Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.JournalofSurgicalResearch.com

Implantation of an Impedance Sensor for Early Detection of Gastrointestinal Anastomotic Leaks

Matan Ben-David, MD,[a,*] *Idan Carmeli, MD,*[b] *Ran Orgad, MD, PhD,*[c,d] *Bar Nathansohn-Levi, PhD,*[e] *Tal Yered, MSc,*[f] *Erez Shor, PhD,*[f] *and Nir Wasserberg, MD*[c,d]

[a] *Upper GI Surgery, Royal Prince Alfred Hospital, University of Sydney, Australia*
[b] *General Surgery, Assuta Ashdod Public Hospital, Ashdod, Israel*
[c] *Department of Surgery, Rabin Medical Center, Petach Tiqva, Israel*
[d] *Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*
[e] *Weizmann Institute of Science, Rehovot, Israel*
[f] *Exero Medical LTD, Or Yehuda, Israel*

ARTICLE INFO

Article history:
Received 3 October 2021
Received in revised form
7 April 2022
Accepted 8 April 2022
Available online 17 May 2022

Keywords:
Anastomotic leak
Bioimpedance
Early diagnosis
Mg electrode

ABSTRACT

Introduction: Accurate early diagnosis of a gastrointestinal anastomotic leak remains a challenge. When an anastomotic leak develops, the electrical properties of the tissue undergoing inflammatory processes change, resulting from the extravasation of inflammatory fluid and cellular infiltration. The method described here intends to provide a novel early anastomotic leak warning system based upon measurable changes in tissue impedance nearby an acute inflammatory process.
Methods: A biodegradable Mg-alloy was compared with a nonabsorbable stainless steel (STS) electrode connected to a wireless recording system for impedance measurement. *In vitro* measurements were made in physiological solutions and small animal (eight mice) and large animal (eight pigs) models with an anastomotic leak simulated by an open colotomy. Measurements were made at 10 mm intervals from the open colon at baseline and up to 120 min comparing these with a sutured colonic wound and normal tissue.
Results: In-vitro biodegradable magnesium electrode impedance evaluation showed good sensitivity to different media due to its environmental corrosion properties. The impedance of an acidic environment (1.06 ± 0.02 kΩ for citric acid) was twice that of phosphate-buffered saline (PBS) (0.64 ± 0.008 kΩ) with a distinction between Normal Saline (0.42 ± 0.013 kΩ) and PBS (0.64 ± 0.008 kΩ). This was in contrast to the performance characteristics of the control STS electrodes, where impedance in an acidic environment was lower than saline or PBS (citric acid:0.76 ± 0.01 kΩ *versus* PBS: 1.32 ± 0.014 kΩ). In a mouse model simulating an anastomotic leak, there was a significant increase in impedance after 120 min when compared with controls (99.7% increase *versus* 9.6% increase, respectively; $P < 0.02$). This effect was confirmed in a pig model when relative impedance measurements of the leak and control groups were compared (1.86 ± 0.46 *versus* 1.07 ± 0.02, respectively; $P < 0.027$).

* *Corresponding author*. UGI and HPB Surgery Department, Royal Prince Alfred Hospital, University of Sydney, 50 Missenden St., Camperdown, Australia 2050. Tel.: +61416058848; fax: +61295156111.
E-mail address: matanbendavid@gmail.com (M. Ben-David).

https://doi.org/10.1016/j.jss.2022.04.041

Conclusions: Electrophysiological measurement shows diagnostic sensitivity for a gastrointestinal leak with potential clinical utility in the postoperative detection of early intra-abdominal sepsis. Further investigation of biodegradable tissue sensors capable of monitoring an early anastomotic leak is required.

Introduction

Anastomotic leak (AL) remains a feared complication after colorectal cancer surgery with an incidence variably reported between 6% and 10%[1] and with deleterious effects on perioperative morbidity and mortality, length of hospital stay, rate of hospital readmission, patient quality of life and overall health economics.[2-4] Early diagnosis and management are crucial in reducing AL-related morbidity and mortality where there may be confusion with other potential causes of postoperative fever and pain and where early radiology may be either equivocal or nonspecific.[5] There is general agreement that early detection of AL with timely intervention reduces overall hospital mortality.[6] In the modern environment of enhanced recovery, early enteral feeding and early discharge from hospital, a high index of suspicion for the diagnosis of AL is required, as its diagnosis is oftentimes based on subtle deviations in the postoperative course of the patient, which can precede more overt signs of sepsis.[7]

There have been many reports describing the predictive factors associated with AL and equally a variety of tests designed for early diagnosis, including serological markers, inflammatory cell ratios, and directed radiologic imaging.[8-10] The current etiopathogenesis of AL is debated implicating a complicated interaction between ischemia, inflammation, the immune response, and the gut microbiome.[11] During the earliest phase of AL the release of mediators will result in focal pH changes and oxidative stress, which alters the electrical properties of the immediate vicinity of an inflammatory process. As there is an increase in tissue edema, hyperemia, and cellular infiltration, there is a concomitant increase in electrical conductivity due to an abundance of charge-carrying ions. The inflammatory process can therefore be observed via measurement of local tissue bioimpedance, which typically decreases around inflamed tissue as has been shown in a variety of tissue models.[12,13] In order to exploit the use of tissue impedance as a marker of inflammation, we report in this study two different types of electrodes used for bioimpedance measurement: (1) A clinically approved nonabsorbable stainless steel (STS) alloy electrode and (2) A biodegradable magnesium alloy electrode, which has the advantage that it can be used for a short period of time after which it will degrade without leaving any foreign elements *in situ*. Further, the use of an implantable magnesium electrode is compatible with laparoscopy-assisted and robot-assisted techniques, which predominate modern GI surgery.

