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Superconducting Quantum Interference Device Magnetometer for Diagnosis of Ischemia Caused by Mesenteric Venous Thrombosis

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Abstract. Although mesenteric venous thrombosis carries a better prognosis than arterial thrombosis, mortality and morbidity are still high. Previous studies have shown that the basic electrical rhythm (BER) of the bowel decreases early after induction of arterial ischemia. Furthermore, our studies have shown that these changes occur prior to pathologic changes and that they can be recorded noninvasively using a superconducting quantum interference device (SQUID). SQUIDs measure magnetic fields that are created by the electrical activity of the gastrointestinal smooth muscle and have been used to measure the BER of the small intestine in human volunteers. This study was conducted to determine if a SQUID could be used for early noninvasive detection of mesenteric venous ischemia in an animal model. Simultaneous recordings from serosal electrodes and a SQUID outside the abdomen were taken from anesthetized New Zealand rabbits. Recordings were made for 15 minutes before and 90 minutes after injection of thrombin into the superior mesenteric vein. The basic electrical rhythm of the small bowel dropped from 16.42 ± 0.69 to 8.80 ± 0.74 cycles per minute at 30 minutes and to 6.82 ± 0.722 after 90 minutes ($p < 0.0001$, paired *t*-test). The correlation coefficient between the SQUID and electrical recordings was 0.954 ($p < 0.0001$). These data suggest that the ischemia caused by mesenteric venous thrombosis results in changes in the bioelectrical activity, which can be noninvasively detected using a SQUID.

Acute mesenteric venous thrombosis (MVT) accounts for only 5% to 15% of cases of mesenteric ischemia [1, 2], but the mortality rate remains high, approaching 20% to 60% if the diagnosis is delayed until intestinal necrosis has occurred [3]. Since the mid-1970s major advances in the diagnosis of MVT have evolved, mainly utilizing duplex ultrasonography and contrast-enhanced computed tomography (CT) scanning. Such scans allow visualization of the thrombus within the superior mesenteric vein (SMV). The next step in confirming the diagnosis is either angiography or a laparotomy, although these procedures are not always necessary. Despite these advances, cases of acute MVT are still misdiagnosed and detected only at laparotomy. If these cases could be diagnosed earlier, anticoagulation therapy might suffice to prevent the propagation of thrombosis [4, 5].

Several investigators have used serosal electrodes to demonstrate that the basic electrical rhythm (BER) of the small bowel decreases with arterial ischemia [6–9]. We have previously shown that this decrease occurs early in arterial ischemia, before pathologic changes take place [10]. The decrease continues as long as the ischemia persists or until smooth muscle necrosis with loss of electrical activity occurs.

The superconducting quantum interference device (SQUID) magnetometer can detect the magnetic fields produced by the electrical current of the smooth muscle of the small intestine [11]. Furthermore, the SQUID can detect the magnetic fields through the layers of the abdominal wall without direct contact with the bowel serosa. The magnetic fields of the stomach [12] and small intestine [13] have been measured on human subjects noninvasively by a number of groups around the world. The advantages of magnetic field measurement over cutaneous electrode measurement of small intestinal electrical activity can be seen in Figure 1. Electrical activity is attenuated and filtered by the multiple layers of electrical insulators of the abdominal wall and omentum, whereas the magnetic fields are not attenuated nearly as much. Measurements from cutaneous electrodes have a much smaller signal-to-noise ratio than do measurements taken from a SQUID outside the abdominal wall in a rabbit [14].

We previously reported that the SQUID magnetometer could be used for early detection of acute arterial mesenteric ischemia in a rabbit model [6, 15]. We hypothesized that acute MVT causes enough ischemia in the small bowel of animals to produce changes in the BER that might be detected noninvasively by the SQUID. Specifically, we sought to determine (1) if the SQUID magnetometer can noninvasively detect the changes in BER associated with ischemia due to acute MVT in a rabbit model; (2) if these SQUID recordings correlate with direct serosal electrical recordings; and (3) if these changes occur before pathologic changes take place,

