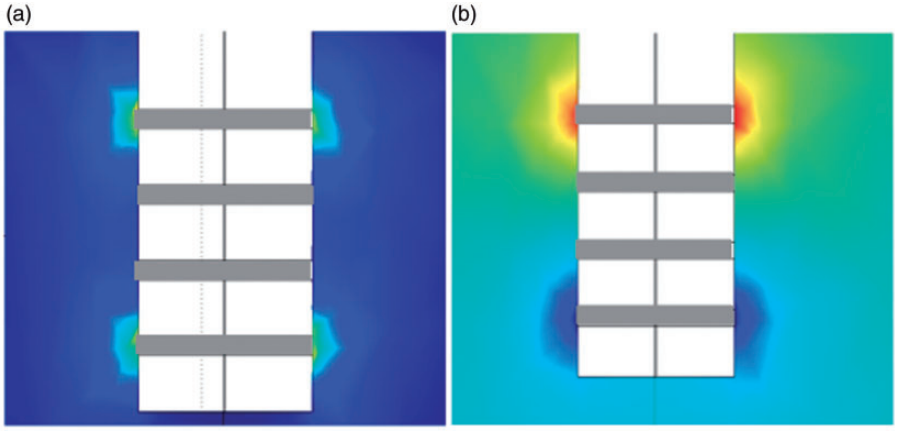

Figure 5 (a) Shows a bidimensional map of the current density distribution in a simulated conductive volume and (b) shows a bidimensional map of the power distribution in the simulated volume. (A color version of this figure is available in the online journal.)

model, based on Antonsson's validation study of Tonometry.[33]

Intestinal ischemia was produced by total occlusion of SMA in 13 anesthetized pigs assigned to four different ischemia/reperfusion groups: sham, 1 h ischemia/reperfusion, 2 h ischemia/reperfusion, and 4 h ischemia. Tonometric pH_i and SMA blood flow measurements were also performed every 30 min. Impedance spectra were reproducible at each time within each group, and those of tissue under prolonged ischemia were significantly differentiable ($P < 0.05$) from those of normally perfused tissue. Spectral changes over time were characterized and compared to changes in perfusion (SMA blood flow) and pH_i (Figure 6(a and b)). We found that resistance and reactance changed proportionally to time of ischemia. Reperfusion after 1 h caused a gradual return of impedance measurements to pre-ischemia levels, whereas reperfusion after 2 h ischemia did not entirely recover. After 3.5 h of total arterial occlusion, a sudden change in the impedance spectra was observed in 4 h ischemia group (Figure 6c), this may correspond to the disruption of the mucosa as cell membranes break down.[34]

Rabbit in MRI study. This study was designed to validate gastrointestinal IS measurements against independent measures of tissue structure and metabolism as ischemia progresses. Magnetic resonance imaging and spectroscopy (MRIS) was used to obtain metabolic measures in a noninvasive way and follow the changes over time.

The ISP, a tonometer and a specially designed dual frequency intraluminal RF antenna were surgically inserted in the small intestine of 15 anesthetized rabbits. An occluder was also placed around the SMA allowing us to easily tighten and release from outside the body. The animals were then placed inside a 4.7 T research magnet and continuously scanned for 4 h. In 30 min cycles, we performed the following measurements:

- A high-resolution T2 weighted MRI image of the intestinal wall. T2 is the transverse relaxation constant of the MRI signal. Trapped water such as intracellular fluid has a shorter T2 than extracellular fluid, so that the signal intensity (SI) of a T2-weighted image is inversely proportional to IV/EV. (This has been used to image ischemic regions of the brain.) This image was also used to measure the intestinal wall thickness (with a resolution of 78 μm) and track changes over time;
- A diffusion-weighted MRI image to map the apparent diffusion coefficient (ADC) of water. Trapped water moves less. Although this variable is not directly the same as T2 SI, as it is also affected by osmosis and membrane permeability, it should track IV/EV;
- A P^{31} spectrum to measure metabolic phosphates (including ATP and inorganic phosphates) and tissue pH;
- A water-suppressed H^1 spectrum to measure changes in lactate;
- Two intestinal impedance spectra (one every 15 min);
- Tonometry, blood gases, and vital signs measurements.