As overall impedance changes are modulated by inflammatory tissue, we aimed to provide support for the concept of early detection of an anastomotic leak based upon the performance characteristics of impedance recording electrodes, first by *in vitro* experimentation and then in two *in vivo* anastomotic leak models.

Materials and Methods

The conduct of the study and its analysis was approved by the Tel Aviv University Ethics Committee Division of the Rabin Medical Center, Israel, with the *in vivo* animal experiments separately approved by the Rabin Institutional Animal Care and Use Committee (IACUC as 022-b13153-010118, 2018). After initial experimentation in mice, a separate approval notice was sought for the establishment of a porcine model (IACUC as 011-b15077-10-13-2019; 2019). All animal experimentation and protocols were conducted in accordance with the previously published Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines.[14] The principle of testing is based upon the detection of an AL (or physiological processes leading to AL) by a change in the electrical impedance of extravasated fluid as measured by electrodes strategically placed in the perianastomotic area.[15,16]

Electrodes, impedance measurement, and experimental groups

Two types of electrodes were used throughout the experiments. The first type is standard stainless steel electrodes currently used for temporary cardiac pacing, and the second type is biodegradable magnesium electrodes that were used because of their specific properties. These electrodes have been proven to be good electrical conductors with acceptable sensitivity for detecting impedance in different media.[17] Electrodes were constructed of thin (0.3 mm diameter) metal cables insulated by silicone/polyethylene tubing, with an exposed length of 10 mm. Electrodes were made of either stainless steel (AE MYO/WIRE, PA) or RESOLOY magnesium alloy (Fort Waine Metal, IA), a resorbable, flexible alloy with Mg-Dy-Nd, Zn, and Zr elements.[18] To provide better flexibility, the electrodes were fashioned with 7×0.1 mm wire cables for use in larger animals as shown in Figure 1. For impedance measurement, a small sine-wave current between 6 and 60 nA (at least two orders of magnitude lower than the maximum safe electrode applied current) at a selectable frequency between 0.1 and 32 Hz was passed through the electrode.

The voltage drop on the electrode-tissue junction was recorded with a sampling rate of 250 Hz. The electrode was connected to a biomedical sensitive analog to digital converter (ADS1299, Texas Instruments, USA), and data were relayed to a laptop computer. Impedance was calculated in accordance with Ohm's Law by dividing the RMS (root mean square) voltage drop on the electrode by the current applied. Bioimpedance measurements with both types of electrodes were

