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ORIGINAL ARTICLE

Others

Usefulness of a real-time bowel sound analysis system in patients with severe sepsis (pilot study)

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Abstract Healthy bowel function is an important factor when judging the advisability of early enteral nutrition in critically ill patients, but long-term observation and objective evaluation of gastrointestinal motility are difficult. In the study, real-time continuous measurement of gastrointestinal motility was performed in patients with severe sepsis using a developed bowel sound analysis system, and the correlation between bowel sounds and changes over time in blood concentrations of interleukin (IL)-6, which is associated with sepsis severity, was evaluated. The subjects were five adult patients in the acute phase of severe sepsis on a mechanical ventilator, with IL-6 blood concentrations ≥100 pg/mL, who had consented to participate in the study. Gastrointestinal motility was measured for a total of 62,399 min: 31,544 min in 3 subjects in the no-steroids group and 30,855 min in 2 subjects in the steroid treatment group. In the no-steroids group, the bowel sound counts were negatively correlated with IL-6 blood concentration, suggesting that gastrointestinal motility was suppressed as IL-6 blood concentration increased. However, in the steroid treatment group, gastrointestinal motility showed no correlation with IL-6 blood concentration ($r = -0.25$, $p = 0.27$). The IL-6 blood concentration appears to have decreased with steroid treatment irrespective of changes in the state of sepsis, whereas bowel sound counts with the monitoring system reflected the changes in the state of sepsis, resulting in no correlation. This monitoring system provides a useful method of continuously, quantitatively, and non-invasively evaluating gastrointestinal motility in patients with severe sepsis. Gastrointestinal motility might be useful as a parameter reflecting disease severity, particularly in patients treated with steroids.

Keywords Bowel sound analysis · IL-6 · Enteral nutrition · Critical care · Sepsis

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Introduction

Recent nutritional guidelines for critically ill patients recommend early enteral nutrition. This should be initiated within 24–48 h after entry to an intensive care unit (ICU) according to the Society of Critical Care Medicine (SCCM)/American Society for Parenteral and Enteral Nutrition (ASPEN) [1] and the Canadian Clinical Practice Guideline (CCPG) [2], and within 24 h after entry to an ICU according to the European Society for Parenteral and Enteral Nutrition (ESPEN) [3]. Enteral nutrition must be abandoned in some patients with severe sepsis because of complications such as vomiting, gastroesophageal reflux, and aspiration pneumonia [4, 5]. Dysfunction of gastrointestinal motility is recognized as one of the factors leading to these complications [6, 7]. It is therefore important to assess gastrointestinal motility during early enteral nutrition.

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) induced by an infection [8, 9], and SIRS becomes more severe due to uncontrollable production of inflammatory cytokines by activated immunocompetent cells. This means that changes in cytokines such as interleukin (IL)-6 are useful for evaluating the severity of sepsis and judging the effects of treatment [10, 11]. There are, however, no studies elucidating the relationship between changes in gastrointestinal motility and severity over time in patients with severe sepsis.

We previously developed a non-invasive monitoring system capable of quantifying and visualizing gastrointestinal motility in real time and reported the usefulness of this system in healthy volunteers [12, 13]. For the current study, we hypothesized that gastrointestinal motility decreases and could thus serve as an indicator of severity in patients with severe sepsis, defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion [4], which involves elevated cytokines. Therefore, the long-term changes in gastrointestinal motility were measured with a real-time bowel sound analysis system in patients with the acute phase of severe sepsis. And then the correlation between bowel sound counts and blood levels of the inflammatory cytokine IL-6 was investigated. The usefulness of bowel sound counts was then investigated in patients with severe sepsis.

Methods

Study design and subjects

The study was a prospective, observational pilot study conducted at our hospital with the approval of the hospital's Institutional Review Board. Consecutive adult patients with severe sepsis, defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion, on a mechanical ventilator with an IL-6 blood concentration of $\geq$100 pg/mL [14] in the acute phase, defined as being up to the 28th day of illness in the ICU, were entered in this study between June 2011 and December 2012. Subjects were divided into those who were treated with steroids (steroid treatment group) and those who were not (no-steroids group) during the target period, because steroids strongly affect IL-6 blood levels [15]. All subjects enrolled in this research have given their informed consent which has been approved by our institutional committee on human research, and this protocol has been found acceptable by them (Authorized No: 731).