Subjects were divided into three groups: control group, ischemic group (SMA was occluded after 30 min of baseline measurements), and ischemia–reperfusion group (occlusion was followed by reperfusion 60 min later).

Tissue pH measurements showed the proper development of the experimental model. The pH dropped almost immediately (within the first 15 min) to highly abnormal values in the ischemia groups and return to acid but almost normal values just as rapidly with reperfusion as CO_2 is cleared, Figure 7(a). ATP/Pi also dropped rapidly but not as rapidly as pH, but only returned gradually with reperfusion. Lactate was produced only in a brief window after occlusion when anaerobic metabolism replaced aerobic metabolism, then metabolism shut down altogether and lactate cleared gradually. As had been seen in earlier experiments, impedance does not change immediately but changes linearly with time of ischemia and then gradually returns with reperfusion (Figure 7b). The changes in impedance tracked the changes in T2 SI almost perfectly, Figure 8.

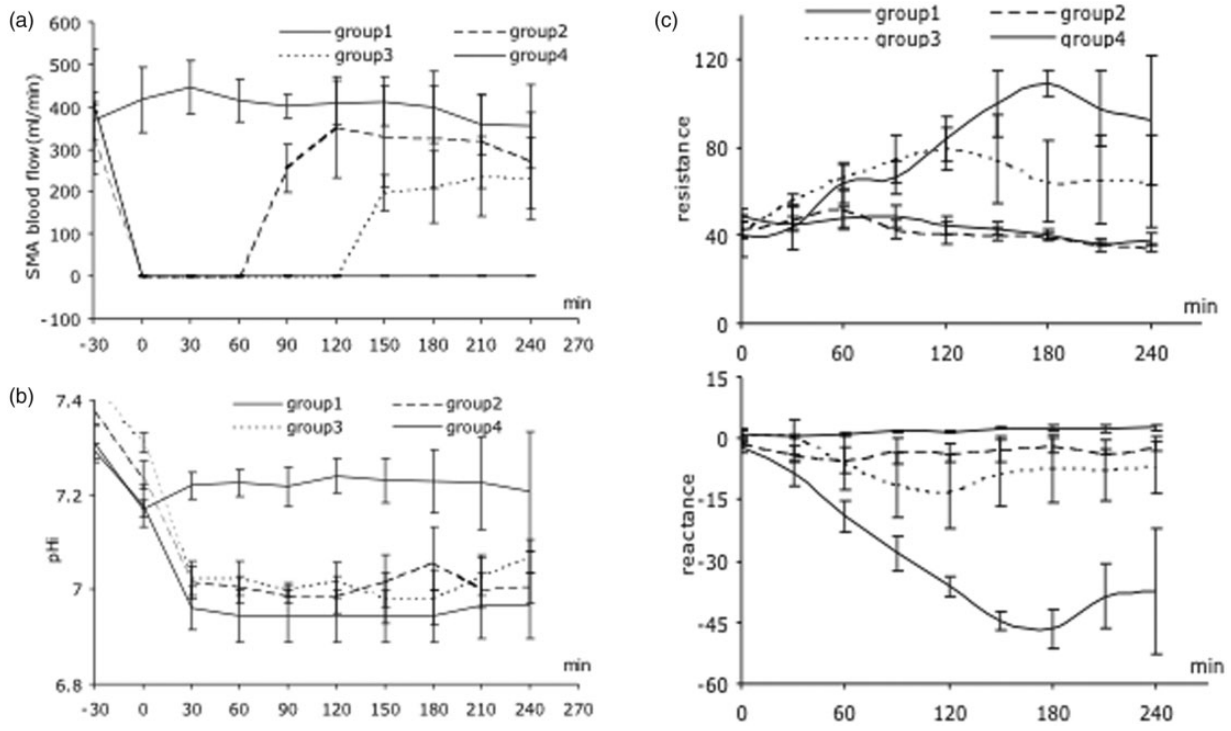

Figure 6 Temporal course of SMA blood flow (a), pHi (b) resistance at 68 KHz (c) and reactance at 68 KHz (d) for each of the four experimental groups ($M \pm SE$). SMA is occluded at $t = 0$

In fact a very high linear correlation was found between changes in resistance and reactance to the log ratio of SI change relative to baseline with $P < 0.001$, Figure 7b. Impedance changes showed a time lag to changes in perfusion. In fact, impedance (as well as T2 SI) did not begin to change until the ATP/Pi has almost reached its minimal value. The ADC measurements showed much more variability from animal to animal and the measurements were noisy because this technique is extremely sensitive to movement artifact, however the average measurements generally tracked T2 SI and impedance. Wall thickness measurements also showed significant variability from subject to subject but the average change relative to baseline seemed to show that the thickness begins to shrink after about 2 h of ischemia presumably as the tips of the villi atrophy. It seems that IS primarily reflects changes in IV/EV produced by tissue ischemia and does not directly measure perfusion.