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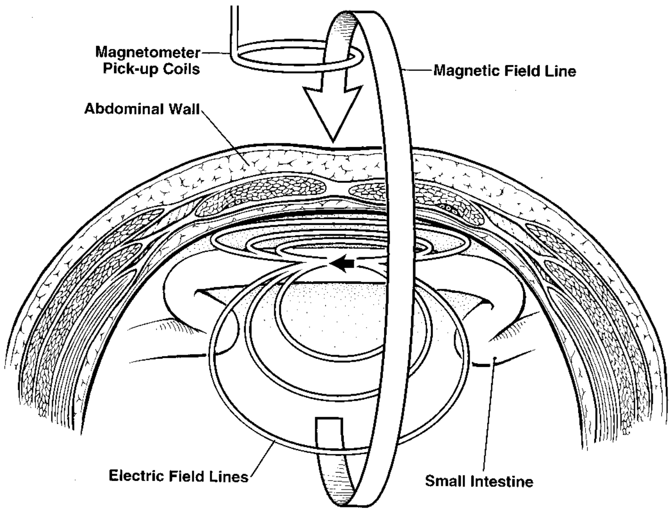

Fig. 1. Cross section of an abdomen illustrating why magnetic fields of the small intestine can be recorded noninvasively in animal and human subjects. The SQUID magnetometers detect the magnetic field generated by the electrical current of the smooth muscle of the small intestine. The magnetic field is relatively insensitive to the alternating layers of insulators present within the abdominal wall (i.e., peritoneum, preperitoneal fat, fascia, muscles, subcutaneous fat, and skin). The electrical field generated layers of insulators present in the abdominal wall. Thus the electrical fields measured by cutaneous electrodes have low signal-to-noise ratio. Because the magnetic fields are not attenuated as much by the insulators of the abdominal wall, the signal-to-noise ratio is much higher than it is for cutaneous recordings.

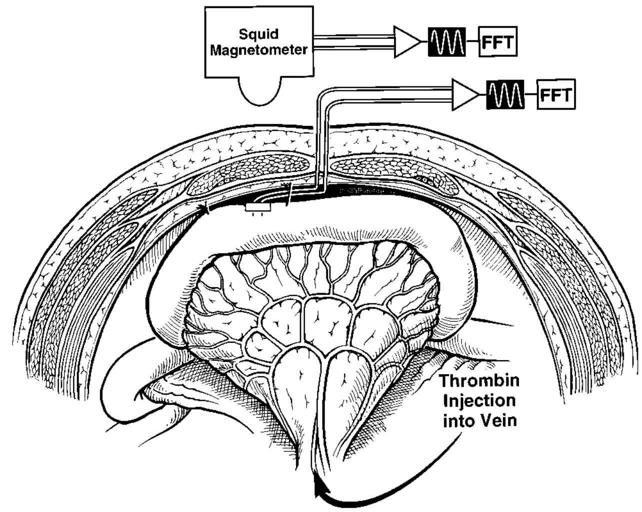

Fig. 2. Experimental setup. Bipolar electrodes are sutured to the bowel, and the abdomen is closed. The SQUID is lowered over the area where the electrodes have been sutured on and tacked to the abdominal wall to ensure that the small section of bowel is measured using the SQUID and the invasive serosal electrodes. After recording the BER of the bowel simultaneously with the SQUID and the invasive electrodes for at least 15 minutes, the abdomen is opened and thrombin is injected into the superior mesenteric vein, which causes immediate thrombosis of the venous drainage of the small intestine. The abdomen is closed with sutures, and the BER of the small intestine is recorded simultaneously with the invasive electrodes and noninvasive SQUID.

enabling us to use this technology to aid in the early diagnosis of this condition.

Materials and Methods

A high resolution SQUID magnetometer (microSQUID) was used in these experiments. It contains four superconducting niobium pickup coils housed within a vacuum space of a liquid helium-filled Dewar to allow cooling to 9° Kelvin. All the studies were performed inside a magnetically shielded room (Vacuumschmelze, Berlin, Germany). This room reduces the earth's magnetic field and magnetic noise to less than 0.15 femtotesla (fT).

A Beckman amplifier (model R612) with an analog-to-digital convertor (Biopac Systems, model MP100; Goleta, CA, USA) and an Apple Powerbook 170 running Acknowledge 3.1.2 software (Biopac Systems) were used to record the signals. The signals were bandpass-filtered from 0.16 to 30 Hz, and the magnetic signal was lowpass filtered at 30 Hz.

