Anesthesiology
1996; 84:1068–76

Alterations in Spectral Characteristics of Heart Rate Variability as a Correlate of Cardiac Autonomic Dysfunction after Esophagectomy or Pulmonary Resection

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Background: Both esophagectomy and pulmonary resection are associated with postoperative cardiac complications, partly because of autonomic perturbations involving the heart. This study was undertaken to determine whether heart rate variability (HRV), employed as an index of cardiac autonomic function, changes in patients undergoing esophagectomy or pulmonary resection.

Methods: Electrocardiographic RR intervals were measured in 20 esophagectomized patients, 10 undergoing right and 10 undergoing left pulmonary resection on the preoperative day as baseline data and on postoperative days 1, 3, 5, 7, 14, and 30. Instantaneous heart rate was calculated every 250 ms from 416-s data of RR intervals. Power spectra of HRV for 128 s were computed using a fast Fourier transform and normalized by squared mean heart rate. The averaged ten sets of normalized HRV power were obtained by integrating the following power spectral bands: the low-, (0.06–0.10 Hz), high- (0.15–0.40 Hz), and total-frequency regions (0.01–0.40 Hz).

Results: In the esophagectomy group, mean low-, high-, and total-frequency HRV power decreased after surgery to 17%, 6%, and 15% of their preoperative values, respectively, and these indexes remained suppressed for up to 30 days. After right pulmonary resection, low- and total-frequency HRV power decreased through 30 and 7 postoperative days, respectively. In the left pulmonary resection group, HRV remained unchanged. In the esophagectomy group, mean (±SEM) heart rate increased from 78 (±3) bpm to more than 90 bpm throughout the study, and body temperature from 36.5 (±0.1)°C to more than 37.0°C through 14 postoperative days. Heart rate and body temperature remained increased for 3 days after pulmonary surgery. Mean arterial pressure remained unchanged in the three surgical groups.

Conclusions: Reductions in HRV after esophagectomy or right pulmonary resection indicate a substantial and prolonged surgical injury to the autonomic nervous control of pulse rate. (Key words: Measurement techniques: electrocardiography; heart rate. Parasympathetic nervous system: heart rate variability. Sympathetic nervous system, autonomic nervous system: cardiac dysfunction; heart rate variability. Surgery: esophagectomy; pulmonary resection.)

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Received from the Department of Anesthesiology, Nagoya University School of Medicine, Nagoya, Japan. Submitted for publication June 5, 1995. Accepted for publication January 5, 1996. Supported in part by a grant-in-aid for Developmental Scientific Research from the Ministry of Education, Science and Culture, Japan (#2557060). Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 26–30, 1991, and the International Anesthesia Research Society, Clinical and Scientific Congress, Honolulu, Hawaii, March 10–14, 1995.

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SPONTANEOUS beat-to-beat fluctuation in heart rate, termed heart rate variability (HRV), reflects ongoing modulation of sinus node activity through centrally mediated neural mechanisms.[1] Heart rate variability can be quantified by power spectral analysis, which calculates the frequency content of time-varying signals derived from noninvasive electrocardiographic (ECG) signals. The power spectral component associated with respiratory sinus dysrhythmia has been solely attributed to parasympathetic activity.[2,3] This peak is respiration related, occurring at a high-frequency band ranging between 0.15 and 0.35 Hz. The second component centered at approximately 0.1 Hz is thought to be associated with oscillations of the carotid baroreceptor reflex system.[4,5] The third peak occurs at frequencies less than 0.05 Hz, and perhaps it is attributed to influences of the peripheral vasomotor tone in relation to thermoregulation and renin-angiotensin control systems.[1] The second and third spectral components of HRV are mediated by both the sympathetic and parasympathetic nervous systems.[1,5] Thus, analysis of HRV has been employed as one of noninvasive measures to detect cardiac autonomic nervous system (ANS) dysfunction after surgery.[6,7]

Resection of the thoracic esophagus with right thoracotomy and three-field (neck, thorax, and abdomen) lymphadenectomy can result in various postoperative circulatory complications such as dysrhythmia, myocardial infarction, and heart failure.[8–10] These complications might be partly caused by autonomic denervation of the heart arising from surgical injury to the cervical and thoracic ANS, because the autonomic nerves may be accidentally or deliberately injured during esophagectomy. Assessment of alterations in pulse rate control during the postsurgical period may thus yield useful information about the influence of esophagectomy on postoperative cardiac ANS function.