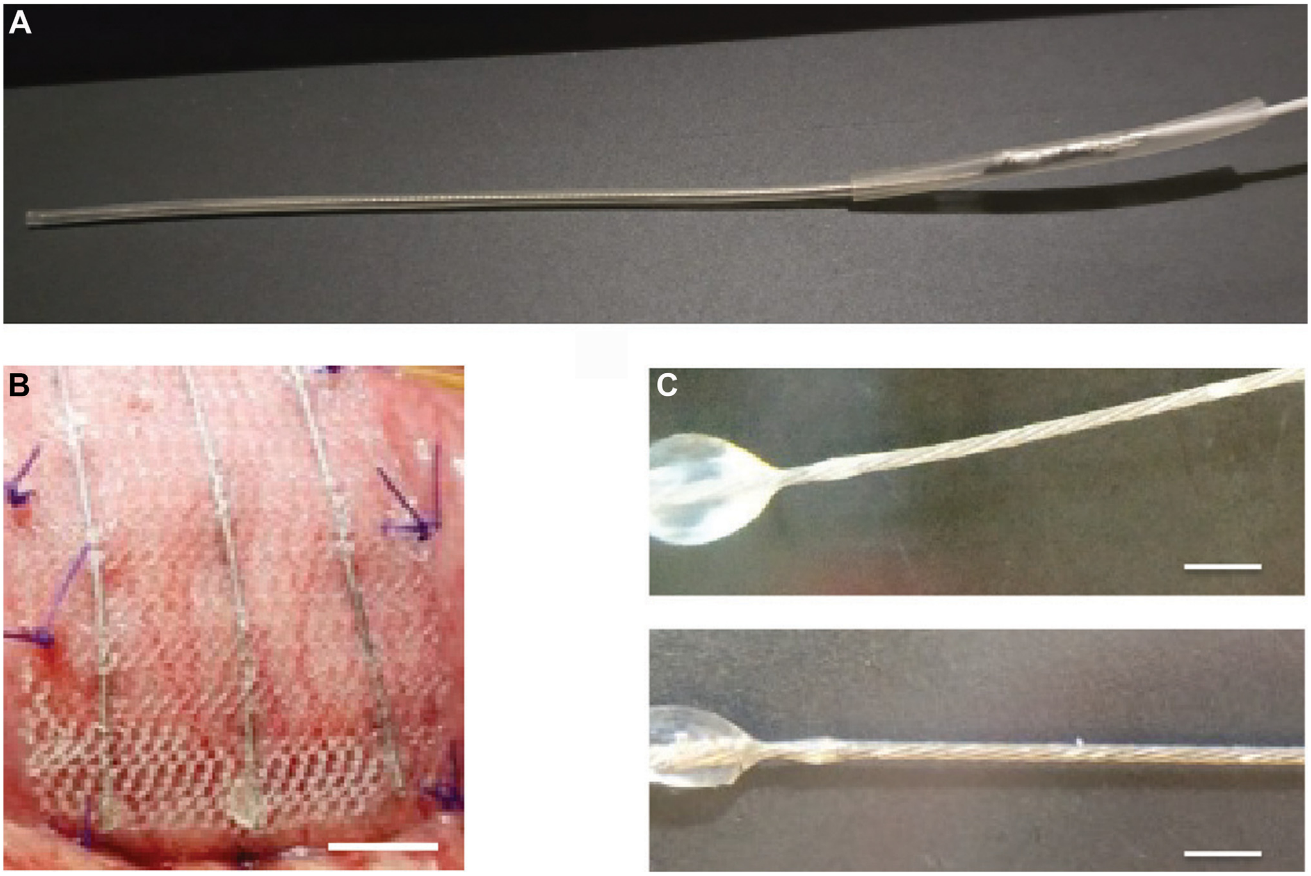

Fig. 1 – Magnesium alloy electrode as used in the study. (A) The electrode is insulated with silicone tubing prior to implantation for *in vivo* use. (B) Three electrodes are weaved onto an absorbable Vicryl mesh for long-term implantation. Scale bar – 10 mm. (C) Active electrode before implantation (*Upper Image*) and after 7 days in physiological conditions (*Lower Image*). Scale bar – 1 mm.

established in three separate experimental groups (one *in vitro* and two *in vivo*). For *in vitro* measurement, the electrodes were immersed in 400 mL of four different solutions, including 0.9% N Saline, PBS (Sigma–Aldrich, Israel) at pH 7.4, 0.1 M Citric Acid, and 0.1 M $NaHCO_3$. Normal saline and PBS were both chosen as media simulating the physicochemical conditions within healthy tissues. Citric acid was chosen to replicate the acidic environment surrounding an AL, and sodium bicarbonate was used to assess electrode measurements across the pH range. Electrodes were cut to length, cleaned and degreased by immersion in acetone and ethanol, and then mounted on 3D-printed spacers that ensured that they remained parallel and equidistant. Electrode pairs were immersed in the different solutions for a 30 min period of initial conditioning prior to impedance measurements. Impedance was measured in 3 s intervals for 30 s (10 measurements per electrode/solution). All electrodes were examined afterward with an optical stereoscope (100 Mag) for signs of degradation or corrosion.

Two animal species (mice and pigs) were used as small and large models. To minimize variability in a small sample, only female mice were used. Eight C57BL/six mice (Harlan, Israel) were anesthetized with Ketamine (100 mg/Kg)-Xylazine (10 mg/Kg) injection. In the mouse model, a group was established (the Leak Group) with a deliberate injury of both the cecum and the gastric wall with the electrodes implanted intraperitoneally. In the control (Nonleak) group, electrodes were similarly implanted into a normal colon and stomach. For the porcine model, eight domestic female pigs (BioTech Farm, Naan Israel) weighing between 60 and 75 Kg were obtained and initially allowed food and water *ad libitum*. The study was limited to female pigs for practical reasons—the animal facility made only female pigs available, and the GI surgical procedure in male pigs is further complicated because of the anatomy of male pig genitalia. The day prior to surgery, they were fasted but had free access to fluid. One hour prior to their procedure, they were administered IM Cefoxitin (40 mg/Kg) and then sedated with tiletamine/zolazepam (5 mg/Kg), xylazine (2.25 mg/Kg), and atropine (0.03 mg/Kg). In these animals, the descending colon was mobilized and delivered. The colon was opened on its antimesenteric border over a 2 cm distance. In the control arm, the colotomy was closed with a single layer of continuous 5/0 Vicryl, whereas in the experimental group, the colonic wound was left open.

For the purposes of measurement, electrodes were implanted using a syringe and needle tunneled seromuscularly to avoid inadvertent luminal entry. Separate electrodes were positioned at different distances from the colotomy (10 mm, 20 mm, 30 mm, and >80 mm away), with the most distant electrode regarded as representative of normal tissue (referred to as intact tissue). Electrical impedance was measured at the time of implantation and then 30, 60, and 120 min after intervention. Measurements in both species were repeated with a minimum of 10 impedance measures taken and with reporting of the average. At the completion of these measurements, the animals were sacrificed by rapid injection of a lethal dose of KCl (75-150 mg/Kg).

Statistical analysis

Analysis was performed with Matlab (The MathWorks, Natick, MA) software. Normality test was applied to experimental data before utilization of statistical tests based on the normal distribution of the results (ANOVA, *t*-test). To verify that the data is normal Kolmogorov-Smirnov test of normality was applied to pooled data of experiments with the same treatment. P values > 0.05 were considered normal. All values in the results section are recorded as mean ± standard deviation. In all box plots, x represents the mean value. Mice impedance comparison was made using a two-tailed t-test. Comparisons of the means for the different distance points with each electrode were made using a one-way ANOVA with the Bonferroni-Holm correction. A P value < 0.05 was considered statistically significant.