Real-time bowel sound analysis system

The real-time bowel sound analysis system consisted of recording equipment and acoustic sensors (Fig. 1) [13]. The recording equipment (Sharp Co., Osaka, Japan) consisted of four sensors with a multi-channel data logger, an isolation transformer, and a personal computer with the analysis software can record and detect bowel sounds in real time. The acoustic sensors attached to the abdomen were silicone-covered, rectangular microphones with built-in amplifiers. With these acoustic sensors attached to the abdomen, bowel sounds were counted if they matched a template power spectrum established from normal bowel sound data in a previous study [12, 13]. The bowel sound counts per minute (cpm) were displayed in real time.

Cytokine measurement

Blood concentrations of IL-6 sampled from subjects each morning were measured by chemiluminescent enzyme immunoassay using an automatic IL-6 blood concentration assay system (Fujirebio, Tokyo, Japan).

Statistical analysis

The correlations between IL-6 blood concentration and 24-h bowel sound counts on the previous day, the same day and the next day, were analyzed. Statistical analysis of the data obtained from these measurements was done using JMP version 10 (SAS Institute Japan, Tokyo, Japan). Correlations were tested using Pearson's method, with a $p < 0.05$ being defined as significant.

Results

Five adult patients with severe sepsis on a mechanical ventilator were entered in this study. The total measurement time of bowel sound counts in these subjects was 62,399 min. Table 1 shows the data for subject age, sex, weight, height, body mass index (BMI), diseases, acute physiological and chronic health evaluation (APACHE) II score [16], sequential organ failure assessment (SOFA) score [17], steroid treatment, use of parenteral nutrition (PN), use of continuous renal replacement therapy (CRRT), length of time on mechanical ventilation, duration in the ICU, and outcome at discharge from the ICU. The no-steroids group contained 3 subjects with a measurement time of 31,544 min, and the steroid treatment group contained 2 subjects with a measurement time of 30,855 min. Figure 2 shows 24-h bowel sound cpm in one patient measured using the real-time bowel sound analysis system. He was 72-year-old man with septic multiple organ failure caused by retroperitoneal abscess, and was treated with critical care including CRRT. The horizontal axis of Fig. 2 represents time, and the vertical axis represents the bowel sound count. It is apparent that the bowel sound counts

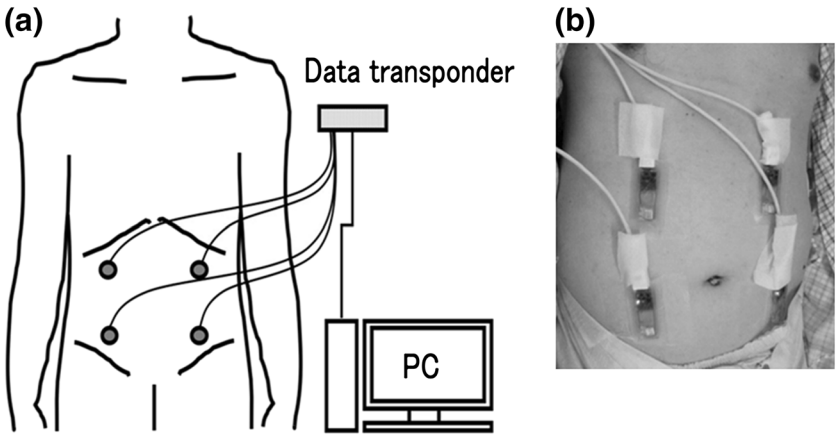

Fig. 1 **a** Schematic diagram of the real-time bowel sound analysis system. **b** Bowel sound sensors attached to the abdomen

Table 1 Data of patients fitted with the real-time bowel sound analysis system

	Mean
Age (years)	54.2 (26–72)
Sex	
Male	2
Female	3
Weight (kg)	63.8 (44.1–79.4)
Height (cm)	152.6 (142.6–160.0)
BMI (kg/m^2)	30.1 (22.7–35.0)
Disease	
Sepsis	3
Severe acute pancreatitis	1
SLE	1
APACHE II score	26.6 (10–47)
SOFA score	11.8 (8–17)
Steroid administration	
Yes	2
No	3
PN	
Yes	5
No	0
CRRT done	
Yes	5
No	0
Mechanical ventilation (days)	27.8 (9–95)
Duration in ICU (days)	30.4 (12–70)
Outcome at discharge from ICU	
Survival	4
Death	1

BMI body mass index, *APACHE II* acute physiology and chronic health evaluation II, *SOFA* sequential organ failure assessment, *PN* parenteral nutrition, *CRRT* continuous renal replacement therapy

were variable rather than uniform throughout the 24-h period, especially bowel sound counts increased after medications were taken orally.