Supraventricular dysrhythmia is well described and frequently observed after pulmonary surgery.[11–13] The potential causes of these dysrhythmias after lung resection may be due to impairment of cardiac ANS function associated with possible injury to the cardiac autonomic nerves, in addition to increased pulmonary vascular resistance, retraction and trauma to the heart, right heart distension, postoperative hypoxemia, and pain.[14] Postoperative HRV in patients undergoing pulmonary resection may, as a result, be altered. Thus, it is important to provide data from a control group of patients undergoing thoracotomy but not esophagectomy to separate any specific effects of esophagectomy from those of thoracotomy itself because resection of the thoracic esophagus requires right thoracotomy.

The purpose of this study was to determine whether HRV as an index of the cardiac ANS function changes in patients undergoing esophagectomy or pulmonary resection.

Materials and Methods

The study was approved by the Department Medical Ethics Committee and written informed consent was obtained from each patient. We studied 20 patients with thoracic esophageal cancer who underwent elective esophageal resection and reconstruction with lymph node dissection of the neck, thorax, and abdomen. We also studied 20 patients with lung cancer who required pulmonary resection. Patients with postoperative anastomotic leak, systemic infection, or prolonged dysrhythmia during the follow-up period were not included in this study.

A standardized general anesthetic technique was used during surgery, consisting of 5 $mg \cdot kg^{-1}$ thiamylal sodium intravenously for induction and 0.5–1.5% isoflurane or 2–3% sevoflurane and 67% nitrous oxide in oxygen for maintenance of anesthesia. Muscle relaxation was achieved with 0.1 $mg \cdot kg^{-1}$ pancuronium or vecuronium, with additional 2-mg doses given up to the end of surgery. To provide analgesia after emergence from anesthesia, 2 or 3 mg morphine or 0.1 mg buprenorphine in 10 ml saline was given *via* a preoperatively inserted thoracic epidural catheter twice a day as required.

Resection of the thoracic esophagus, lymph node dissection, and reconstruction with right thoracotomy and laparotomy were carried out by two surgical groups in a one-stage procedure. In the intensive care unit, mechanical ventilation (7200a, Puritan-Bennett, Carlsbad, CA) was continued in esophagectomized patients until cough reflex recovered and maximal expiratory pressure exceeded more than 40 cm H_2O, then the trachea was extubated. When cardiopulmonary function was stable and no evidence of infection was confirmed, the patient was transferred to the ward. The same anesthetic technique and postoperative analgesia were used in patients undergoing pulmonary resection except that the trachea was extubated after emergence from anesthesia in the operating room and transferred to the intensive care unit. Perioperative arterial *p*H, arterial oxygen tension, and arterial carbon dioxide tension were measured using a blood gas analyzer (ABL300, Radiometer, Copenhagen, Denmark) for 7 postoperative days.

Data Collection

While subjects were resting quietly and supine, the surface ECG (standard limb lead II), with stable baseline and well differentiated R wave was monitored for periods of longer than 10 min. The stationary ECG segments for 416 s chosen for power spectral analysis had the fewest alterations in measured heart rate because of artifacts (such as electrical noise or arm and/or chest muscle contractions) by visual inspection of RR-trendgraph in the computer display.

The ECG monitor (BP306, Colin Corporation, Komaki, Japan) has flat frequency characteristics ranging between 0.05 and 100 Hz. Successive RR intervals were precisely measured as follows: ECG signal was fed to an R wave detector circuit (custom made, NEC-Sanei, Tokyo, Japan), which generated a square pulse synchronous with the upward point of each R wave. Using this pulse-generation method, the timing of each pulse wave was minimally influenced by respiratory changes in QRS amplitude and duration, and baseline drift arising from motion artifact and impedance changes of electrodes. The triggered pulse wave was detected by a universal counter board (UCM-4398BPC, Micro Science, Tokyo, Japan) with an accuracy of 1 ms plugged in an expansion chassis (Note-pack (98)-2A, Contec, Tokyo, Japan) connected to the computer (PC9801NS/E, NEC, Tokyo, Japan) for measuring electrocardiographic RR intervals and storing these as a series for subsequent spectral analysis.

