Non-invasive Biomagnetic Detection of Intestinal Slow Wave Dysrhythmias in Chronic Mesenteric Ischemia

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ABSTRACT

Chronic mesenteric ischemia (CMI) is a challenging clinical problem which is difficult to diagnose noninvasively. Diagnosis early in the disease process would enable life-saving early surgical intervention. Previous studies established that Superconducting QUantum Interference Device (SQUID) magnetometers detect the slow wave changes in the magnetoenterogram (MENG) noninvasively following induction of mesenteric ischemia in animal models. The purpose of this study was to assess functional physiological changes in the intestinal slow wave MENG of patients with chronic mesenteric ischemia. Pre- and postoperative studies were conducted on CMI patients using MENG and intra-operative recordings using invasive serosal electromyograms (EMG). Our preoperative MENG recordings showed that patients with CMI exhibited a significant decrease in intestinal slow wave frequency from $8.9 \pm 0.3$ cpm preprandial to $7.4 \pm 0.1$ cpm postprandial ($p < 0.01$) that was not observed in postoperative recordings ($9.3 \pm 0.2$ cpm preprandial and $9.4 \pm 0.4$ cpm postprandial, $p=0.86$). Intraoperative recording detected multiple frequencies from the ischemic portion of jejunum before revascularization, whereas normal serosal intestinal slow wave frequencies were observed after revascularization. The preoperative MENG data also showed signals with multiple frequencies suggestive of uncoupling and intestinal ischemia similar to intra-operative serosal EMG. Our results showed that multichannel MENG can identify intestinal slow wave dysrhythmias in CMI patients.
INTRODUCTION

Chronic mesenteric ischemia (CMI) is underdiagnosed with increasing prevalence, generally caused by fixed stenoses or occlusion of visceral arteries (17, 33). Vascular compromise results in ischemic segments of bowel which can progress to complete necrosis with sepsis and death without early intervention. Current clinical diagnostic techniques like computerized tomography angiography (CTA), color duplex ultrasound, gadolinium-enhanced magnetic resonance angiography (MRA) (14, 20, 23, 33, 34) and gastrointestinal tonometry (1, 22) can be used to identify stenosis and/or occlusion of the mesenteric vasculature but none of these techniques identifies the functional degree of ischemia caused by the anatomic lesions. Misdiagnosis of CMI may result in overemployment of therapy, particularly stenting. A functional test could identify CMI and the patients that actually need treatment. Functional changes in the intestinal slow wave electrical activity may be more sensitive indicators of these conditions.

The small intestine exhibits a natural, stepwise gradient in slow wave frequency from about 12 cpm in the human duodenum to between 9 and 11 cpm in the jejunum and around 8 cpm in the terminal ileum (10, 31). The difficulty of obtaining direct access to the gastrointestinal (GI) tract has limited the potential use of invasive electromyogram (EMG) for recording the slow wave activity. Therefore, a noninvasive system for detecting GI slow wave activity is highly desirable in a clinical setting (8, 12). Previous studies by several researchers have reported measuring GI slow wave activity using cutaneous electrodes (19, 26). However, the success of their method relies on the body-mass-index (BMI) of the subject as alternating low- and high-conductivity abdominal fat and muscle layers significantly attenuate and distort cutaneous measurements of electrical potentials generated by GI slow wave activity (7, 11). With
obesity prevalence increasing, this consideration will further weaken the efficacy of cutaneous electrodes to evaluate the GI slow wave (24).

The magnetoenterogram (MENG) records the magnetic fields associated with intestinal slow wave activity which are not as affected by low conductivity fat layers as cutaneous potentials (7). Our group was the first to record the MENG from the intestinal slow wave in animals and in human subjects (28, 32). Functional physiological changes in the intestinal slow wave in response to ischemia were also investigated in animal models using noninvasive MENG (12, 13, 27). Our most recent studies in porcine models demonstrated that the ischemic changes in the intestinal slow wave can be detected early and noninvasively even with incomplete vascular occlusion (21). To date, however, no studies have examined the effect of ischemia in human patients on intestinal slow wave activity using non-invasive biomagnetic technique. We hypothesized that preoperative SQUID measurements of the intestinal magnetic field activity could distinguish postprandial bowel slow wave activity in CMI patients. Furthermore, we expect that the revascularization will normalize any aberrant slow waves.