Results

Magnesium electrodes can provide tissue monitoring over days

The extent of degradation of the Mg electrode was assessed first. In this respect, implanted electrodes have a balance between flexibility and longevity, whereas thicker electrodes, which last longer, have a greater rigidity that makes them less suitable for longer-term implantation. Our 300 mm diameter cable remained functional for more than 5 days, but by this time, 24 (±10)% of the cable threads were shown to be corroded and broken.

Impedance measurement can indicate chemical, environmental changes

In the initial *in vitro* experiment, there was a high sensitivity for the detection of impedance in different media with both the Mg and STS electrodes. The Mg electrode, however, consistently showed better discrimination between the solutions used. With the Mg electrode, the measured impedance of Citric acid was 1.06 ± 0.02 kΩ, whereas it was 0.64 ± 0.008 kΩ for PBS ($P < 3 \times 10^{-6}$) and 0.42 ± 0.013 kΩ for normal saline ($P < 0.002$). This permitted discrimination of the solutions at the same pH and showed a progressive increase in the impedance measurement the more acidic the environment. By contrast, the STS electrodes showed a reverse effect with differences in impedance measurement between PBS and Citric acid (1.32 ± 0.014 kΩ *versus* 0.76 ± 0.01 kΩ, $P < 0.04$, respectively) and overall lower impedance measurements in more acidic environments. Of note, while the magnesium electrode was able to distinguish acidic from alkaline solutions (1.06 ± 0.02 kΩ citric acid *versus* 0.26 ± 0.005 kΩ, $P < 0.02$), the STS electrode was unable to make this distinction (0.76 ± 0.01 kΩ citric acid *versus* 0.60 ± 0.13 kΩ, $P < 0.17$) These differences are shown graphically in Figure 2.

Impedance change is indicative of a leak in the small animal model

The first *in vivo* model was established in eight mice with impedance measurements made at baseline and from then up to 2 h after the relevant surgical intervention (Leak *versus* sutured GI tissue). Comparisons were made with measurements from electrodes implanted in the wall of the intact bowel (Control group). In the Leak group, Mg electrodes recorded a baseline impedance of 0.7 ± 0.32 kΩ and an impedance of 0.61 ± 0.68 kΩ in intact tissue. After 60 min, the impedance of the Leak group increased to 1.23 ± 0.91 kΩ compared with 0.76 ± 0.32 kΩ recorded from intact tissue. Impedance achieved a steady state by 120 min with a measurement of 1.41 ± 0.40 kΩ in the Leak group *versus* 0.67 ± 0.41 kΩ from intact tissue ($P < 0.025$). There was also a significant percentage increase in impedance measurement noted in the leak model when compared with the sutured control group (99.7% *versus* 9.6%, respectively; $P < 0.02$). These changes are shown graphically in Figure 3.

Spatial impedance characterization of different electrodes following leak induction

After our initial experience with the mouse model, a second *in vivo* porcine model was established. In this case, electrodes were implanted at different distances from the epicenter of the leak (10 mm, 20 mm, and 30 mm away) with comparisons made with the sutured group. The impedance measured from intact tissue was also compared. As with the mouse model, a similar increase in impedance was observed in the porcine model. The absolute impedance of electrodes implanted in the animals was between 1.97 kΩ and 2.34 kΩ. For comparing animals over time, relative impedance was used (impedance measured divided by the baseline impedance). No difference was evident in the baseline measurements between the leak and the control groups (1.06 ± 0.02 *versus* 1.0 ± 0.01, respectively); however, there was a

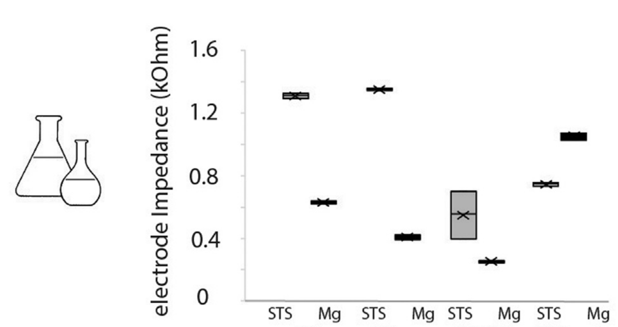

Fig. 2 – *In vitro* impedance measurements with a biodegradable Mg and a nonbiodegradable stainless steel alloy electrode in different media (Phosphate-buffered saline, Normal saline, Sodium bicarbonate solution, and Citric Acid solution). Values are recorded for three separate measurements.

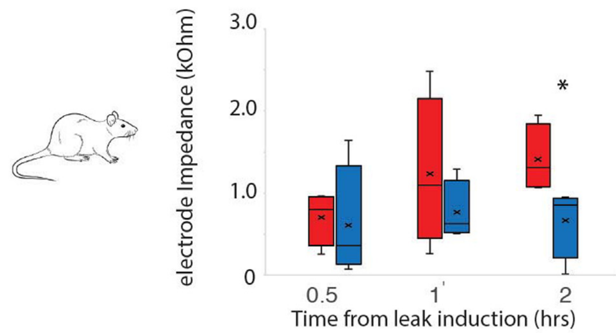

Fig. 3 – Impedance measurements with the Mg electrode in the mouse model (Leak *versus* Intact tissue). *n* = 8, *indicates *P* < 0.025.

significant increase in recorded impedance after 120 min in the Leak group when compared with the controls (1.85 ± 0.46 *versus* 1.06 ± 0.02, respectively; $P < 0.02$; Figure. 4B). For this model, the Leak group showed a 75% increase in impedance measurement, whereas there was only a 6% increase noted in the control group.

