



Cohort Study

Preoperative heart rate variability analysis is as a potential simple and easy measure for predicting perioperative delirium in esophageal surgery

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ABSTRACT

Background: Delirium is one of the most common but severe perioperative complications. Autonomic activity evaluated by heart rate variability (HRV) has been recently reported as a useful tool for prediction and for early detection of delirium in acute care medicine, especially in postoperative intensive care unit (ICU) patients. We hypothesized that HRV, by 3-lead electrocardiogram (ECG), one day prior to surgery might correlate with the presence of postoperative delirium.

Materials and methods: This study was cohort prospective pilot study. We measured preoperative HRV and postoperative delirium in patients who underwent surgery for elective esophageal cancer. ECG of the participants was performed for 10 min 6–12 h preceding surgery. Postoperatively, patients were admitted to the ICU or critical care unit and stayed for at least 3 days. Delirium was diagnosed by psychiatrist rounds twice a day.

Results: Delirium was assessed for 3 days after surgery and 30 patients performed the study. Seven patients developed delirium during their ICU stay, while the remaining twenty-three did not. After HRV analysis, the preoperative high frequency power in delirium patients was significantly lower than that in non-delirium patient. Other parameters of HRV, including lower frequency power, total power and the ratio showed no statistically significant difference between the groups.

Conclusion: The results of current study demonstrated that preoperative measurement of HRV may be a useful predictor of delirium. Further investigation could pave the way to a non-invasive, minimally stressful method of predicting postoperative delirium.

1. Introduction

Delirium is one of the most common and severe postoperative complications [1]. The prevalence of delirium in acute care patients has been reported as 22–41% [1,2]. Delirium can develop not only in acute care patients, but also in the general population as a component of chronic diseases including cognitive dysfunction and dementia [3]. Up to the 80% of patients received intensive care are developing delirium in acute care medicine, especially in postoperative intensive care unit (ICU) [4,5]. Postoperative delirium is associated with poor outcomes including longer hospitalization, greater costs, functional decline, postoperative cognitive dysfunction and higher mortality [6].

Historically, delirium has been considered as a psychological and

pathophysiological disorder. Psychologists often identify acute mental abnormality as delirium using the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5). Matsushima et al. [7] reported that electrooculography (EOG) analysis provides quantitative and successive evidence for assessment of delirium. However, perioperative successive evaluation of delirium is burden task in daily clinical practice, particularly in the ICU. It is important to identify an examination method that can be performed easily before the starting of acute or intensive care in consideration of each patient's factor. Preoperative assessment should be mandatory [4,8,9]. Moreover, if it can be predicted by preoperative measurement which patients will have postoperative delirium, prevention of developing delirium might appropriately save the medical cost.

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Therefore, we conducted a pilot study to evaluate preoperative predictors of postoperative delirium in continuous measurements from the day before surgery. Perioperative heart rate variability (HRV) is easily automatically calculated from the fluctuation of RR intervals on electrocardiogram (ECG). We hypothesized that HRV measured on a 3-lead ECG from the day before surgery may correlate with the development of postoperative delirium.

2. Materials and methods

2.1. Trial registration

This study was approved by Tokyo Medical and Dental University Review Board (M2016-036-02; trial registration no.: UMIN000022355). Written informed consent was obtained from all participants. Patients aged 20–90 years scheduled to undergo esophageal cancer surgery were prospectively enrolled into the study. This study is cohort, single center, prospective pilot study. The work has been reported in line with the STROCSS criteria [10]. Sample size was calculated as 19 with 95% confidence level and 5% margin of error. The incidence of postoperative delirium was set to 16% with reference to Ref. [11]. Total patients needed 38. Since 50 cases of esophageal cancer undergo surgery annually, the data acquisition period was planned to be one year. There were fewer operations than planned, and 36 cases were entered.

2.2. Preoperative assessments

Preoperative ECG and EOG data were obtained 6–12 h preceding surgery, or the day of the surgery. Three lead ECG was recorded with 1000 Hz sampling rate for 10 min using LabChart (ADINSTRUMENTS, Dunedin, New Zealand). EOG data was recorded by using BlueGain EOG Biosignal Amplifier (CAMBRIDGE RESEARCH SYSTEMS, Rochester, UK) for 6 min.

ECG data was processed and analyzed using the Heart Rate Variability Add-On for LabChart (ADINSTRUMENTS). The 5 min of data showing the least noise were extracted from 10 min of raw ECG data. Every ectopic beat was eliminated and automatically supplemented with an average beat. Low-frequency power (LF), high-frequency power (HF), and the ratio thereof (LF/HF) were calculated. LF is related to sympathetic and parasympathetic nerve activity. HF correlates with parasympathetic nerve activity. LF/HF reflects sympathetic nerve activity.