Radial arterial blood pressure was invasively measured when the patient was in the intensive care unit. In the ward, arterial blood pressure was determined with an oscillometric device (BP306, Colin Corporation, Komaki, Japan) at the end of each measurement. Body temperature was measured on the axillary skin surface using a digital thermometer (C21, Terumo, Tokyo, Japan) that requires no user calibration and has an accuracy of ±0.01°C.

Postoperative dysrhythmias in the intensive care unit were continuously monitored with ECG display. In the ward, postoperative dysrhythmia was diagnosed when we measured postoperative RR intervals for this study.

We measured data on the preoperative day as baseline data and 1, 3, 5, 7, 14, and 30 days after surgery. The measurements were performed in the afternoon (12:00 PM to 6:00 PM), except for the first postoperative day, when data were sampled after 24 h from the end of surgery to avoid the reductions in HRV due to residual effects of anesthetics. The measurement was done at least after 4 h after epidural analgesia and avoided during dysrhythmia.

Data Processing

Instantaneous heart rate was constructed as 1/RR interval length and sampled at 4 Hz for 416 s using the method described by de Boer *et al.*,[15] and band-pass filtered between 0.01 and 0.89 Hz by a digital filter. Each 128-s epoch was analyzed with a fast Fourier transform, and the squared magnitude, termed power spectral density, was computed.[16] A Hanning window was applied in the time domain to diminish the height of side lobes.[16] Power spectra of HRV were updated every 32 s. Averaged power spectra of HRV were calculated from ten sets of power spectral HRV data, which meant 416-s periodgram. The application of averaged power spectra of HRV can obtain a consistent power spectrum estimate of HRV by reducing the variance of estimated spectra.[16] To consider the fluctuations in heart rate relative to the mean heart rate of each subject, the power spectra of heart rate that had units of squared heart rate (beats per minute) per hertz are normalized by squared mean heart rate as in previous studies.[1,17,18] Normalizing for heart rate, acquired by division by the squared mean heart rate, makes power spectral density independent of the units of measurement and expresses fluctuations as fractional variation about the mean heart rate. The integral over a specific frequency band will thus be unitless. The spectral areas within each measurement were integrated and divided into low-frequency (LF: 0.06–0.10 Hz) and high-frequency power spectral areas (HF: 0.15–0.4 Hz).[19] The total-frequency area of power spectrum was obtained by integrating the entire power spectral region from 0.01 to 0.4 Hz.[19]

Statistical Analysis

Data are presented as mean ± SEM. Statistical significance of differences among three groups were assessed using Fisher's exact test for binomial data (gender) and the unpaired *t* test for continuous data (age). Differences between baseline values and values at postoperative periods in hemodynamic and HRV values were compared by repeated-measures analysis of variance and followed by Bonferroni procedure multiple comparisons. Some data on the 30th day after surgery were lost because some patients were discharged or transferred to other hospitals. The differences between the preoperative baseline data and the data on the 30th day after surgery were compared within the patients who had been admitted to the hospital until the 30th day after surgery. Statistical significance was assumed for $P < 0.05$.