Comparisons have been made between the simulated leak model, the sutured colonic laceration, and normal tissues at a range of distances and times after the intervention. These differences are shown in Table 1 and graphically represented in Figure 4. With the Mg electrode, after 2 h the impedance measurement of 10 mm from a colonic leak was significantly higher than that measured 10 mm from a sutured colonic laceration (1.859 + 0.46 *versus* 1.065 + 0.02; $P = 0.027$) and higher than that recorded from intact tissue ($P = 0.009$). Equally, the impedance measured 10 mm from a sutured laceration was significantly higher than that of normal tissue ($P = 0.011$). All comparisons between groups measured >10 mm from the surgical epicenter of intervention were not statistically different. By contrast, the STS electrode recorded a decrease in impedance near a simulated leak with significant differences between the leak and the sutured laceration groups at 10 mm and at 20 mm from the intervention ($P = 0.015$ and 0.025, respectively). There were significant differences in measured impedance between the Leak group and intact tissue over 10, 20, and 30 mm ($P = 0.013$, 0.022, and 0.07, respectively). Equally, significant differences were evident over 10, 20, and 30 mm between the sutured laceration and intact tissue ($P = 0.004$, 0.009, and 0.013, respectively).

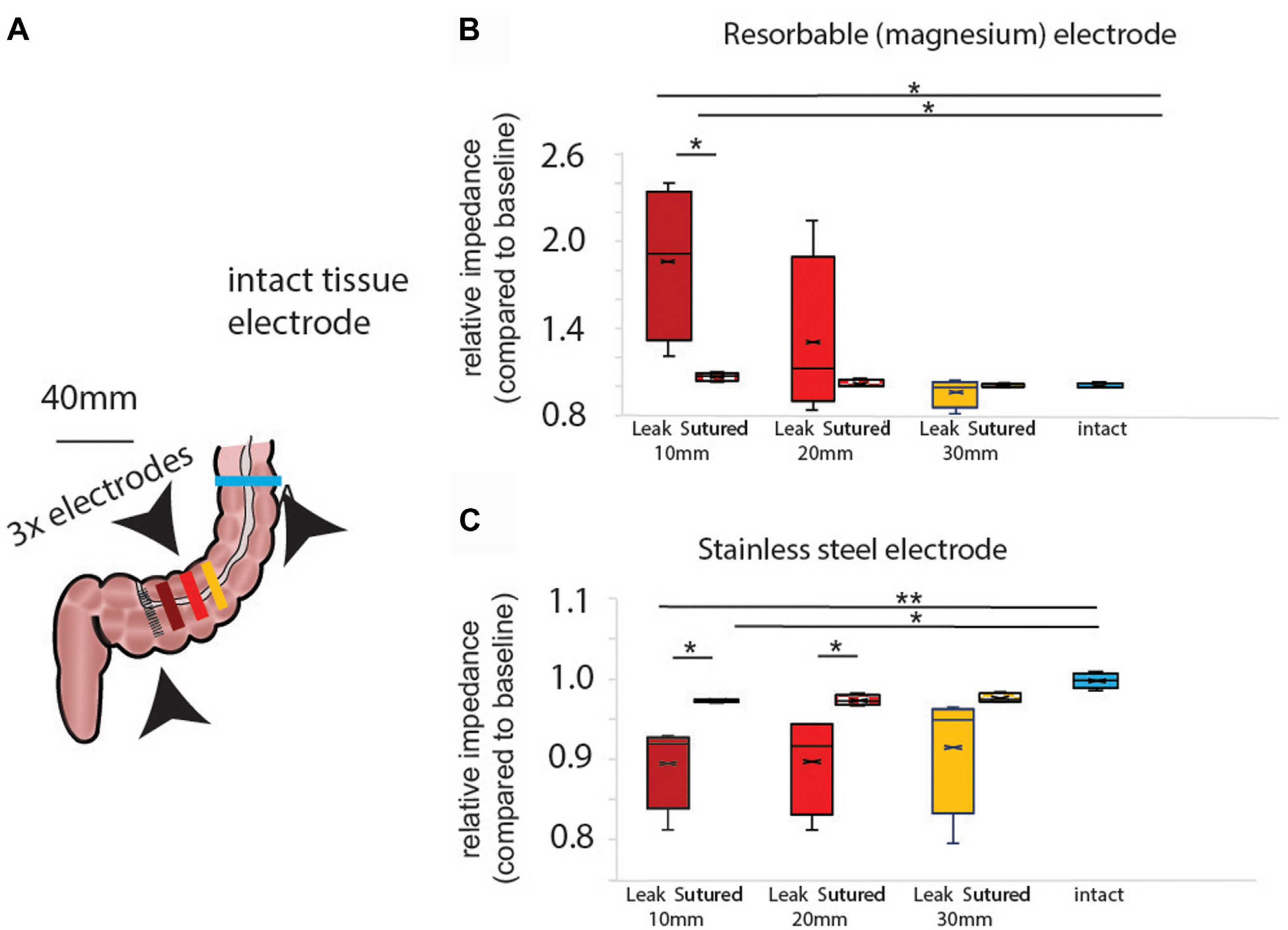

Fig. 4 – Pig leak model. (A) Shows the positioning of electrodes in relation to a colonic laceration, which is either left open or sutured (three electrodes are placed at 10 mm, 20 mm, and 30 mm distance from the epicenter). A distant electrode (>80 mm away from the epicenter) is implanted onto intact tissue. (B) Relative impedance measurements of Mg electrodes 120 min after leak induction. *n* = 8. (C) Relative impedance measurements of stainless steel (STS) electrodes 120 min after leak induction. *n* = 8. *indicates *P* < 0.05, **indicates *P* < 0.01. Refer to Table 1 for summary of all *P* values.