2.3. Anesthesia and postoperative care

Epidural catheters were placed for analgesia, and general anesthesia was induced with propofol, fentanyl and rocuronium. Anesthesia was maintained with propofol or sevoflurane, remifentanyl and epidural administration of ropivacaine. Continuous epidural infusion of 1-mg morphine, 500-mg levobupivacaine and 5-mg droperidol (total of 300 ml at 4 ml/h) was administered over a 75-h postoperative period. Postoperatively, patients were admitted to the ICU or critical care unit and stayed for at least 3 days.

2.4. Postoperative evaluations

Patients underwent daily psychiatric examinations during their stay in the ICU. The patient was diagnosed with delirium in a psychiatrist's rounds in the morning and evening after surgery in the ICU. They evaluated patients using confusion assessment method for the ICU (CAM-ICU) and 6 min EOG recordings. Since EOG helps diagnose delirium reported by Matsushima et al. [7], EOG waveforms were also used in this study to help psychiatrists diagnose delirium. EOG was measured in the morning and evening for 3 days after surgery. The diagnosis of delirium based on the EOG pattern was made by the same psychiatrist who was in charge of interviewing the patient. Recruitment ends up to 3 days after surgery.

2.5. Statistical analysis

Statistical analysis was performed using R software (version 3.4.3; R Development Core Team). Data are presented as mean \pm SD. The two groups were compared using the Wilcoxon Rank-Sum Test and Chi-squared test. A *P*-value less than 0.05 was considered significant.

3. Results

In total, 36 patients agreed to participate, 30 of whom completed the study and were included in the analysis. Seven patients experienced delirium (delirium group) and twenty-three did not (non-delirium group) (Fig. 1). Of the 36 patients enrolled, 2 withdrew agreement. Four patients dropped out due to medical problems such as reoperation, continuous atrial fibrillation and reintubation for 3 days after surgery. HRV cannot be measured with atrial fibrillation.

The patients' demographic data are shown in Table 1. The average age was significantly higher in the delirium group compared to the non-delirium group (76.3 ± 6.5 and 69.6 ± 6.7 years, respectively).

The preoperative HRV data are shown in Table 2. HF power in the delirium group was significantly lower than in the non-delirium group (57.4 ± 93.9 and 264 ± 525 , respectively, $P < 0.05$). LF power and LF/HF ratio did not show significant differences between the two groups.

4. Discussion

No published study has used preoperative 3-lead ECG simple recording 6–12 h preceding surgery to predict postoperative delirium; data on the reliability of HRV to predict delirium in the ICU are still limited [12]. Therefore, the findings of the present study, which assessed the usefulness of ECG before surgery, have shown possibility for improving the perioperative management of patients prone to delirium.

HRV is calculated from the fluctuation of RR intervals on ECG, which reflects the autonomic effects on the cardiovascular system. A previous study suggested that dynamic parameters of HRV in psychophysiological stress are sensitive and practical for a diagnosis of schizophrenia [13]. In addition, a recent study suggested that changes in the HRV of ICU patients may be related to the development of delirium [14,15]. HRV measurement is very easy and non-invasive, so postoperative continuous HRV measurement is useful to understand major changes in the autonomic nervous system, such as infection, pain, insomnia, or delirium. HF power reflects parasympathetic nerve activity [16]. The significant decrease of HF power the day before surgery in delirious patients indicates that preoperative impairment of the autonomic nerve system might be related to postoperative delirium. Although there were large variations, there was a significant difference in HF power.

Ernst et al. [15] reported a significant difference in preoperative HRV between hip fracture patients with and without postoperative delirium. They demonstrated increased standard deviation of the RR interval (SDNN), total power and HF power, and decreased LF power, in preoperative ECG of delirious patients. In addition, Ernst's study showed that preoperative HRV was associated with postoperative complications [17], and that it was also associated with stroke, myocardial infarction, and pneumonia six months after surgery [18]. They [18] concluded that preoperative HRV analysis might be a simple and effective tool for identifying and following up at-risk patients.

In this study, the incidence of postoperative delirium after surgical treatment of esophageal cancer was 28%. Previous studies have reported incidences of 16% [11] and 50% [4] following the same surgery. The rate varies depending on how the delirium is evaluated and the accuracy of the method used. For example, the onset of delirium after cardiac surgery varies from 16% [19] to 48.5% [20].

