Noninvasive biomagnetic detection of intestinal slow wave dysrhythmias in chronic mesenteric ischemia

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Submitted 30 December 2014; accepted in final form 16 April 2015

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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 noninvasive biomagnetic technique. We hypothe-
esized 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.

**PROCEDURES**

**Materials and methods.** Patients diagnosed with CMI using standard diagnostic tests including computed 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 provided written informed consent to participate in the study. Preoperative recording before mesenteric revascularization was performed in eight patients, intraoperative recording in four, and postoperative recording in four patients. Two patients underwent all pre-, intra-, and postoperative studies. The interval between revascularization and postoperative study varied from a minimum of 2 wk to a maximum of 17 wk depending on individual patient recovery.

For pre- and postoperative 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 to record primarily the small intestinal signals. After an 8- to 12-h overnight fast, a baseline recording was obtained for a period of 30 min. 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 1 h. 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 interelectrode distances of 7 mm in the longitudinal and 5 mm in the transverse direction were used for serosal recording. After exposing the intestine, the platform was placed atriumally onto the serosal surface of the intestine for 2 min of recording on the proximal duodenum, proximal jejunum, and ileum. We attempted to record from at least two healthy intestinal segments and one suspected pathological segment, subject to restrictions in the surgical procedure.

**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.

**Data analysis.** MENG signals recorded pre- and postoperatively, and serosal signals recorded intraoperatively, were subjected to spectral analysis. Analysis was performed in MATLAB (Mathworks, Natick, MA). 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 that 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 Refs. 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), bradyrhythmic (<8 cpm), and tachyarrhythmic (between 13 and 60 cpm) (5). Respiration frequency ranges were excluded from PPD calculation. The results are expressed as means ± standard error of the mean (SE). 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 1, A and B, shows 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 Fig. 1, C and D, 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 Fig. 1D). The reconstructed SOBI-MENG spatial maps and power spectra (Fig. 1, E and F) 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 postprandial, 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 Fig. 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 Fig. 4). Before revascularization, bradyenteric PPD increased significantly during the postprandial period (P < 0.01), and power in regions associated with normal slow wave activity decreased compared with preprandial data. After revascularization, the percent power distribution decreased significantly from the preprandial period (81 ± 7%) to the postprandial (47 ± 10%; P < 0.01) before revascularization. After revascularization, the percent power distribution of bradyenteric power remained stable during the postprandial period (53 ± 4% and 43 ± 1%, respectively; P > 0.05), and tachyenteric power increased significantly from the preprandial period (10 ± 1%) to the postprandial period (21 ± 3%, P < 0.01). No significant changes in the percent power distribution of tachyenteric power were observed after revascularization (P = 0.84).
Fig. 1. A and B: spatial distribution of the filtered magnetoenterogram (MENG) signals during baseline period and its corresponding power spectra. C and D: second-order blind identification (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 *.
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 5, \(B\) and \(D\), shows 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 were observed after revascularization. The preprandial SQUID recording of the same CMI patient before and after revascularization is also shown for comparison (see Fig. 5, \(A\) and \(C\)). SQUID recordings could not be performed during the operative procedure because of logistical considerations.

**DISCUSSION**

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. (12) first reported the feasibility of early detection of intestinal smooth muscle abnormalities resulting from arterial ischemia using noninvasive MENG. 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. (27) demonstrated the clinical utility of biomagnetic diagnosis of acute total artery occlusion by detecting a significant drop in the enteric slow wave.

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**Fig. 2.** Reconstructed SOBI-MENG components \((A\ and \(B\)) and corresponding power spectra \((C\ and \(D\)) during pre- and postprandial period in a chronic mesenteric ischemia (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.

**Fig. 3.** Intestinal slow wave frequency (mean \(\pm\) SE) determined by SOBI-MENG components in CMI patients pre- and postrevascularization. *Dominant frequencies of SOBI-MENG components show a statistically significant postprandial decrease before revascularization. No statistically significant change between pre- and postprandial frequency was observed after revascularization.

**Fig. 4.** Percent power distributed (PPD) in brady-, normo-, and tachyenteric frequency ranges for MENG recordings in CMI patients pre- and postprandial period, both before and after revascularization. *Statistically significant postprandial PPD changes.
wave frequency in rabbit models, noninvasively through the intact abdominal wall. A recent study by Martin et al. (21) detected partial mesenteric ischemia that occurs with progressive occlusion of SMA in swine models using MENG. Although intensive research effort has been focused on noninvasive 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. (11) reported that 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 pathological 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 compared with 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. (30) reported the detection of intestinal tachyarrhythmias during small bowel ischemia in rabbit models using serosal EMG recordings. 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 Ref. 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 wk). 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 pathological 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 spatiotemporal activation patterns of slow waves to MENG represents the next vital step in improving the diagnostic accuracy of noninvasive biomagnetic techniques in the 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 multichannel 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 noninvasive diagnostic modality to determine the presence of intestinal ischemia early in the course of the disease process prior to irreversible tissue loss to improve the dismal results of surgical intervention currently available.

ACKNOWLEDGMENTS
We thank the staff of SR Light Lab Surgical Research Center, the Vascular Surgery Service, and operating room personnel at Vanderbilt University Medical Center. We gratefully acknowledge the work of Dr. J. Erickson who developed the SOBI algorithm for the analysis of gastrointestinal slow wave activity.

GRANTS
This work is supported in part by National Institute of Diabetes and Digestive and Kidney Diseases Grants R01-DK-58697, R01-DK-64775, and R01-DK-58197.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: S.S. and N.D.M. analyzed data; S.S., N.D.M., and L.K.C. interpreted results of experiments; S.S. drafted manuscript; N.D.M., L.K.C., L.A.B., and W.O.R. revised manuscript; L.K.C., L.A.B., and W.O.R. conceived and designed research; L.K.C., L.A.B., T.C.N., and W.O.R. performed experiments; L.A.B. and W.O.R. written the manuscript; L.A.B., T.C.N., and W.O.R. obtained funding; T.C.N. contributed analytic or technical help; A.S., A.H., and F.K. performed statistical analysis; S.S. and N.D.M. interpreted the data analysis; L.A.B. and W.O.R. obtained the clinical data; L.K.C., A.He, P.D., and M.M. contributed substantial materials or patients; and S.S., L.A.B., T.C.N., and W.O.R. provided administrative, technical, or logistic support. All authors have approved the final version of the manuscript.

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