

## Assessment of physical stress during the perioperative period of endoscopic submucosal dissection

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### Abstract

The advantage of endoscopic submucosal dissection (ESD) is that it is less invasive than surgery. ESD is one of the best treatments for older patients as surgery in this age group of patients is difficult. However, it is unclear how much lower the physical stress of ESD is compared with that of surgery. Thus, objective methods are required to assess physical stress in patients who have undergone ESD. The current review of ESD aimed to summarize the recent advancements in the assessment of physical stress during the perioperative period, focusing on changes in energy metabolism and serum opsonic activity (SOA). Based on metabolic changes, resting energy expenditure (REE) was measured using an indirect calorimeter. The stress factor calculated from the REE and the basal energy expenditure computed using the Harris-Benedict equation can be used to assess physical stress. SOA was assessed using the chemiluminescence method, wherein the use of chemiluminescent probes (*i.e.*, lucigenin and luminol) allowed quantification of reactive oxygen species generated by neutrophils. Using an auto luminescence analyzer, the results were evaluated based on the maximum light emission and area under the emission curve. These quantifiable results revealed the minimal invasiveness of ESD.

**Key Words:** Physical stress; Endoscopic submucosal dissection; Indirect calorimeter; Resting energy expenditure; Chemiluminescence; Serum opsonic activity

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**Core Tip:** Concerning the degree of physical invasiveness of patients before and after endoscopic submucosal dissection (ESD), assessment methods based on changes in energy metabolism using an indirect calorimeter and serum opsonic activity (SOA) measured by lucigenin- and luminol-dependent chemiluminescence are useful and easy to measure. During the perioperative period of ESD, the increase in resting energy expenditure and stress factor were lower than those reported for surgery, and SOA changes involved a minor increase in the production of lower-toxicity reactive oxygen species. These assessment methods demonstrated that the physical stress of ESD is less invasive than that of surgery.

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## INTRODUCTION

Endoscopic treatment for early-stage cancer is indicated when there is a very low probability of lymph node metastasis and when curative en bloc resection is possible[1-3]. Endoscopic submucosal dissection (ESD) is widely used for early gastrointestinal cancer because it is a safe and effective treatment that can preserve function[4-7]. In addition, ESD has a higher rate of en bloc curative resection than endoscopic mucosal resection[8]. Therefore, ESD enables a more precise histopathological diagnosis. ESD is also performed on early gastrointestinal cancer lesions, where surgery was previously common, and often results in a curative resection[9,10]. The most significant advantage for patients is that the physical stress associated with ESD is less than that associated with surgery. From the above, ESD is one of the best treatment options for older patients who are considered difficult to operate on[11-14]. However, it is unclear how much lower the physical stress of ESD is than that of surgery; thus, objective methods are required to assess the physical stress of patients who have undergone ESD. With the increase in the number of older people, the number of patients undergoing ESD for early intestinal cancer is increasing. With advances in endoscopic diagnosis, intestinal cancer will be detected at an earlier stage, and more patients will be treated with ESD. Therefore, it is desirable to develop a method that can evaluate physical stress, even in older patients who are subjected to ESD.

Moreover, ESD is an endoscopic surgery performed on various gastrointestinal tracts, and it is expected that physical stress will differ depending on the organ involved. There is a difference between gastric and colorectal ESD in terms of both technical difficulty and perioperative management. In our facility, because gastric ESD is performed orally, patients fasted after dinner the night before ESD and underwent ESD with pethidine hydrochloride and midazolam or diazepam. In contrast, colorectal ESD requires bowel cleansing prior to colonoscopy. During fasting for ESD, patients are supplied with a drip transfusion and undergo whole bowel irrigation the previous evening and the day of ESD. As patients may need to change their posture to make the ESD procedure easier, colorectal ESD is performed in the awakened state with the analgesic pethidine hydrochloride. Thus, it can be presumed that physical stress in the perioperative period of gastric ESD differs from that of colorectal ESD. Therefore, an assessment method that can compare the physical stress of ESD procedures for different organs is needed.