Summary of published studies. Our research group reported bioimpedance increase with tissular damage generated by ischemia, and found general alterations in cellular and tissular integrity by confocal endomicroscopy and light microscopy during ischemia.[21]

Besides two animal shock models, we developed some human studies to evaluate the clinical significance of the impedance measurements. The first study was made in healthy volunteers to characterize human spectra, to determine subject-to-subject reproducibility, and to evaluate the ISP/NGT performance under different clinical usage conditions. One of the main findings of this study was the characterization of the impedance spectrum of the gastric mucosa in healthy adults. Feeding and suction are not contraindications for use of the impedance spectrometer, also improper placement or excessive fluid was detected by the software.[24] The second study was designed to characterize impedance spectral changes under differing degrees of splanchnic hypoperfusion during elective cardiovascular surgery. Gastric reactance shows high sensitivity to predict outcome, compared with some hemodynamic and regional perfusion variables.[25,26] Low-frequency gastric reactance, X_L, had a significant predictive value of postoperative persistent shock requiring more than 48 h of vasopressors and associated complications, before, during, and after surgery ($P < 0.05$) (see Table 1). Patients with a high reactance ($X_L > 26$) before surgery had a significantly higher incidence of complications, higher mortality, and more days in the intensive care unit (ICU) than patients with a low reactance ($X_L < 13$). Setting X_L threshold at 13, sensitivity was 0.9 and specificity was 0.25, and this value better identified patients at risk. Below this level, all healthy volunteers would be classified as normal. Setting the X_L threshold at 26, specificity was 0.9 and sensitivity was 0.5, allowing the more accurately identify patients who developed complications. Based on the results of this study, we proposed that X_L values of 13 and 26 may be considered as useful thresholds for patient classification relative to complication status. Figure 9 shows cardiovascular surgery patients' classification based on X_L proposed thresholds of 13 and 26. Normal is below the threshold of 13 (green), very abnormal is above the threshold of 26 (red). The figure shows the number of patients at the top of each branch, the number of patients who developed complications and its