II. PROCEDURE

A. Materials and Methods

Patients diagnosed with CMI using standard diagnostic tests including computerized tomography angiography (CTA) were recruited prior to surgical revascularization at Vanderbilt University Medical Center. All the experimental procedures were approved by the Vanderbilt University Institutional Review Board and registered with clinicaltrials.gov (NCT00179036). All patients gave informed consent to participate in the study. Pre-operative recording before mesenteric revascularization was performed in eight patients, intra-operative recording in four
and postoperative recording in four patients. Two patients underwent all pre-, intra- and post-
operative studies. The interval between revascularization and postoperative study varied from a
minimum of two weeks to a maximum of seventeen weeks depending on individual patient
recovery.

For pre- and post-operative recordings, we measured MENG using the Tristan Model 637
SQUID magnetometer. The magnetometer consists of a collection of SQUID gradiometers that
record data at 19 sensor locations using an array of detection coils located in a plane at the
bottom of a liquid-helium filled dewar. The detection coils are inductively coupled to SQUID
sensors that convert magnetic flux threading the detection coils to voltage signals. The voltage
data were then amplified (Model 5000, Quantum Design), digitized, and stored on a PC. The
SQUID was positioned over the abdomen of the subject with center of the SQUID dewar located
5 cm cephalad to the umbilicus in order to record primarily the small intestinal signals. After an
8-12 hour overnight fast, a baseline recording was obtained for a period of 30 minutes. The
volunteers then ate a standardized 300 kcal turkey sandwich meal with 240 ml of juice or soft
drink followed by recording of the postprandial signal for a period of one hour. The patients
periodically suspended respiration to allow the comparison of noise reduction techniques (4).

To provide independent validation of the biomagnetic slow wave recording, we also recorded
the slow wave intraoperatively using serosal electrodes during the revascularization procedure in
four of the patients. A custom built, rigid, epoxy based electrode platform containing sixteen
electrodes with inter-electrode distances of 7mm in the longitudinal and 5mm in the transverse
direction were used for serosal recording. After exposing the intestine, the platform was placed
atraumatically onto the serosal surface of the intestine for two minutes of recording on the
We attempted to record from at least two healthy intestinal segments and one suspected pathological segment, subject to restrictions in the surgical procedure.

B. Data Acquisition

Electrode signals were acquired at 256 Hz with the electrode amplifier and SQUID data were collected with a sampling rate of 3 kHz. Both sets of data were resampled to 30 Hz. For all studies, two SQUID sensors were not in service and data was only obtained in the remaining 17 sensors.