The study was performed on 10 white male New Zealand rabbits weighing 3 to 5 kg. All the animal manipulations in this study were performed in accordance with guidelines established by the Animal Care and Use Committee at Vanderbilt University and the Nashville Veterans Administration Medical Center. The rabbits were fed fresh vegetables for a minimum of 3 days to reduce the interference by magnetic contamination of the food. Anesthesia was induced by ketamine (30 mg/kg) and acepromazine (0.75 mg/kg) intramuscularly with maintenance doses of ketamine (10–15 mg boluses) by intravenous injection. An intravenous catheter was placed for administration of fluids and medication.

Table 1. Swerdlow and Antonioli grading scale

Grade	Criteria
0	No pathologic changes
1	Mucosal infarction: focal loss of surface epithelium
2	Mucosal infarction: extensive loss of surface epithelium and intact muscularis mucosa
3	Mural infarction: loss of muscularis muscosa
4	Mural infarction: complete necrosis of the mucosa and submucosa
5	Transmural infarction: complete necrosis of entire bowel wall

This grading scale [16] was used by the pathologist (S.H.) to score the degree of pathologic injury.

Following a midline laparotomy, four pairs of silver electrodes on a Silastic platform were attached to a loop of jejunum, which was fixed to the inside of the anterior abdominal wall (Fig. 2). The abdomen was closed, and simultaneous baseline recordings of both electrical and magnetic BER were performed for 15 minutes. The incision was then reopened, the SMV dissected, and 1000 units of thrombin injected into the main vein. The abdomen was then closed again and recordings continued; there was a delay of 10 to 15 minutes between injection of thrombin and recording. The recording was continued for 90 minutes, following which the animal was killed and the segment of small bowel resected and sent for histopathologic examination to determine the extent of ischemia. The physician (S.H.) reading the slides to determine pathologic grade was blinded to the identity of specimen. Histopathologic grading was based on a modification of the pathologic classification of Swerdlow and Antonioli [16] (Table 1).

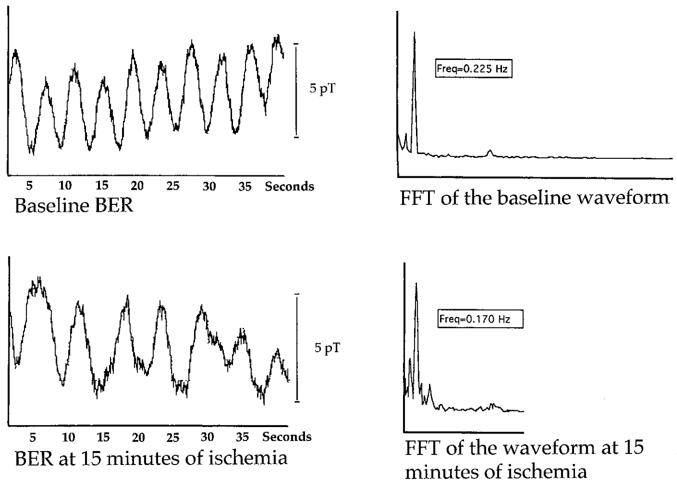

Fig. 3. Samples of the BER recordings and their corresponding FFTs during baseline and after 15 minutes of ischemia. Note the decrease in the frequency and amplitude of the waveform. These waveforms can be seen in real time on the monitor similar to the waveforms recorded by the invasive serosal electrodes.

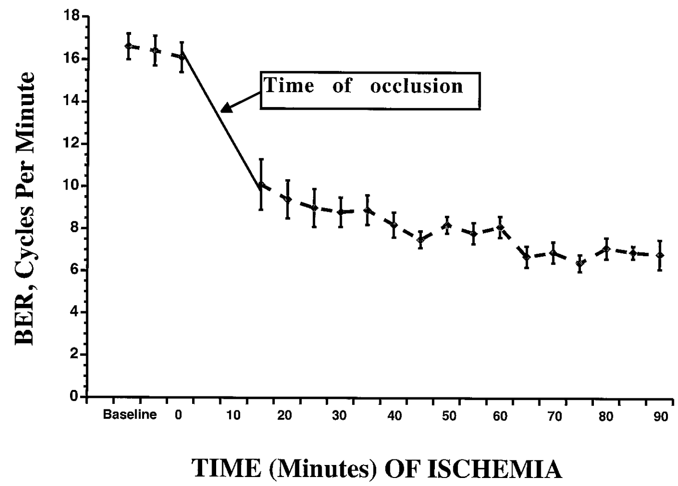

Fig. 4. BER (mean ± SEM) in cycles per minute as recorded by the SQUID during baseline and after 90 minutes of ischemia. Note the immediate reduction of the BER after occlusion of the superior mesenteric vein followed by the gradual decline as ischemia continues.