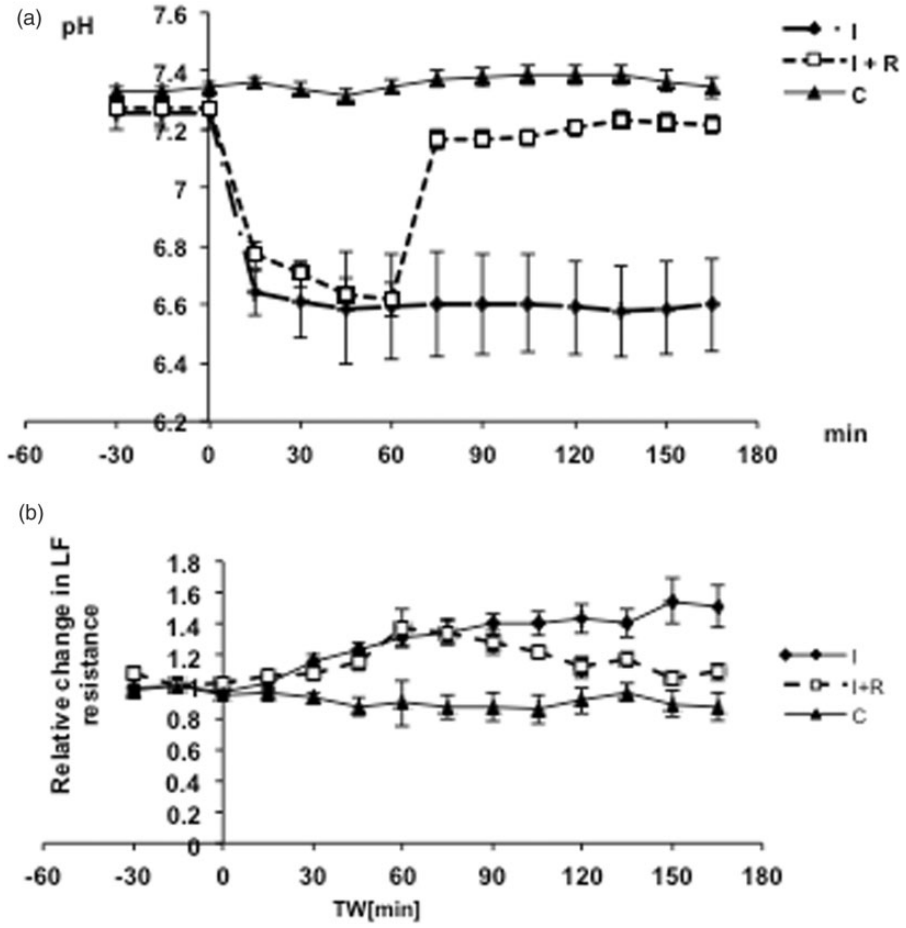

Figure 7 Changes over time of the three experimental groups. (a) Shows changes in tissue pH as measured by P31 spectroscopy. (b) The relative change to baseline of the average resistance in the 1 kHz range

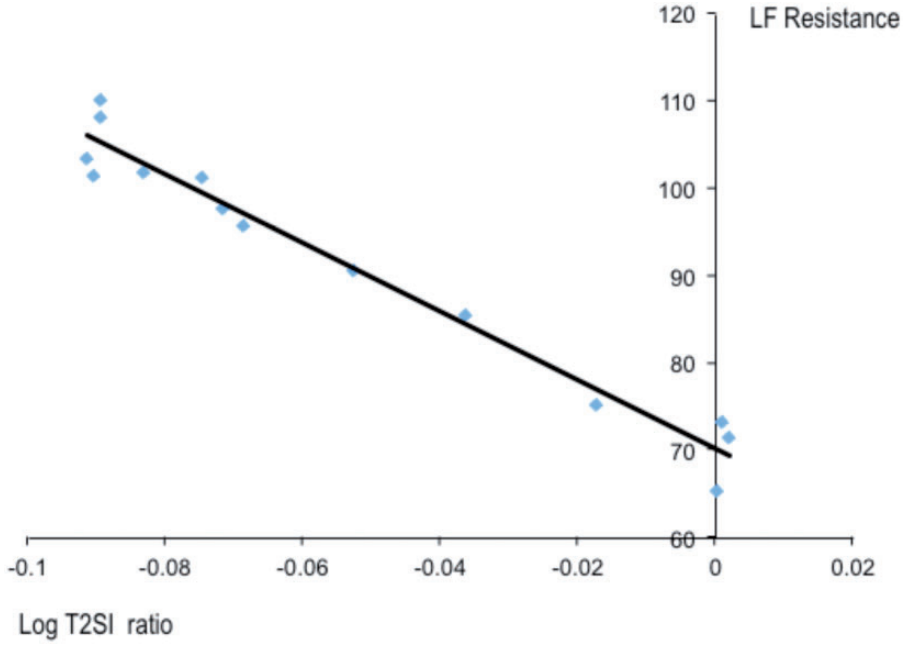

Figure 8 The relative change in T2 signal intensity of the mucosa is inversely proportional to intracellular to extracellular volume ratio and also linearly related to the resistance in the 1 kHz range. (A color version of this figure is available in the online journal.)

Table 1 Analysis of receiver operating curves of impedance parameters and scoring systems obtained before, during, and after surgery (adapted from Beltran et al.[27]).