Results

Patient demographic data for each group are listed in table 1. Fourteen of 20 esophagectomized patients, 8 of 10 patients undergoing right pulmonary resection and 6 of 10 patients undergoing left pulmonary resection had stayed in the hospital until the 30th day after operation. The patients undergoing left pulmonary resection were significantly older than those undergoing esophagectomy. The differences of the mean ages between the esophagectomized patients and the right pulmonary resection patients and between the two lung surgery groups were not significant. The distributions of gender of the patients in three groups were similar. Preoperative medications varied among three groups. There were two patients with diabetes, which was well controlled with dietary therapy, who showed no signs of autonomic dysfunction arising from diabetic neu-

Table 1. Patient Demographic Data

	Esophagectomy	Right Pulmonary Resection	Left Pulmonary Resection
n	20	10	10
Gender (M/F)	18/2	8/2	6/4
Age (yr)	54 ± 2	58 ± 5	64 ± 2
Patients with preoperative complications (n)			
Hypertension	2	1	4
Dysrhythmia	1	1	
DM	1		1
IHD*	1		1
CNS†	1	1	1
Patients with preoperative medication (n)			
Calcium-channel blockers	1		3
ACE inhibitor			1
Antidepressant		1	
Aspirin	1		
Mexiletine		1	
Dirazep			1
Dipyridamole		1	

Data are mean ± SEM.

DM = diabetes mellitus; IHD = ischemic heart disease; CNS = central nervous system disorders; ACE = angiotensin converting enzyme.

* Preoperative IHD include one old myocardial infarction (esophagectomy) and one angina pectoris (left pulmonary resection group).

† Preoperative CNS include one cerebral infarction (esophagectomy), one neurosis (right pulmonary resection group), and one cerebral infarction (left pulmonary resection group).

ropathy. Mean duration of mechanical assisted ventilation in esophagectomized patients was 6 ± 1 postoperative days ranging from 2 to 20 days after surgery. Postoperative pain was controlled by epidural narcotic administration. The mean duration of the use of epidural opioids in the patients undergoing esophagectomy, right pulmonary resection and left pulmonary resection was 6, 6, and 5 postoperative days, respectively.

Postoperative cardiac dysrhythmias occurred in three patients in the esophagectomy group (atrial fibrillation), two patients in the right pulmonary resection group (supraventricular premature contraction), and one patient in the left pulmonary resection group (atrial fibrillation). Postoperative atrial fibrillation was initially treated with administration of 0.25 mg to 0.5 mg digoxin and/or sodium channel blocker (aprindine 100 mg). Digitalis was administered in the three patients undergoing esophagectomy. Serum concentration of digoxin was maintained from 0.6 to 0.8 ng/ml. We obtained HRV after atrial fibrillation was successfully converted. Supraventricular premature contraction in patients undergoing right pulmonary resection was treated with 100 mg oral mexiletine every 8 h.

Perioperative hemodynamic values are listed in table 2. There were no differences among three groups with respect to the baseline hemodynamic values. After esophagectomy, resting heart rate increased significantly to more than 90 bpm throughout the study. In the right pulmonary resection group, heart rate increased on the third postoperative day. In the left pulmonary resection group, heart rate increased on the first day after surgery. Mean arterial pressure in three groups did not differ during perioperative periods.

Respiratory rate remained unchanged except for the first day after surgery in the patients undergoing esophagectomy who were mechanically ventilated (table 2). Perioperative changes of body temperature are summarized in table 2. Body temperature in the esophagectomized patients increased significantly through 14 postoperative days. In the right pulmonary resection group, body temperature increased through three postoperative days. Body temperature in the left pulmonary resection group increased significantly on the third day.

In three surgical groups, arterial blood gas tensions and *p*H were maintained within normal range. Arterial carbon dioxide tension ranged between 35 and 45 mmHg. The mean perioperative values of arterial oxygen tension showed more than 70 mmHg. Arterial *p*H was maintained between 7.39 and 7.45.

Typical examples of perioperative HRV changes are shown in figure 1. Esophagectomy and resection of right pulmonary lobes resulted in loss of spontaneous oscillations in pulse rate. Left pulmonary resection, on the contrary, did not change HRV. Alterations in HRV obtained through the perioperative periods in three groups are summarized in table 3. There were no significant differences among three groups in baseline HRV data. Postoperative LF, HF, and total-frequency components of HRV in esophagectomized patients were reduced significantly throughout the study. The LF/HF ratio in the esophagectomy group was significantly increased on the first postoperative day.