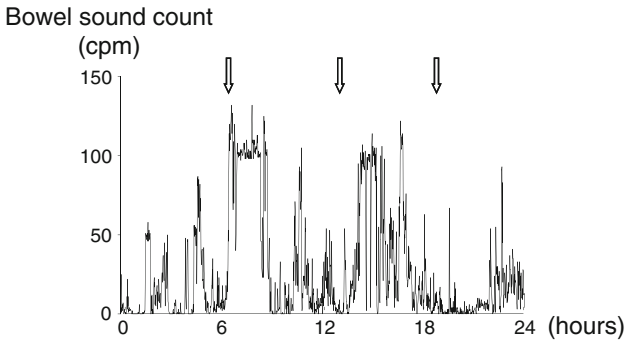

Fig. 2 24-h bowel sound counts (cpm) in one patient measured using the real-time bowel sound analysis system medications taken were Da Jian Zhong Tang, Liu Jun Zi Tang (traditional Chinese medicines), bio-three, lansoprazole, and ursodeoxycholic acid

Figure 3 shows IL-6 blood concentrations and 24-h bowel sound counts measured on the same day in each case. From these data, the correlation between IL-6 blood concentrations and 24-h bowel sound counts on the same day or next day was analyzed.

Figures 4, 5 show IL-6 blood concentrations and 24-h bowel sound counts on the same day and on the next day. IL-6 blood concentration and bowel sound counts showed a negative correlation in the no-steroids group (Fig. 4a; $r = -0.62$, $p < 0.01$, Fig. 5a; $r = -0.76$, $p < 0.01$), but no correlation in the steroid treatment group (Fig. 5a; $r = -0.25$, $p = 0.27$, Fig. 5b; $r = -0.17$, $p = 0.48$). The correlation coefficient in the no-steroids group on the same day was slightly smaller than the correlation seen on the next day. There was no correlation between IL-6 blood concentration and 24-h bowel sound counts on the previous day was seen in either the no-steroids group or the steroid treatment group (no-steroids group: $r = -0.35$, $p = 0.12$; steroid treatment group: $r = 0.02$, $p = 0.95$, figure not shown).

No adverse events related to this study were reported during the study period.

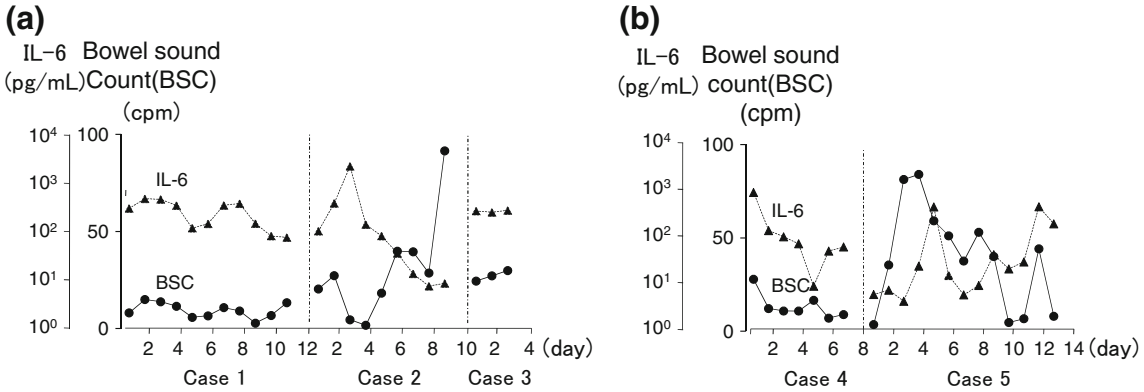

Fig. 3 IL-6 blood concentrations and 24-h bowel sound counts on the same day in each case; **a** no-steroids group, **b** steroid treatment group; *filled triangle*: IL-6 blood concentration, *filled circle*: 24-h bowel sound counts