The data were analyzed using fast fourier transformation (FFT) (Hamming window, mean and trend were removed) to determine the dominant BER frequency. Segments of 2.5 minutes were analyzed at 5-minute intervals. Statistical analysis was performed using the paired *t*-test; a *p* value was considered significant at < 0.05. Correlation between the magnetic and electrical recordings was determined by calculating the correlation coefficient (*r*) value.

Results

Samples of the SQUID recordings with their FFTs during baseline and after 15 minutes of venous ischemia are shown in Figure 3. The mean BER of the small intestine dropped from 16.42 ± 0.69 cycles per minute (cpm) at baseline to 10.078 ± 1.250 cpm at 15 minutes and to 8.80 ± 0.74 cpm after 30 minutes of ischemia ($p < 0.0002$) (Fig. 4). This drop was noted in all 10 animals studied. After 60 minutes of ischemia the recordings became irregular, with a reduction in amplitude of the waveforms, making determination of BER difficult. The SQUID and electrical recordings were highly correlated with a correlation coefficient (*r*) value of 0.945 ($p < 0.0001$) (Fig. 5).

After 90 minutes of induced ischemia, the histopathologic examination showed mucosal sloughing and venous congestion in both the mucosal and muscular layers. There was no evidence of muscle necrosis. All the specimens were at +1 or +2 histopathologic stage.

Discussion

These data demonstrate that acute SMV thrombosis causes significant changes in the BER of rabbit small bowel, and that they can be detected noninvasively using the SQUID magnetometer. These changes, produced by ischemia due to venous thrombosis, were consistent, just as they were in our previous studies of ischemia caused by arterial occlusion [6, 10, 15]. Furthermore,

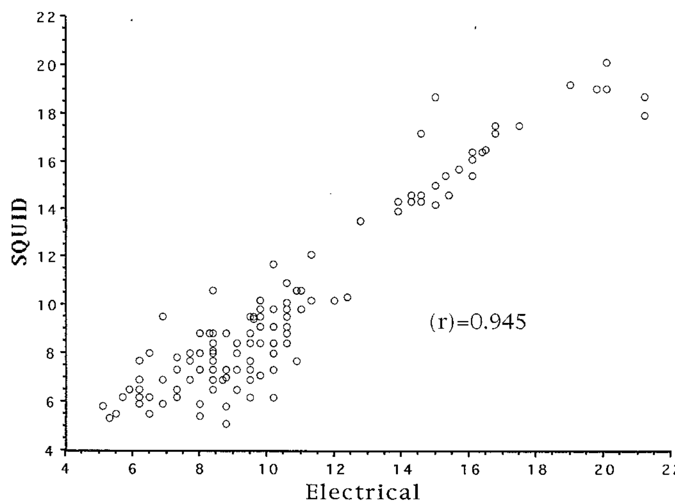

Fig. 5. Scattergram showing the correlation between the simultaneously recorded SQUID and invasive electrical recordings. The correlation coefficient ($r = 9.45$) shows excellent correlation between the BER frequency determined using the SQUID transabdominally and the invasive electrode recordings.

these results show that there is a direct relation between the degree of ischemia and the magnitude of changes in the BER frequency, as demonstrated by the gradual but constant slowing of the BER. The reduction in BER frequency occurred at 90 minutes, prior to pathologic changes. We are able to use the SQUID magnetometer to noninvasively detect small bowel ischemia caused by SMV thrombosis.

The diagnosis of acute MVT has changed dramatically since the mid-1970s. Early on, the diagnosis was made only at laparotomy or at autopsy. Most of the reported cases were primary (i.e., of unknown origin), although some were secondary to trauma, including after surgery, or were associated with sepsis or abdominal malignancies. Currently, most cases are suspected based on the patient's history: 30% have a history of deep venous thrombosis, and up to 80% are secondary to other underlying conditions [17]. In particular, abnormal coagulation profiles (e.g, antithrombin III, protein C, and protein S deficiencies) are likely to play a pathogenic role. Since the introduction of heparin in 1945, anticoagulation therapy has figured prominently in the treatment of MVT. Anticoagulation can prevent the progression of thrombosis. Thus if the diagnosis is made early enough, the progression of partial ischemia to transmural necrosis of the bowel wall might be prevented. However if full-thickness necrosis of the bowel wall occurs, the patient usually presents with sepsis and peritonitis [18].