C. Data Analysis

MENG signals recorded pre- and post-operatively, and serosal signals recorded intra-operatively were subjected to spectral analysis. Analysis was performed in MATLAB (Mathworks, Natick, MA, USA). Data were filtered using continuous wavelet transform (CWT) digital filter with a bandpass of 6–120 cpm. Power spectra were computed using the Fast Fourier Transform. For MENG signals, in addition to filtering, second order blind identification (SOBI) signal processing algorithm was used to identify the dominant signal components. SOBI is a blind-source separation (BSS) technique which exploits the second-order statistics of the measurements to compute an estimate of the mixing matrix connecting sources with sensors [full details can be found in (2, 11)]. After applying SOBI, primary sinusoidal signals in the enteric frequency range and artifact-related components were identified. For human small intestine, we selected SOBI components defined as primarily sinusoidal in the enteric frequency range from brady- to tachyenteric (typically 6-60 cpm). These criteria were formulated on the basis of the inherently sinusoidal, or at least periodic, nature of the slow wave, with a period that is typically
stable over several minutes (11). Enteric SOBI signals were reconstructed onto the sensor array, allowing us to localize enteric sources. Using the reconstructed SOBI-MENG components, we chose to select the primarily, central channel of the SQUID array for computation of the dominant enteric slow wave frequency. The central SQUID channel was chosen due to its centrality in reference to the subject’s anatomy. The mean frequencies were calculated during baseline and postprandial periods for each subject. We also computed the percentage of power distributed (PPD) in the intestinal frequency range classified as normal (slow wave in 8-13 cpm range), bradyarrhythmic (< 8 cpm), and tachyarrhythmic (between 13 and 60 cpm) (5). Respiration frequency ranges were excluded from PPD calculation. The results are expressed as mean ± standard error of the mean. Student’s t-test was used to compare pre and postprandial data with p-values < 0.05 considered to be statistically significant.

RESULTS

Figure 1 illustrates how the SOBI-MENG components reconstructed to the sensor array enable the identification of enteric slow wave components. Figure 1a and 1b show CWT filtered MENG spatial maps during baseline in a CMI patient after mesenteric revascularization along with its power spectra. Although the enteric slow wave is apparent in the frequency spectra, other confounding noise sources complicate its identification and isolation. SOBI components computed from the filtered MENG and its power spectra shown in Figure 1c and 1d isolate specific signal components at different frequencies. We selected primarily sinusoidal SOBI components in the enteric frequency range and reconstructed the SOBI-MENG using only these signal components (indicated by asterisks in Figure 1d). The reconstructed SOBI-MENG spatial maps and power spectra (Figure 1e and 1f) show enteric slow wave sources with a higher signal-to-noise ratio than raw or filtered data.
Figure 2 shows representative MENG data illustrating the effect of ischemia on enteric slow wave activity in a CMI patient pre- and post-prandial, both before and after revascularization. Before revascularization, postprandial recordings showed both brady- and tachyarrhythmia, with the dominant frequency clearly decreased compared with preprandial data. Similar changes were not observed after revascularization.

The average intestinal slow wave dominant frequency of CMI patients determined by SOBI-MENG dropped significantly from the preprandial period (8.9 ± 0.3 cpm) to the postprandial (7.4 ± 0.1; \( p < 0.01 \)) before revascularization. After revascularization, the intestinal slow wave frequency determined from SOBI-MENG was 9.3 ± 0.2 cpm preprandial and 9.4 ± 0.4 cpm postprandial, as illustrated in Figure 3. No significant difference in pre- and postprandial frequencies was observed after revascularization (\( p=0.86 \)).

In addition to computing the dominant signal frequency, the percent power distribution (PPD) in frequency ranges associated with normal slow waves, bradyenteria and tachyenteria in CMI patients before and after revascularization were determined (see Figure 4). Before revascularization, bradyenteric PPD increased significantly during the postprandial period (\( p < 0.01 \)), and power in regions associated with normal slow wave frequency decreased (\( p < 0.01 \)). No significant change in power was observed before revascularization in tachyenteric frequencies (\( p = 0.8 \)) during the postprandial period. After revascularization, there was no significant postprandial change in PPD for brady-, normal, or tachyenteric frequency ranges.

Intraoperative serosal recordings were obtained in four CMI patients before and after surgical intervention by placing electrodes on to the proximal duodenum, proximal jejunum and ileum. Due to poor contact between the electrode and intestinal serosa, motion artifacts, and
limited intraoperative recording time, we were able to detect the intestinal slow wave signal in only one patient. Figure 5b and 5d show the intraoperative serosal EMG recordings and its corresponding power spectra from the ischemic jejunum in a CMI patient before and after completion of the revascularization procedure. Intraoperative recording detected multiple frequencies from the ischemic portion of jejunum before revascularization (dominant frequency 9.2 cpm), whereas single dominant slow wave frequencies of 10.1 cpm was observed after revascularization. The preprandial SQUID recording of the same CMI patient before and after revascularization is also shown for comparison (see figure 5a & 5c). SQUID recordings could not be performed during the operative procedure because of logistical considerations.