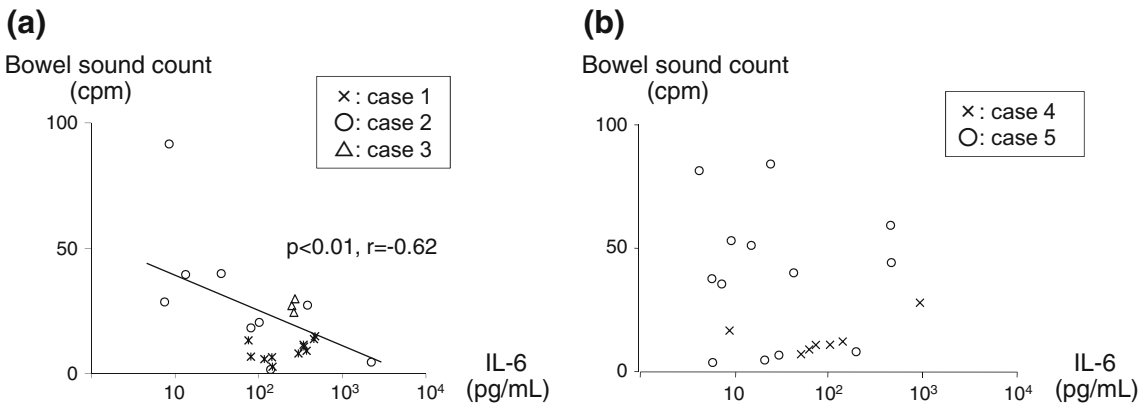

Fig. 4 Correlation between IL-6 blood concentration and 24-h bowel sound counts on the same day; **a** no-steroids group; *multi symbol*: case 1, *open circle*: case 2, *open triangle*: case 3. The graph's *straight line* represents a linear approximation ($*p < 0.01$, $r = -0.62$). **b** Steroid treatment group; *multi symbol*: case 4, *open circle*: case 5

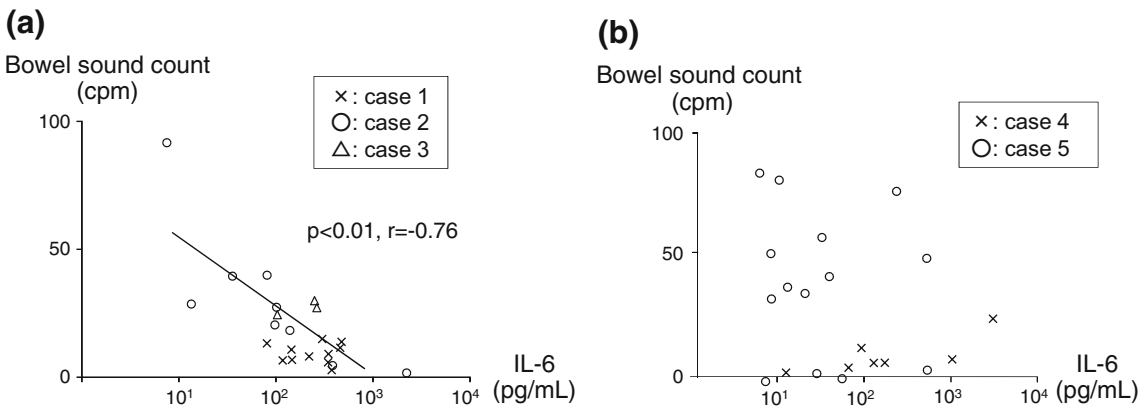

Fig. 5 Correlation between IL-6 blood concentration and 24-h bowel sound counts on the next day; **a** no-steroids group; *multi symbol*: case 1, *open circle*: case 2, *open triangle*: case 3. The graph's *straight line* represents a linear approximation ($*p < 0.01$, $r = -0.76$). **b** Steroid treatment group; *multi symbol*: case 4, *open circle*: case 5

Discussion

The recording of bowel sounds has a long history, and the sound itself was already known by the term borborygmus in the time of Hippocrates. Cannon recorded his own bowel sounds in 1905 [18], and in 1975, Daniel et al. announced the complete computerization of bowel sound recording [19]. Since then, many studies have been done with the aim

of developing instruments for measuring gastrointestinal motility as a way of quantitatively evaluating digestive tract function, but none of these approaches has led to real-time, continuous monitoring [18–21].