Table 1 – Relative impedance values for Mg and STS electrodes in the three different groups (Colonic leak, sutured colonic laceration, and normal intact tissue) at different distances from the surgical intervention recorded at 120 min.

A. Mg electrode

Distance	Leak model	Sutured laceration ($n = 4$ pigs)	*P* values
10 mm	1.859 (0.46)	1.065 (0.02)	0.027
20 mm	1.304 (0.497)	1.016 (0.02)	0.17
30 mm	0.957 (0.088)	1.003 (0.01)	0.21

B. STS electrode

Distance	Leak model	Sutured laceration ($n = 4$ pigs)	*P* values
10 mm	0.903 (0.06)	1.001 (0.002)	0.015
20 mm	0.906 (0.068)	1.001 (0.01)	0.025
30 mm	0.928 (0.09)	1.005 (0.006)	0.08

The means of three measurements are presented. The standard deviation is in brackets.
The relative impedance of intact tissue with the Mg electrode was 1 (±0.008) and for the STS electrode 1.032 (±0.007).

Discussion

Anastomotic leaks may have devastating consequences increasing mortality and leading to substantial morbidity and functional disturbance that impairs patient quality of life. Early diagnosis, particularly during a subclinical phase, remains a challenge but is necessary in order to reduce morbidity and mortality. Experienced surgical assessment alone tends toward a high sensitivity for AL diagnosis, but with a comparatively low specificity.[19] Techniques involving serial CRP measurements, the measurement of a range of inflammatory biomarkers in blood, and peritoneal drain fluid[20,21] or prospective scoring instruments[22] have all been tried in an attempt at earlier diagnosis. The analysis of drain fluid in particular[20] does not provide a definitive diagnosis and has not generally been used in clinical practice. With minimally invasive surgery routinely used in colorectal resection and with enhanced recovery programs centered around shorter hospital stay, some of these tests lack clinical utility for an AL, which occurs after discharge and hence outside the hospital setting.[9] As far as we are aware, this is the first study to use an implanted biodegradable sensor for the detection of a colonic leak.

It is accepted that the buffering capacity of varied immersion solutions will affect the degree of *in vitro* corrosion and that in physiologic conditions, the pH will influence measurements via the bicarbonate/carbonic anhydrase buffer system. Our preliminary experiments show that biodegradable Mg electrodes are more reliable than nonabsorbable stainless steel (STS) electrodes in detecting impedance changes in an environment mimicking that around an anastomotic leak (AL). The performance of magnesium electrodes in acidic and alkaline environments would suggest their potential utility in the detection of either gastric or colonic leaks. The design of the electrode offered excellent flexibility with easy handling and implantation. Initial *in vitro* experimentation confirmed early absorption of the electrode with consistent discrimination by the Mg electrode for different physiological solutions at the same pH and an increase in impedance in more acidic environments. An inverse relationship between pH and impedance was found with the STS electrodes.

The *in vivo* data in the mouse model consistently showed an increase in impedance, which reached a steady state at 2 h around a simulated GI leak when compared with measurements made near a sutured GI laceration or in normal tissue. In this leak model, changes in impedance displayed a pattern of spatial and temporal variation. Similar changes were confirmed in the porcine model, where the closer the placement of the Mg electrode to the leak site, the greater the increase in recorded impedance. By contrast, the STS electrodes showed impedance reduction near a leak when compared with measurements near a sutured laceration or from intact tissue. These differences remained evident with the STS electrode at some distance from the leak site.

The magnesium electrode was able to reliably detect a leak 10 mm from the epicenter of the GI intervention. As the circumference of the GI tract can be up to 60 mm and the surgeon cannot precisely predict where a leak might develop, it currently remains unclear whether that 10 mm distance is sufficient for clinical purposes. In this regard, both the length and the width of the sensor can be modified, where in the case of bowel with a circumference of 60 mm, using a sensor that is 30 mm long, for example, the maximum distance from the sensor that would be uncovered would only be 15 mm. In addition, as the impedance recorded by the electrode is a proxy measurement for inflammation and edema, there will naturally be an enhanced detection as the inflammatory process spreads. Moreover, the presence of such an electrode will enable the added recording of myoelectric data indicative of the sorts of functional changes in the tissue properties with an AL, which are typically disrupted along the entire circumference of the GI tract.[23] Future studies will examine these potential advantages of electrode warning systems in a larger animal series.