**DISCUSSION AND CONCLUSION**

Previous studies have demonstrated that SQUID magnetometers detect slow wave changes in the MENG with induced mesenteric ischemia in animal models (18, 29, 31). Golzarian et al. first reported the feasibility of early detection of intestinal smooth muscle abnormalities resulting from arterial ischemia using non-invasive MENG (12). These studies showed a decrease in enteric slow-wave frequency associated with intestinal ischemia in the exteriorized small intestine of anesthetized rabbits. Subsequently, Richards et al. demonstrated the clinical utility of biomagnetic diagnosis of acute total artery occlusion by detecting a significant drop in the enteric slow wave frequency in rabbit models, noninvasively through the intact abdominal wall (27). A recent study by Martin et al. detected partial mesenteric ischemia that occurs with progressive occlusion of SMA in swine models using MENG (21). Although intensive research effort has been focused on non-invasive detection of induced mesenteric ischemia, a detailed study on identification of CMI in humans has not been previously reported.
In the present study, we employed MENG to study the functional physiological changes in the intestinal slow wave in response to CMI in human patients.

The ability of MENG to spatially identify slow wave activity in different parts of the small intestine is instrumental in distinguishing ischemic bowel from surrounding normal bowel. Previous studies by Erickson et al. reported that Second Order Blind Identification (SOBI), a blind source separation technique, is capable of detecting enteric slow wave activity from noisy, artifact-contaminated SQUID measurements. Several blind source separation (BSS) algorithms to identify intestinal slow waves from SQUID recordings have been tested, including fast ICA and JADE, but to date, SOBI has proved superior to these methods for identification of pathologic intestinal magnetic fields (11, 16). Our most recent results show that analyzing signals using SOBI allows the distinction of normal and pathological states (3, 6). In the present study, SOBI applied to multichannel MENG reliably eliminated confounding noise factors and allowed the noninvasive identification of postprandial slow wave changes caused by ischemic bowel in CMI patients.

SOBI-MENG analysis showed that patients with CMI exhibited a significant postprandial decrease in intestinal slow wave frequency that was not observed in postoperative recordings. These slow wave changes likely result from mesenteric insufficiency: the intestinal blood flow is not sufficient to meet the high postprandial intestinal oxygen requirements in CMI patients (9, 15). We also observed a significant increase in the postprandial bradyenteric PPD as compared to fasting in CMI patients, indicative of postprandial functional changes in the ischemic bowel. A similar PPD effect was observed in both serosal and MENG recordings during segmental ischemia in porcine subjects (31). A previous study by Seidel et al. reported the detection of
intestinal tachyarrhythmias during small bowel ischemia in rabbit models using serosal EMG recordings (30). In our study, we analyzed higher frequencies between 13 and 60 cpm to identify tachyarrhythmias in CMI patients but did not observe any significant postprandial changes. The tachyarrhythmias observed in (30) were low amplitude and it is possible that anatomical differences between rabbit and human subjects obscure tachyarrhythmic signatures in human MENG data.

No postprandial change in brady-, normo- or tachyenteric PPD was observed in postoperative MENG recordings, which supports the hypothesis that the operative procedure normalizes the irregular slow wave activity. Intraoperative serosal EMG recordings are challenging to acquire due to difficulties in gaining adequate access and reliable contact to the intestinal serosa, limited intraoperative recording time and the electrically noisy conditions present in the operating room. In the intraoperative study in which we were able to obtain reliable recordings, normalization of slow wave activity was observed after revascularization. These findings await validation in a large patient population. Improved methodology for intraoperative recording should substantially enhance the ability to obtain reliable serosal EMG recording quickly in the time-sensitive operative environment (25).