Early enteral nutrition is recommended for critically ill patients in the ICU [1], but given the complications associated with severe sepsis, some evaluation method is needed that can measure gastrointestinal motility in real time to judge the advisability of enteral nutrition. We therefore developed the first bowel sound analysis system capable of non-invasively visualizing and quantifying gastrointestinal motility in real time. Using this monitoring system, we quantitatively evaluated gastrointestinal motility in patients with severe sepsis, analyzed changes in bowel sound counts over time, and studied the relationship between the gastrointestinal motility and severity of the patient. It is shown in this study that IL-6 blood concentration and bowel sound counts were negatively correlated in the no-steroid group. The strongest correlation with IL-6 blood concentration was seen in the 24-h bowel sound counts on the next day ($r = -0.76, p < 0.01$). Oda et al. reported that there was significant correlation between the peak IL-6 blood level and the maximum SOFA score [22]. Since severity of sepsis is associated with IL-6 blood concentration, it is suggested that gastrointestinal motility is more strongly suppressed by higher IL-6 blood concentrations. Similarly, there was no correlation between IL-6 blood concentration and 24-h bowel sound counts on the previous day. From this we can surmise that suppression of gastrointestinal motility results from an increase in IL-6 blood concentration and, therefore, a deterioration in overall condition due to severe sepsis.

In the steroid treatment group, there was no correlation between IL-6 blood concentration and bowel sound counts. IL-6 blood concentrations have been found to fall significantly after steroid administration. Oppert et al. showed a randomized control study compared with placebo-treated patients, administration of hydrocortisone significantly decreased IL-6 blood concentration in septic shock [23]. In the present study, there was no correlation between IL-6 blood concentration and bowel sound counts in the steroid treatment group. This could be because, despite the decrease in IL-6 blood concentration resulting from steroid administration, disease severity did not abate in parallel with this decrease. Conversely, it is possible that bowel sounds, which are not affected by steroid administration, could be a parameter that reflects disease severity better than IL-6 blood concentration, and it would therefore be of significance to actively measure the bowel sound counts continuously in patients treated with steroids.

It may be possible to identify the indicators for successful early enteral nutrition by elucidating the factors affecting gastrointestinal motility. For example, animal experiments have shown that hyperglycemia lowers gastrointestinal motility [24]. In cases of severe sepsis where hemodynamic instability requires high-dose catecholamine administration, there is a risk of ischemia and reperfusion injury in the digestive tract and other internal organs, and it has therefore been proposed that enteral nutrition should be postponed until hemodynamic stability is regained [1]. Furthermore, catecholamine administration is known to suppress gastrointestinal peristalsis [4, 5], and while there is evidence that enteral nutrition is possible with low-dose catecholamine administration [25], high-dose catecholamine administration has been associated with discontinuation of enteral nutrition [26]. Using this real-time bowel sound analysis system to investigate the correlations between bowel sound counts and various clinical data, it is possible to study the links between these data and gastrointestinal motility. We plan to conduct further research on this topic in the future. We also expect that it will be possible to ascertain in real time the timing of administration of enteral nutrients and, particularly in critically ill patients on mechanical ventilation, the optimum dose of enteral nutrients. There are two limitations in this study. One is that number of subject was small. The other is that we did not survey how IL-6 blood concentration and bowel sound counts changed before the steroid administration in the steroid treatment group.

Conclusion

We developed the first monitoring system capable of non-invasively visualizing and quantifying gastrointestinal motility in real time. When using this system to measure bowel sound counts in patients with severe sepsis, the strongest correlation was seen between IL-6 blood concentration and 24-h bowel sound counts on the next day in no-steroids group. This result indicates that suppression of gastrointestinal motility increases as IL-6 blood concentration increases. Suppression of gastrointestinal motility was suspected to result from deterioration in patients' overall condition due to severe sepsis. This monitoring system provides a useful method of continuously, quantitatively, and non-invasively evaluating gastrointestinal motility in patients with severe sepsis.

Conflict of interest All the authors have declared no conflict of interest.

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