In the right pulmonary resection group, no significant change in HF component of HRV occurred postoperatively. The LF region of HRV declined significantly through the study, with a significant decrease in the LF/HF ratio through 3 days after surgery. Total-fre-

Table 2. Cardiorespiratory Data and Temperature Change in Patients Undergoing Esophagectomy or Pulmonary Resection

	Preoperative	Day 1	Day 3	Day 5	Day 7	Day 14	Day 30
HR (beats/min)							
Esophagectomy group	78 ± 3	105 ± 4*	105 ± 4*	105 ± 4*	103 ± 4*	98 ± 3*	92 ± 5*
Right pulmonary resection group	77 ± 5	86 ± 5	88 ± 3*	84 ± 3	85 ± 4	77 ± 3	77 ± 3
Left pulmonary resection group	78 ± 4	89 ± 4*	84 ± 4	80 ± 3	80 ± 2	74 ± 2	75 ± 2
MAP (mmHg)							
Esophagectomy group	90 ± 2	92 ± 2	94 ± 3	96 ± 2	98 ± 3	89 ± 2	86 ± 4
Right pulmonary resection group	93 ± 3	91 ± 4	88 ± 4	89 ± 4	86 ± 4	83 ± 4	84 ± 4
Left pulmonary resection group	92 ± 4	95 ± 4	94 ± 4	95 ± 4	99 ± 5	94 ± 3	98 ± 6
Respiratory rate (breaths/min)							
Esophagectomy group	18 ± 0.7	16 ± 0.8*	18 ± 0.8	20 ± 1.0	19 ± 0.8	19 ± 0.7	21 ± 0.8
Right pulmonary resection group	19 ± 0.8	19 ± 1.1	19 ± 1.0	19 ± 0.9	18 ± 0.9	19 ± 0.9	19 ± 0.9
Left pulmonary resection group	21 ± 1.1	20 ± 1.0	19 ± 0.8	19 ± 0.9	20 ± 0.4	21 ± 0.6	22 ± 1.7
Temperature (°C)							
Esophagectomy group	36.5 ± 0.1	37.8 ± 0.2*	37.4 ± 0.1*	37.2 ± 0.1*	37.0 ± 0.1*	37.0 ± 0.1*	37.0 ± 0.1
Right pulmonary resection group	36.1 ± 0.2	37.3 ± 0.2*	36.9 ± 0.2*	36.1 ± 0.2	36.5 ± 0.1	36.2 ± 0.2	36.5 ± 0.2
Left pulmonary resection group	36.2 ± 0.1	37.2 ± 0.2*	36.6 ± 0.3	36.4 ± 0.2	36.4 ± 0.2	36.4 ± 0.1	36.4 ± 0.1

Data are mean ± SEM.

HR = heart rate; MAP = mean arterial pressure.

* $P < 0.05$ *versus* preoperative data.

quency component of HRV in the right pulmonary resection group reduced significantly for up to 7 days after surgery. In contrast, HRV values and the LF/HF ratio remained unchanged in the left pulmonary resection group. There was no significant difference between patients undergoing right pulmonary resection and left