As previously reported, EOG analysis might contribute accurate detection of delirium [7,21]. In our study, two psychiatrist diagnosed delirium using DSM-5 while referring EOG in addition to CAM-ICU, the most popular assessment tool. Compared to diagnosis of delirium only

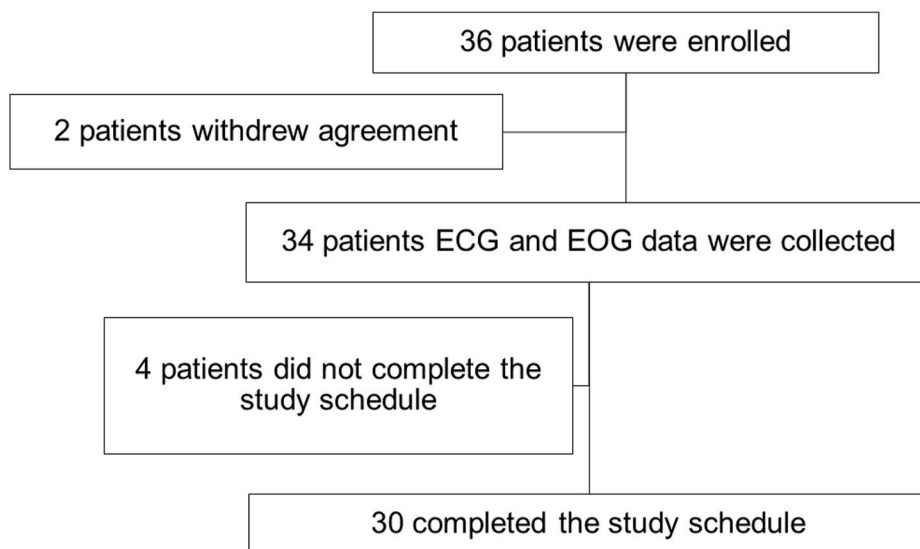


Fig. 1. Flowchart of subjects included in the study.

Table 1
Preoperative and intraoperative characteristics of patients' delirium and non-delirium groups.

Characteristic	Delirium group, N = 7	Non-Delirium group, N = 23	P value
Age, mean (SD)	76.3 (7)	69.6 (7)	<0.05 with t-test
Men, n (%)	6 (86)	15 (65)	
Duration of surgery, mean (SD)	7.6h (1.3h)	7.9h (1.4h)	
Duration of anesthesia, mean (SD)	9.1h (1.3h)	9.4h (1.8h)	
Intra-operative bleeding (g), mean (SD)	598 (324)	522 (237)	
Score of preoperative MMSE, mean (SD)	27.9 (2.5)	27.5(2.7)	
ASA physical status, mean (SD)	2.4 (0.5)	2.3 (0.5)	
Charlson Comorbidity Index, mean (SD)	2.9 (0.9)	2.8 (1.0)	

MMSE: Mini-Mental State Examination, ASA: American Society of Anesthesiologist.

Table 2
Preoperative Heart rate variability (HRV) data between delirium and non-delirium patients.

		LF Power	HF Power	LF/HF
Delirium group (n = 7)	Average	57.7	57.4	4.1
	SD	31.1	93.9	4.9
Non-Delirium group (n = 23)	Average	303	264	2.2
	SD	444	525	2.4
Wilcoxon Rank-Sum Test	P value		P < 0.05	
Normal value	Average	1170	975	1.5–2.0
	SD	416	203	

HRV: heart rate variability, LF: low-frequency, HF: high-frequency, LH/HF: ratio low-frequency power/high frequency power.

by CAM-ICU, we believe that the comprehensive diagnosis of delirium by a psychiatrist can diagnose delirium at an earlier stage.

We should address the limitation of the current study. The low HF power of delirium patients may be due to their tendency to be older than patients who do not experience delirium. Aged people showed lower HF power [22,23]. Due to the small sample size of this study, it was not possible to analyze the effects of age. In subsequent studies, we will aim

to adjust analyses of HF power for age.

5. Conclusion

Preoperative HRV analysis might predict the onset of delirium undergone esophageal cancer surgery. Since perioperative HRV analysis, which is calculated using routine three-lead ECG, is a non-invasive, minimally stressful method, it could be used continuously during perioperative period and might contribute to early detection of post-operative complications.

Ethical approval

Tokyo Medical and Dental University Review Board (M2016-036-02, 6/28/2016).

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Author contribution

ME and MS designed and conducted this study, ME, MS, MM, YA and EM collected and analyzed the data. ME, MS and YA wrote the manuscript. All authors approved the final manuscript.

Consent

Explained to patients and obtained written consent before starting the study.

Registration of research studies

Name of the registry: The development using EEG for prediction of delirium

Unique Identifying number or registration ID: UMIN000022355
 Hyperlink to your specific registration (must be publicly accessible and will be checked): https://upload.umin.ac.jp/cgi-bin/ctr_e/ctr_view.cgi?recptno=R000025771.

Guarantor

Maiko Satomoto is the Guarantor of this work.

Provenance and peer review Paragraph

Not commissioned, externally peer-reviewed.

Declaration of competing interest

None.

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