Although the diagnosis of acute SMV thrombosis has greatly improved since the introduction of ultrasound duplex and contrast-enhanced CT scanning (which has an approximate overall reliability of 90% in diagnosis [19–21]), these tests reflect anatomic changes and thus cannot differentiate between early and late thrombosis. Perhaps even more importantly, they cannot determine the extent of ischemia produced by the MVT. The BER changes associated with acute ischemia appear within 15 minutes of ischemia and last as long as the ischemia continues or until the smooth muscle loses its electrical activity. In a previous study we showed that the BER returned to normal if the blood flow to the bowel was restored before smooth muscle necrosis occurred [6]. The reduction in BER frequency occurred during ischemia, and disappearance of the BER indicates dead or necrotic bowel. There are three recognized causes of slow BER frequency: ischemia, hypothermia, and hypothyroidism. Because the latter two are easy to exclude, once they are eliminated as potential causes slow BER frequency can be presumed to result from bowel ischemia.

For example, with chronic SMV thrombosis, the degree of ischemia is not as marked because collateral circulation is well established. Patients with this condition are either asymptomatic or present with vague abdominal pain and discomfort; they may have extension of the thrombosis into the portal vein and thus present with signs and symptoms of portal hypertension. It is unlikely that in these cases any changes in BER will be found. Thus the SQUID measurements may not be helpful for detecting the thrombosis but are helpful for excluding a significant degree of ischemia. Interestingly, this limitation might ultimately prove to be an advantage as contrast-enhanced CT scans detect thromboses but fail to differentiate between acute thrombosis causing ischemia and chronic thrombosis without significant ischemia. Thus the SQUID may be superior to the CT scan in this respect as it measures physiologic impairment. This situation could lead to the institution of earlier medical interventions, such as anticoagulation or thrombolytic therapy, and thus may avert the need for surgery.

Additional work is needed before the SQUID magnetometer can become a useful clinical tool. Limitations of currently available SQUIDs include high cost, the need for cryogens, and the fact that the recordings must be done in a shielded room to prevent noise contamination. We have used the SQUID successfully to record both gastric and small intestinal BER in normal human volunteers [6, 13], and we are working on an optimized device for the detection of mesenteric ischemia in human subjects.

The demonstration of clinical utility will undoubtedly lead to engineering improvements that address the shortcomings. We believe that with the development of high-temperature superconducting materials the cost of manufacturing and maintenance of SQUIDs can be lowered. We are working on strategies to eliminate the need for a shielded room, further simplifying the use of SQUIDs in clinical practice. Other investigators have already been able to record the magnetogastrogram in human subjects in an unshielded environment [12]. Thus with additional studies this technology may eventually evolve into a useful clinical tool that may lead to improved noninvasive detection of bowel ischemia.

Conclusions

This study was conducted to determine if a SQUID could noninvasively record changes in the BER of the small intestine after induction of mesenteric venous thrombosis. In this animal model the SQUID was able to noninvasively measure decreases in BER frequency that occurred before the onset of irreversible pathologic changes in the small intestine. Furthermore, the magnetic field recordings were highly correlated with the recording frequencies determined using invasive serosal electrodes. This technology has many of the ideal characteristics for a diagnostic tool: It is fast, is noninvasive, detects ischemia prior to irreversible changes, and can be repeated multiple times to follow the progress of disease or response to therapy. These promising results have encouraged us to continue investigations in animal and human subjects.