	Pre-CPB		CPB		ICU	
Variable	**AUC**	***P* value**	**AUC**	***P* value**	**AUC**	***P* value**
Impedance parameters						
R_L, Ω	0.695 ± 0.069	0.010*	0.739 ± 0.065	0.003*	0.710 ± 0.068	0.007*
X_L, $-j\Omega$	$\mathbf{0.690 \pm 0.070}$	**0.013***	$\mathbf{0.766 \pm 0.062}$	**0.001***	$\mathbf{0.728 \pm 0.066}$	**0.004***
Scoring systems						
NYHA	0.609 ± 0.073	0.087				
Parsonnet, score	0.673 ± 0.072	0.021*				
APACHE II					0.695 ± 0.068	0.010*
SOFA, score					0.713 ± 0.067	0.012*

Note: Pre-CPB, before cardiopulmonary bypass; CPB, cardiopulmonary bypass; ICU, intensive care unit; AUC, area under the receiver operating characteristic (ROC) curve; R_L, central resistance at low frequencies; X_L, central reactance at low frequencies. NYHA, New York Heart Association; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment. Data are represented as $M \pm SE$.
P values are for a one-sided *z* test of significance that AUC > 0.5. *Is considered statistically significant ($P < 0.05$).

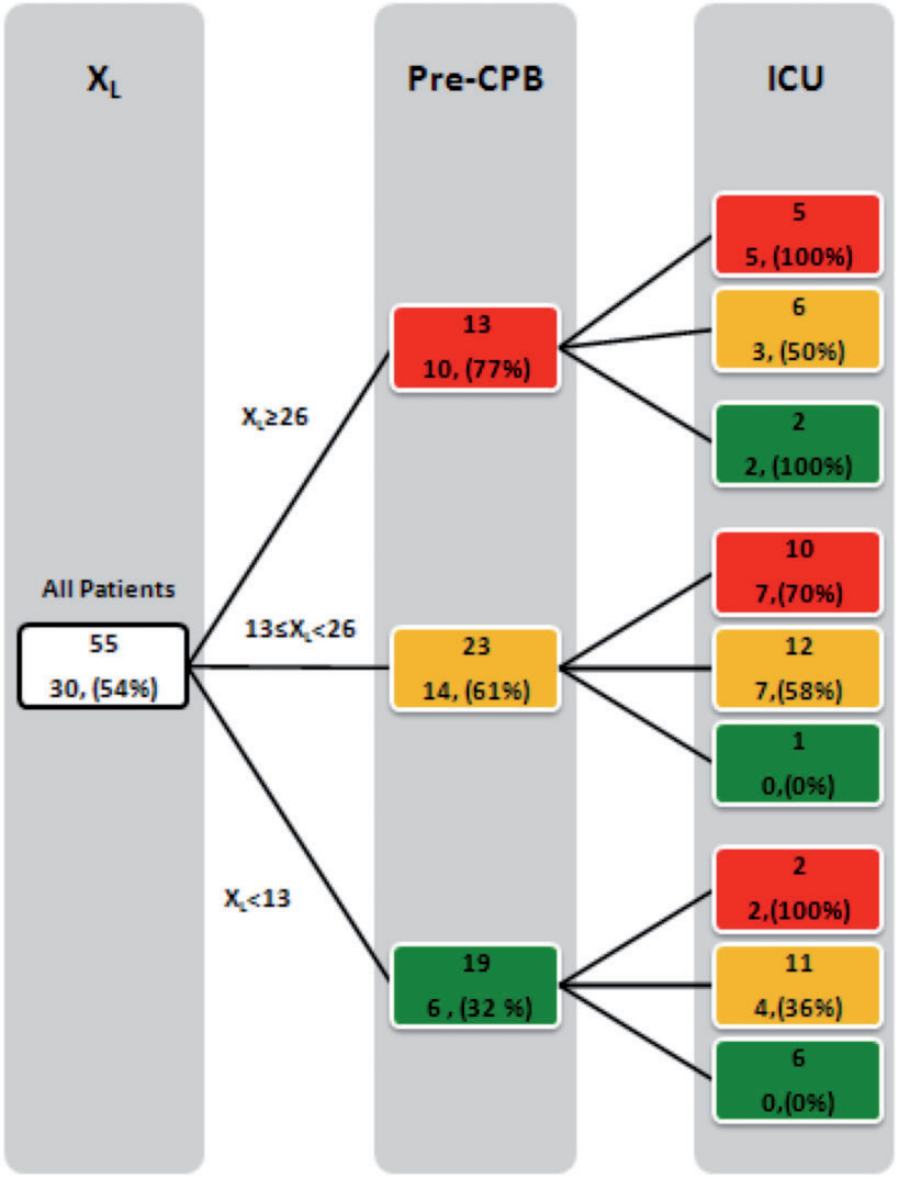

Figure 9 Classification tree of gastric reactance at low frequencies (X_L) according with proposed thresholds of 13 and 26. Normal is defined as patients with a mean X_L value below the threshold of 13 (green), very abnormal as above the threshold of 26 (red). The number presented at the top of each branch is the number of patients, followed by the number of patients who developed complications and its percentage