Because of variation in patient recovery times, there was a wide difference in the time between the operative procedure and the postoperative MENG study (range: 2-17 weeks). Ideally, this time would be standardized between subjects and correlated with symptom relief. Nonetheless, postoperative MENG indicated normalization of enteric slow wave activity in revascularized patients.
Our results showed that noninvasive multichannel MENG identified intestinal slow wave
dysrhythmias in patients with CMI and also tracked the normalization of dysrhythmic activity
after revascularization in patients with CMI. These results encourage further investigation of the
biomagnetic assessment of functional bowel electrical activity in a larger patient cohort to detect
pathologic signals of intestinal ischemia before irreversible changes occur. In the present study,
frequency and PPD parameters were used as key indicators of electrical abnormality in CMI
patients. In addition to frequency dynamics, relating the spatio-temporal activation patterns of
slow waves to MENG represent the next vital step in improving the diagnostic accuracy of non-
invasive biomagnetic techniques in clinical setting. Recent upgrades in both our magnetometer
system and signal processing algorithms will allow us to study the MENG signals with higher
signal fidelity and spatial resolution than ever before. Moreover, comparing high-resolution
serosal electrical mapping with multi-channel biomagnetic mapping in CMI patients will enable
a more robust understanding of how tissue-level slow wave changes translate to extracellular
bioelectric and transabdominal biomagnetic signatures.

Ultimately, we aim to develop a non-invasive diagnostic modality to determine the
presence of intestinal ischemia early in the course of the disease process prior to irreversible
tissue loss in order to improve the dismal results of surgical intervention currently available.
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DISCLOSURE

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Somarajan S: analyzed the data and drafted the manuscript
Muszynski ND: analyzed the data and edited the manuscript
Cheng LK: designed the experiments and edited the manuscript
Bradshaw LA: designed the experiments, performed the experiments and edited the manuscript
Naslund TC: designed the experiments and performed the experiments
Richards WO: designed the experiments, performed the experiments and edited the manuscript
REFERENCES


**FIGURE CAPTIONS**

Figure 1: (a) and (b) Spatial distribution of the filtered MENG signals during baseline period and its corresponding power spectra. (c) and (d) SOBI- MENG components and its corresponding power spectra. (e) and (f) Reconstructed SOBI- MENG components and its power spectra showing how the SOBI- MENG components are distributed around the sensor array. The SOBI components used in the reconstruction are marked with *.

Figure 2: (a-b) Reconstructed SOBI- MENG components and (c-d) corresponding power spectra during pre- and postprandial period in a CMI patient before and after revascularization. Patient suffering from ischemia showed a decrease in the postprandial slow wave frequency. Similar changes were not observed after revascularization.

Figure 3: Intestinal slow wave frequency (mean ±SE) determined by SOBI- MENG components in CMI patients pre- and post- revascularization. Dominent frequencies of SOBI- MENG components show a statistically significant postprandial decrease before revascularization.
denoted by *). No statistically significant change between pre-and postprandial frequency was observed after revascularization.

Figure 4: Percent power distributed (PPD) in brady-, normo- and tachyenteric frequency ranges for MENG recordings in CMI patients pre- and post-prandial period, both before and after revascularization. Statistically significant postprandial PPD changes were denoted by *.

Figure 5: Baseline recording using SQUID and serosal electrodes in a CMI patient and its corresponding power spectra: Typical tracings recorded using (a) SQUID (reconstructed SOBI-MENG components corresponding to the jejunal segment, four days before revascularization/seventeen weeks after revascularization), and (b) serosal recording (EMG) from the ischemic jejunum just before/after surgical intervention. (c-d) power spectra corresponding to reconstructed SOBI- MENG and EMG components.
Figure 2
Figure 5

a) MENG recording (pre/post surgery)

b) Intra-op recording (pre/post surgery)

c) MENG recording (pre/post surgery)

d) Intra-op recording (pre/post surgery)