Résumé

Le pronostic de la thrombose veineuse mésentérique est meilleur que celui de la thrombose artérielle mais la morbidité et la mortalité restent élevées. Des études antérieures ont montré que le Basic Electrical Rhythm (BER) de l'intestin diminue lorsque l'on provoque une ischémie artérielle. Nos études indiquent que ces modifications précèdent les changements anatomopathologiques et qu'elles peuvent être enregistrécs de façon non-invasive en utilisant l'apparell SQUID (Superconduction QUantum Interference Device). Le SQUID mesure le champs magnétique créé par l'activité électrique du muscle lisse de l'intestin grêle et a déjà été utilisé pour mesurer le BER de l'intestin grêle chez des volontaires humains. Cette étude a eu pour but de déterminer si le SQUID peut être utilisé pour la détection non-invasive de l'ischémie veineuse mésentérique dans un modèle animal. Des enregistrements simultanés à partir d'électrodes sur la séreuse et d'un SQUID placé en dehors de l'abdomen ont été réalisés chez le lapin New Zealand. On a enregistré l'activité 15 minutes avant et 90 minutes après l'injection de thrombine dans la veine mésentérique supérieure. L'activité électrique de base a chuté de 16.42 ± 0.69 à 8.80 ± 0.74 cycles/minute après 30 minutes et à 6.82 ± 0.722 après 90 minutes ($p < 0.0001$, test de Student apparié). Le coefficient de corrélation entre le SQUID et les enregistrements électriques étaient de 0.954 ($p < 0.0001$). Ces données indiquent que l'ischémie en rapport avec la thrombose mésentérique veineuse est responsable d'une modification d'activité bioélectrique détectable de façon non-invasive par le SQUID.

Resumen

Aunque la trombosis venosa mesentérica conlleva un mejor pronóstico que la trombosis arterial, su mortalidad y morbilidad todavía son altas. Estudios previos han demostrado que el Ritmo

Eléctrico Básico (REB) del intestino se disminuye luego de la inducción de isquemia arterial. Además, nuestros propios estudios han señalado que tales cambios se presentan con anterioridad a las alteraciones patológicas y que pueden ser registrados mediante una técnica no invasora que utiliza un SQUID (Superconducting Quantum Interference Device). Los SQUIDs miden los campos magnéticos que se crean por la actividad eléctrica de la musculatura lisa gastrointestinal y se han utilizado para medir la REB del intestino delgado en voluntarios humanos. El presente estudio fue realizado para determinar si se podría utilizar un SQUID para la detección temprana y no invasora de isquemia venosa mesentérica en un modelo animal. Registros simultáneos a partir de electrodos serosos y de un SQUID por fuera del abdomen fueron tomados en conejos anestesiados. Se tomaron registros a los 15 minutos antes y a los 90 minutos después de la inyección de trombina en la vena mesentérica superior. El REB de intestino delgado disminuyó de 16.42 B1 0.69 a 8.8 B1 0.74 ciclos por minuto a los 30 minutos y a 6.82 B1 0.722 a los 90 minutos ($p<0.0001$, prueba apareada). El coeficiente de correlación entre los registros del SQUID y los eléctricos fue 0.954 ($p<0.0001$). Estos datos sugieren que la isquemia causada por trombosis venosa mesentérica resulta en cambios en la actividad bioeléctrica que puedan ser detectados de manera no invasora utilizando un SQUID.

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Invited Commentary

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This paper expands on the authors' previous studies of the measurement of the basal electrical rhythm (BER) of the bowel as a means of early identification of intestinal ischemia. They have properly identified the strengths of the technique: that it "is fast, is noninvasive, detects ischemia prior to irreversible changes," and can be repeated as frequently as necessary. They also have pointed out that at present the instrumentation and physical requirements make the test impractical as a clinical tool. There are other problems that must be solved as well if this technique is going to have a role in the clinical management of intestinal ischemia.

Although in this experiment early changes in the BER were identified, their validity disappeared after 60 minutes of ischemia. It is doubtful that most patients with clinically significant MVT present early enough in the course of their disease for the BER measurement to be helpful. Moreover, the authors have not demonstrated that they can differentiate ischemia of venous origin from that of arterial origin by this technique.

The successful management of acute mesenteric ischemia requires early suspicion of the diagnosis with prompt studies to establish both its presence and the nature and site of the cause of the ischemia. In our experience early mesenteric angiography has been the best means for reaching these goals. The use of a SQUID as a rapid, noninvasive screening test before the more invasive angiographic study would be a useful application of the technique, but it would not provide the information of the angiogram or the access the latter provides for administration of intraarterial vasodilators.

It has long been known that chronic mesenteric arterial ischemia can interfere with bowel function without loss of tissue viability. Measurement of the intestinal BER in that situation would be helpful for differentiating an SMA occlusion that is not producing clinical problems with one that is causing intestinal ischemia. It might also be of value in patients with chronic MVT, as suggested by the authors, but in the absence of any symptoms a MVT rarely requires therapy.

The noninvasive measurement of intestinal BER is worthy of further study as a means of diagnosing intestinal ischemia before loss of tissue viability, as its possible clinical role and application have not yet been established.