The current review aimed to summarize the recent advances in physical stress assessment during the perioperative period of ESD, focusing on the changes in energy metabolism and serum opsonic activity (SOA). Additionally, the physical stresses during the perioperative period of gastric and colorectal ESD in comparison to surgery are discussed.

## EARLY INVESTIGATIONS

Serum levels of interleukin (IL)-6, IL-8, tumor necrosis factor- $\alpha$ , and C-reactive protein fluctuate during the perioperative period[15-18]. Myre *et al*[19] reported that high and low doses of remifentanyl affect the release of catecholamines (norepinephrine and epinephrine) differently during laparoscopic fundoplication. However, there have been no effective blood tests to assess physical invasiveness to date.

A report on ESD in the early stages of gastric cancer points out that increased salivary amylase activity in patients may indicate intraoperative stress[20]. However, this change is a hyperacute reaction of the endocrine system, and it is not possible to assess the physical invasion of ESD throughout the perioperative period.

## ASSESSMENT OF PHYSICAL STRESS BY ENERGY METABOLISM

Surgical invasion alters metabolism, and the increased physical stress causes an increase in the patient's energy requirements[21-23]. The patient is subject to two principal metabolic responses: The responses to starvation and stress[24-26]. In addition, the energy requirements are associated with a degree of physical invasiveness[27].

Therefore, changes in resting energy expenditure (REE) measured using an indirect calorimeter can be used to evaluate physical stress. An indirect calorimeter measures the amount of oxygen consumed and the amount of carbon dioxide produced during metabolism and the energy consumption[21]. On the other hand, basal energy expenditure (BEE) is calculated using the Harris-Benedict equation based on the patient's height and body weight. It reflects the energy requirements of each patient[28]. Previous studies have compared BEE during the surgical perioperative period[29-32], but there are few reports using REE measurements. It is presumed that the measurement of REE is more complicated than that of BEE, and few facilities have the calorimeter required for the measurement. On the other hand, the greatest advantage of this method is acceptability for the patients. Because these methods require only exhalation, the patient can rest on the bed, and the measurement time is approximately 5 min each time.

The stress factor (SF) can be done by measured energy expenditure divided by the predicted energy expenditure using the Harris-Benedict equation and the active factor and assess the perioperative physical stress of ESD, even in older patients. According to Long's method[28], the total energy expenditure is defined as the product of BEE, SF, and the activity factor, and it is theoretically the same as the REE measured at rest. Since the activity factor on the day of ESD is the same as that on postoperative day (POD) 1, the SF on POD 1 can be calculated by setting SF on the day to be 1.0[33,34]. From the above, SF is a marker indicating the degree of hypermetabolic state[33,34]. The values of SFs are recognized as 1.1 for low invasiveness, 1.2 for medium invasiveness, and 1.8 for high invasiveness [28], and these values are used as indicators to determine perioperative energy management.

As shown in Table 1, the changes in the perioperative REE and SFs differed between gastric and colorectal ESD[33,34]. Regarding gastric ESD, the REE and REE/BEE increased significantly from the day of gastric ESD to POD 1. The SF for gastric ESD on POD 1 was calculated as 1.07, setting the SF on the day to 1.0[33]. There was no significant difference in REE on the day of ESD and POD 1 for colorectal ESD. However, REE/BEE was significantly higher on POD 1 than on the day of ESD. The SF for colorectal ESD on POD 1 was calculated as 1.06[34].

Regarding the perioperative REEs in surgery for gastric and colorectal cancer, Fredrix *et al*[26] reported that REE on the 7<sup>th</sup> and 8<sup>th</sup> PODs was 1.069% compared to the preoperative value. With respect to the SF on the third day after the surgery, Inoue *et al*[35] reported it was 1.4 for moderate invasive surgery such as subtotal gastrectomy or colectomy, and 1.6 for highly invasive surgery such as total gastrectomy. In our previous studies, REEs and SFs were evaluated on POD 1 when the patient was presumed to have the highest degree of physical and psychological stress; however, they remained low compared to those for surgeries[33,34].