The principle behind the measurement of impedance for the diagnosis of AL relies upon the observation that there are noted differences between healthy and inflamed tissues.[12,13] In particular, there is an expected increase in the electrical conductivity of inflammatory tissue resultant from the exudation of conductive fluids around a cellular infiltrate. Bioimpedance measurement has been widely used to monitor tissue remodeling[24] and is an inexpensive, minimally invasive option capable of characterizing the different electrical properties of a range of tissues through varying physiological and pathological states.[25,26] This approach has specifically been used to detect the presence of inflammation in the breast,[27] in bronchial asthma and inflammation[28,29] and around dental implants.[30] Our results suggest the effect recorded by the electrode is indeed tissue remodeling: the porcine model showed impedance change in-line with acidic environment although the content of the colon is likely alkaline, as stress factors such as interleukins and lactic acids are secreted from the affected tissue. Our findings are similar to those reported by DeArmond *et al*.[15,16] using an electrolyte-gated resistance detection method in rats where steel electrodes were placed adjacent to an artificially created punch gastrotomy wound. The method of DeArmond, however, requires the tissue to be perforated, followed by continuous irrigation of the GI tract with an electrolyte solution, whereas our design is simpler to establish and more readily represents real-life conditions, and it is capable of providing early detection of severe inflammation, critical for clinical efficacy. In the DeArmond model, hypertonic saline was instilled via a small cervical esophagotomy, resulting in a consistent reduction in measured resistance around the point of a leak when compared with measurements recorded by electrodes placed near a sutured gastrotomy. In their study, although there was a high sensitivity for the detection of very small leak volumes, there was considerable baseline variability, most likely a consequence of poor insulation either from omental adherence or electrode entanglement. Further, their approach was not particularly user-friendly, necessitating a reopening of the celiotomy after each set of resistance measurements had been taken in order to evacuate the peritoneum of its electrolyte solution.

There are several limitations to our study. For technical reasons, only female specimens were used in the animal study. Further human studies will enroll subjects from both sexes. Furthermore, although our data showed impedance differences between normal tissue, a sutured laceration, and a point of intestinal leakage, it is appreciated that a small colotomy is not equivalent to the pathophysiology of an AL and that the system will need to determine the bioimpedance of a normal inflammatory process around a healing anastomosis in order to establish diagnostic sensitivity. This challenge might be addressed in a clinical study where bioimpedance sensors monitor the healing of anastomoses over time. Input and output impedances are also a source of measurement error and may vary with each system.[31] The physical factors affecting variable electrical conductivity in complex tissues, the degree of inflammation and the optimal electrode positioning, as well as the application and compatibility with robotic and laparoscopic procedures, will all need to be further investigated so as to ascertain working sensitivity thresholds for a leak diagnosis.[32]

Conclusions

Our preliminary animal experiments show that impedance is an early, reliable marker for anastomotic leaks. A biodegradable Mg electrode may be sensitive in recording impedance near a simulated colonic leak with the capacity to degrade after the monitoring period is complete. The placement of perianastomotic electrical impedance sensors may provide a continuous and sensitive mechanism for monitoring the local tissue environment and could be developed as an early warning detector for patients at higher risk of an anastomotic leak. The utilization of bioresorbable electrodes would appear to be a compelling method to detect an AL early, potentially circumventing serious complications and minimizing the impact a leak might have on patient outcomes. Given the wide availability of biodegradable, biocompatible magnesium alloys along with their low cost (when compared with the high cost of patient imaging and ancillary management after a confirmed AL), it is anticipated that these electrodes could be integrated into GI surgical management as an early warning system.

Author Contributions

MBD, ES, and NW designed the study framework. TY, ES, and MBD designed the experiments. IC, RO, BN-L, TY, and ES carried out the experiments. TY and ES designed the experimental system. MBD, TY, ES, and NW wrote the manuscript.

Acknowledgments

We thank Dr. Andrew Zbar for the fruitful discussion and the editing of the manuscript. We thank Gilad Lavi, Shai Policker, Gal Atarot, and Adir Koreh for the technical assistance.

Disclosure

TY and ES are employees of Exero Medical LTD. MBD is a director of Exero Medical. NW is a consultant for Exero Medical. The rest of the authors have no disclosures to make.

Funding

Exero Medical LTD and Clalit HMO funded the research.

REFERENCES

1. Hammond J, Lim S, Wan Y, Gao X, Patkar A. The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes. *J Gastrointest Surg*. 2014;18:1176–1185.
2. Ashraf SQ, Burns EM, Jani A, et al. The economic impact of anastomotic leakage after anterior resections in English NHS hospitals: are we adequately remunerating them? *Colorectal Dis*. 2013;15:e190–e198.
3. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg*. 2015;102:462–479.
4. Turrentine FE, Denlinger CE, Simpson VB, et al. Morbidity, mortality, cost, and survival estimates of gastrointestinal anastomotic leaks. *J Am Coll Surg*. 2015;220:195–206.
5. Foppa C, Ng SC, Montorsi M, Spinelli A. Anastomotic leak in colorectal cancer patients: new insights and perspectives. *Eur J Surg Oncol*. 2020;46:943–954.
6. Ferko A, Rejholoc J, Skrovina M, Tacheci I, Sirak I. Colorectal anastomosis dehiscence: a call for more detailed morphological classification. *Wideochir Inne Tech Maloinwazyjne*. 2021;16:98–109. https://doi.org/10.5114/wiitm.2020.97367.
7. Rink AD, Kienle P, Aigner F, Ulrich A. How to reduce anastomotic leakage in colorectal surgery-report from German expert meeting. *Langenbecks Arch Surg*. 2020;405:223–232.