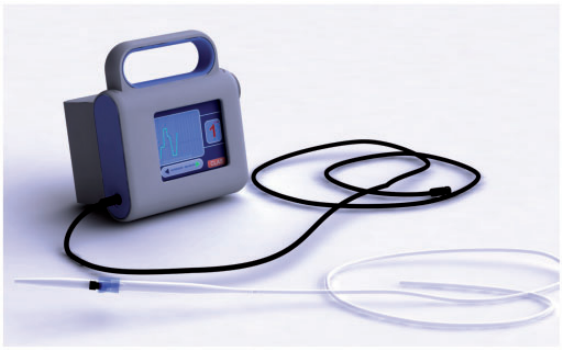

Figure 10 Impedance spectrometer monitor (ISMO) prototype. (A color version of this figure is available in the online journal.)

percentage. The last human study was designed to obtain a database of human gastric impedance spectra under varied clinical conditions and pathologies to identify subgroups of patients who may benefit with this technology. This study shows that gastric ischemia as estimated by gastric reactance has a very high incidence in the critically ill, independently of the reason for admission. High reactance is related with higher morbidity in agreement with other reports using different methods of assessing splanchnic hypoperfusion in this patient population.[28]

Perspectives for the future

All of the research completed to date has been designed to understand the performance and limitations of the proposed device as a monitoring tool for gastrointestinal ischemia. Our device (Figure 10) has been shown to provide reproducible measurements under clinical conditions that contain relevant information on the patient's progress.[25,26,28] The impedance spectra also provide a distinctive shape or fingerprint that will be effective to identify improper placement, excessive movement artifact or noise and device failures, and therefore improve our confidence in the measurement. The challenge was to reduce the dimensionality of the complex measurements to one or two simple variables that were robust and easy to interpret so that this system could be used effectively in clinical practice. We have learned that, in general terms, the central resistance at low frequency (R_L) and the central reactance at low frequency (X_L) reflect changes in IV/EV and membrane ion permeability as a consequence of tissue ischemia, and usually track each other, but under certain circumstances such as fluid overload they diverge. We are using theoretical models to try to extract from the overall spectral shape simple parameters that are more robust to noise and more importantly have a physiological meaning that will be more easily interpreted. We proposed that low-frequency central reactance (X_L) was the principal parameter that reflects tissue edema caused by prolonged ischemia,[26,28] also it only appears in live tissues. We used that parameter to classify injured mucosa (patients in red in Figure 9) in human gastric tissue with the proposed thresholds, showing a very high incidence of gastric ischemia in the critically ill.[28] We also observed alterations in cellular and tissular integrity by light microscopy analysis that confirmed gastric reactance increments obtained during ischemia in a rat model.[21]

Gastric ischemia results from diffuse or localized vascular insufficiency due to etiologies such as systemic hypotension, vasculitis, or disseminated thromboembolism.[35] Recently it has been reported that gastrointestinal dysfunction is common in critically ill patients, and may have bad prognosis,[1,36] so improving diagnosis techniques in critically ill patients help the generation of guided therapies in a faster and more efficient way, preventing Multiple Organ Dysfunction Syndrome (MODS) and death.[37] Moreover, gastric ischemia is associated with a poor prognosis, and early diagnosis is critical to guide potential interventions.[35] Despite the fact that there is still more to be learned about the information provided by the spectrometer, we believe we have a device that is safe and easy to use that will provide relevant information for further study and it is time to move on to clinically oriented research aimed at learning how this device may be used clinically with specific patient populations. We believe that if a technology becomes available that allows us to easily and reliably monitor ischemia and hypoperfusion, we will eventually learn how to use this information to significantly improve critical patient outcome.

Author contributions: Both authors participated in the design of the proposed technology, design of animal and human studies, interpretation of the studies and analysis of the data, and review of the manuscript.

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