## ASSESSMENT OF PHYSICAL STRESS BY SOA

Opsonization is a humoral immune response involving the complement system that facilitates the capture and uptake of foreign substances by neutrophils and other phagocytes. An increase in SOA causes neutrophil activation and stimulates the secretion of reactive oxygen species (ROS)[36,37], which is associated with physical stress[38-40]. Among ROS, superoxide anions ( $O_2^-$ ) and hydrogen peroxide ( $H_2O_2$ ) induce DNA fragmentation in cells, causing inflammation and tissue damage[37]. In sports medicine, there have been many reports that physical stress is evaluated by changes in SOA, an index of the immune capacity of non-specific neutrophils[39-41].

The chemiluminescence method is easy to perform, requiring only a blood sample and enabling the quantification of ROS produced by neutrophils[38-40]. This method is useful because the collected biological samples can be measured simultaneously under the same conditions. It detects ROS using chemiluminescent probes (*i.e.*, lucigenin and luminol).

$O_2^-$  is produced by neutrophils. Its formation is mediated by NADPH oxidase, which is activated by phagocytosis, and converted to  $H_2O_2$  by superoxide dismutase[36,37]. Furthermore, each ROS has a different oxidation potential. When neutrophils release azurophilic granules containing myeloperoxidase (MPO),  $H_2O_2$  reacts with  $Cl^-$  to produce hypochlorous acid (HOCl), which is a more powerful oxidant than  $H_2O_2$ [36,37]. Lucigenin is associated with the detection of  $O_2^-$ , whereas luminol reflects the total amount of ROS produced by MPO, including HOCl[36,37]. Thus, the oxidative stress measured by luminol-dependent chemiluminescence is generally considered more toxic as it reflects all types of ROS in a sample.

To measure SOA in the peripheral blood, zymosan, an activator of the alternative complement pathway found in *Saccharomyces cerevisiae*, was opsonized in serum samples of patients who underwent ESD. Lucigenin- and luminol-dependent chemiluminescence were used to detect and quantify the ROS secreted by the neutrophils of a healthy volunteer against these opsonized zymosan molecules[36,37,

**Table 1 Perioperative changes in resting energy expenditure, resting energy expenditure/basal energy expenditure, and stress factors by endoscopic submucosal dissection**

	ESD preoperative state	ESD postoperative state
Gastric cancer		
REE (kcal)	1170.3 ± 209.0	1238.4 ± 235.5 <sup>c</sup>
REE/BEE	0.96 ± 0.11	1.03 ± 0.14 <sup>c</sup>
Stress factor		1.07
Colorectal cancer		
REE (kcal)	1107.0 ± 204.4	1139.9 ± 185.2 <sup>c</sup>
REE/BEE	0.96 ± 0.12	1.00 ± 0.13 <sup>c</sup>
Stress factor		1.06

<sup>c</sup>*P* < 0.001 *vs* endoscopic submucosal dissection (ESD) preoperative state.

Data are presented as mean ± SD. The stress factor on ESD in the postoperative state was computed by setting the stress factor on the day of ESD to be 1.0. ESD: Endoscopic submucosal dissection; REE: Resting energy expenditure; BEE: Basal energy expenditure.

42]. The emission curve measured by the chemiluminescence method was evaluated using an autoluminescence analyzer, focusing on the peak height and the area under the curve. For each measurement, the serum of a healthy volunteer was used as the standard value for ROS production. The results of the chemiluminescence method were calculated as a percentage compared to standard serum levels[36,37, 42]. Changes in SOA, measured by the chemiluminescence method, are valuable in assessing the physical stress associated with endoscopic treatment of early-stage cancer[42].