8. Hyman NH. Managing anastomotic leaks from intestinal anastomoses. *Surgeon*. 2009;7:31–35.
9. Marres CCM, van de Ven AWH, Leijssen LGJ, Verbeek PCM, Bemelman WA, Buskens CJ. Colorectal anastomotic leak: delay in reintervention after false-negative computed tomography scan is a reason for concern. *Tech Coloproctol*. 2017;21:709–714.
10. Kornmann V, van Ramshorst B, van Dieren S, van Geloven N, Boermeester M, Boerma D. Early complication detection after colorectal surgery (CONDOR): study protocol for a prospective clinical diagnostic study. *Int J Colorectal Dis*. 2016;31:459–464.
11. Pantoja Pachajoa DA, Gielis M, Palacios Huatuco RM, et al. Neutrophil-to-lymphocyte ratio vs C-reactive protein as early predictors of anastomotic leakage after colorectal surgery: a retrospective cohort study. *Ann Med Surg (Lond)*. 2021;64:102201.
12. Gaines S, Shao C, Hyman N, Alverdy JC. Gut microbiome influences on anastomotic leak and recurrence rates following colorectal cancer surgery. *Br J Surg*. 2018;105:e131–e141.
13. Cosoli G, Scalise L, Tricario G, Russo P, Cerri G. Bioimpedance measurements in dentistry to detect inflammation: numerical modelling and experimental results. *Physiol Meas*. 2017;38:1145–1157.
14. Cosoli G, Scalise L, Cerri G, Russo P, Tricario G, Tomasini EP. Bioimpedancemetry for the assessment of periodontal tissue inflammation: a numerical feasibility study. *Comput Method Biomech Biomed Engin*. 2017;20:682–690.
15. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLos Biol*. 2010;8:e1000412.
16. DeArmond DT, Cline AM, Johnson SB. Anastomotic leak detection by electrolyte electrical resistance. *J Invest Surg*. 2010;23:197–203.
17. DeArmond DT, Carswell A, Louden CL, et al. Diagnosis of anastomotic leak: electrolyte detection versus barium fluoroscopy. *J Surg Res*. 2013;182:192–197.
18. Witecka A, Bogucka A, Yamamoto A, et al. In vitro degradation of ZM21 magnesium alloy in simulated body fluids. *Mater Sci Eng C Mater Biol Appl*. 2016;65:59–69.
19. Maier P, Clausius B, Wicke J, Hort N. Characterization of an extruded Mg-Dy-Nd alloy during stress corrosion with C ring tests. *Metals*. 2020;10:584.
20. Damrauer SM, Bordeianou L, Berger D. Contained anastomotic leaks after colorectal surgery: are we too slow to act? *Arch Surg*. 2009;144:333–338.
21. Singh PP, Zeng IS, Srinivasa S, Lemanu DP, Connolly AB, Hill AG. Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. *Br J Surg*. 2014;101:339–346.
22. Su'a BU, Mikaere HL, Rahiri JL, Bissett I, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. *Br J Surg*. 2017;104:503–512.
23. Yanagida H, Yanase H, Sanders KM, Ward SM. Intestinal surgical resection disrupts electrical rhythmicity, neural responses, and interstitial cell networks. *Gastroenterology*. 2004;127:1748–1759.
24. den Dulk M, Witvliet MJ, Kortram K, et al. The DULK (Dutch leakage) and modified DULK score compared: actively seek the leak. *Colorectal Dis*. 2013;15:e528–e533.
25. Khalil SF, Mohktar MS, Ibrahim F. The theory and fundamentals of bioimpedance analysis in clinical status monitoring and diagnosis of disease. *Sensors (Basel)*. 2014;14:10895–10928.
26. Gabriel S, Lau RW, Gabriel C. The dielectric properties of biological tissues: III. Parametric models for the dielectric spectrum of tissues. *Phys Med Biol*. 1996;41:2271–2293.
27. Martinsen O, Grimnes S. *Bioimpedance and Bioelectricity Basics*. 2nd ed. Amsterdam: Elsevier; 2008.
28. Tornuev YV, Koldysheva EV, Lapiy GA, et al. Bioimpedancemetry in the diagnostics of inflammatory process in the mammary gland. *Bull Exp Biol Med*. 2014;156:381–383.
29. Peroni DG, Bodini A, Loiacono A, Paida G, Tenero L, Piacentini GL. Bioimpedance monitoring of airway in inflammation in asthmatic allergic children. *Allergol Immunopathol*. 2009;37:3–6.
30. Villa Jr A. The monitoring of bronchial inflammation by bioimpedance. *Allergol Immunopathol (Madr)*. 2009;37:1–2.
31. Cosoli G, Scalise L, Tomasini EP, Russo P, Cerri G, Tricarico G. Measure of bioimpedance to detect tissue inflammation. Development of an electromedical device for the treatment of peri-implantitis based on the application of radiofrequency alternating current. 16th Int Conf Electr Bio-Impedance (Icebi). Stockholm 2016. Abs. 116, p 18.
32. Swanson DK, Webster JG. Errors in four-electrode impedance plethysmography. *Med Biol Eng Comput*. 1983;21:674–680.