As shown in Table 2, a significant increase in the peak height and area under the curve of lucigenin-dependent chemiluminescence was observed for gastric ESD on POD 1 and 4. Both of these percentages tended to decrease on POD 4 compared with those on POD 1. However, there was no significant increase in these parameters for luminol-dependent chemiluminescence on POD 1 and 4. In contrast, for colorectal cancer, the peak height and area under the curve of lucigenin-dependent chemiluminescence showed no significant difference in POD 1 but a significant increase in POD 4 compared with those on the day of ESD. Furthermore, no significant changes in these parameters were noted on luminol-dependent chemiluminescence during the perioperative period, similar to gastric ESD[42]. In contrast, previous studies on patients undergoing gastrointestinal surgery with different degrees of surgical stress found higher SOA measured by luminol-dependent chemiluminescence[43,44]. The difference in SOA between ESD and surgery suggests that ESD is less invasive.

Based on the results of the chemiluminescence method, changes in SOA during the perioperative period of ESD were associated with a slight increase in the production of less toxic ROS. The difference in the peak height of SOA between gastric and colorectal ESD, measured by lucigenin-dependent chemiluminescence, may be related to the difference in stimulation to post-ESD ulcers. Both gastric and colorectal ESD patients started eating meals 2 d after the procedure. Post-gastric ESD ulcers are immediately stimulated by gastric acid and oral bacteria. In cases of colorectal ESD, feces are defecated by intestinal tract-cleaning compositions, and the population of gut microbiota is markedly reduced before ESD. Therefore, SOA may have increased significantly on POD 4 because the post-ESD ulcer is stimulated by feces after resuming meals.

## CONCLUSION

The current review summarizes the methods to assess the physical invasiveness of ESD in patients based on changes in REE measured using an indirect calorimeter and SOA measured by the chemiluminescence method. These methods are easy to perform and non-invasive, even in older patients. In addition, the results showed that changes in perioperative physical stress differed between gastric and colorectal ESD. The increases in perioperative REE and SF after ESD were lower than those reported for surgery. The perioperative changes in SOA after ESD were associated with slight increases in the production of less toxic ROS. These findings suggest that ESD does not cause significant physical stress.

In recent years, laparoscopic and less-invasive surgeries have become widespread. Further multicenter studies are needed to compare the changes in REE and SFs between ESD and less-invasive surgeries. There are also new procedures for endoscopic therapies, such as peroral endoscopic myotomy (POEM) and laparoscopic endoscopic cooperative surgery (LECS). In the future, it will be important to evaluate the physical stress of these procedures as well.

**Table 2 Endoscopic submucosal dissection perioperative changes in serum opsonic activity measured by lucigenin- and luminol-dependent chemiluminescence**

	The day of ESD	POD1	POD4
Gastric cancer			
Lucigenin			
Peak height (%)	100.6 (71.4-178.5)	106.3 <sup>b</sup> (78.5-282.4)	105.9 <sup>b</sup> (77.6-214.4)
Area under the curve (%)	98.4 (48.7-184.7)	105.6 <sup>b</sup> (64.8-265.3)	103.5 <sup>b</sup> (66.0-222.8)
Luminol			
Peak height (%)	98.4 (62.7-168.3)	100.1 (63.6-199.2)	99.6 (69.7-186.6)
Area under the curve (%)	99.7 (68.2-155.7)	102.6 (68.0-182.9)	101.8 (73.2-170.7)
Colorectal cancer			
Lucigenin			
Peak height (%)	102.3 (71.4-132.7)	105.2 (61.8-137.4)	105.3 <sup>a</sup> (65.7-137.1)
Area under the curve (%)	99.4 (68.2-134.3)	101.9 (60.9-140.0)	102.6 <sup>a</sup> (64.0-139.7)
Luminol			
Peak height (%)	97.3 (70.9-132.5)	100.2 (76.6-132.0)	99.9 (74.9-134.7)
Area under the curve (%)	99.1 (75.8-131.4)	102.1 (78.3-128.6)	102.3 (77.4-134.3)

<sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$  vs the day of endoscopic submucosal dissection.

Data are expressed as median with interquartile range in parenthesis. ESD: Endoscopic submucosal dissection; POD: Postoperative day.

## FOOTNOTES

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