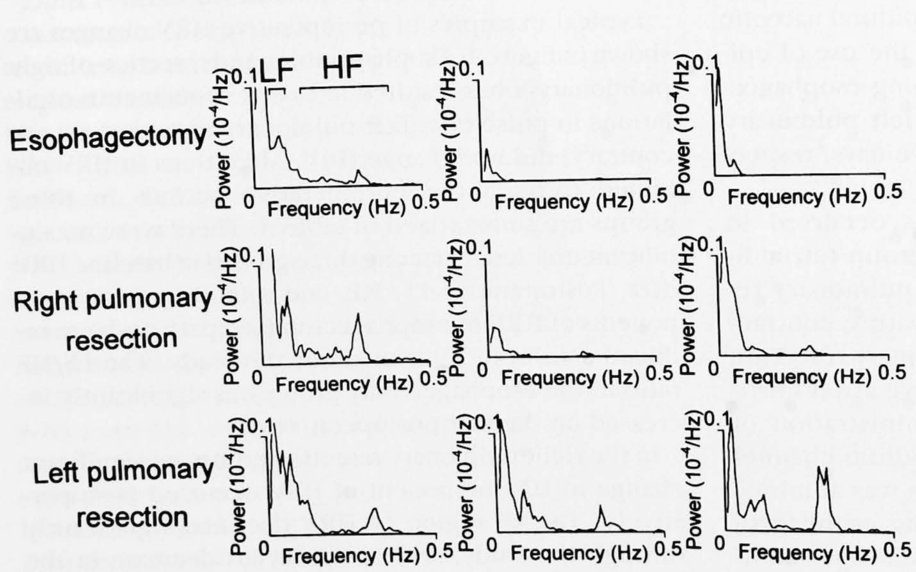

Fig. 1. Typical power spectral changes of heart rate variability in patients undergoing esophagectomy (51 yr, male), right pulmonary resection (57 yr, male), and left pulmonary resection (57 yr, male). In each panel, power spectrum of heart rate variability ($10^{-4} \cdot Hz^{-1}$) plotted up to the frequency of 0.5 Hz. Note the power spectral peak in the low range below 0.2 Hz (low frequency) and the respiratory peak located at the frequency of breathing (high frequency) in the upper left panel. Both esophagectomy and right pulmonary resection diminished heart rate variability. In contrast, left pulmonary resection did not alter heart rate variability.

Table 3. Perioperative Normalized Power Spectral Data of Heart Rate Variability in Patients Undergoing Esophagectomy or Pulmonary Resection

	Preoperative	Day 1	Day 3	Day 5	Day 7	Day 14	Day 30
Low-frequency HRV							
Esophagectomy group	0.18 ± 0.03	0.03 ± 0.01*	0.04 ± 0.01*	0.09 ± 0.03*	0.09 ± 0.03*	0.07 ± 0.02*	0.09 ± 0.04*
Right pulmonary resection group	0.16 ± 0.04	0.08 ± 0.02*	0.05 ± 0.01*	0.08 ± 0.02*	0.05 ± 0.01*	0.10 ± 0.02*	0.07 ± 0.02*
Left pulmonary resection group	0.14 ± 0.03	0.14 ± 0.04	0.12 ± 0.03	0.10 ± 0.02	0.10 ± 0.02	0.19 ± 0.06	0.20 ± 0.09
High-frequency HRV							
Esophagectomy group	0.24 ± 0.08	0.02 ± 0.01*	0.02 ± 0.01*	0.07 ± 0.03*	0.09 ± 0.05*	0.06 ± 0.02*	0.11 ± 0.03*
Right pulmonary resection group	0.15 ± 0.04	0.14 ± 0.07	0.17 ± 0.11	0.11 ± 0.04	0.14 ± 0.07	0.13 ± 0.05	0.10 ± 0.02
Left pulmonary resection group	0.09 ± 0.02	0.21 ± 0.13	0.11 ± 0.02	0.13 ± 0.04	0.18 ± 0.06	0.23 ± 0.08	0.18 ± 0.11
Total-frequency HRV							
Esophagectomy group	1.33 ± 0.21	0.20 ± 0.08*	0.32 ± 0.08*	0.75 ± 0.27*	0.88 ± 0.36*	0.52 ± 0.11*	0.82 ± 0.30*
Right pulmonary resection group	1.20 ± 0.22	0.68 ± 0.18*	0.51 ± 0.14*	0.61 ± 0.15*	0.59 ± 0.13*	0.82 ± 0.16	0.70 ± 0.10
Left pulmonary resection group	0.94 ± 0.15	1.21 ± 0.43	0.86 ± 0.19	1.04 ± 0.19	0.80 ± 0.14	1.37 ± 0.36	1.49 ± 0.62
Ratio of low-frequency HRV to high-frequency HRV							
Esophagectomy group	1.5 ± 0.4	2.9 ± 0.8*	1.5 ± 0.3	1.4 ± 0.3	1.2 ± 0.2	1.6 ± 0.3	1.2 ± 0.4
Right pulmonary resection group	2.3 ± 0.7	1.1 ± 0.4*	1.1 ± 0.4*	1.3 ± 0.4	1.5 ± 0.5	1.5 ± 0.4	1.2 ± 0.4
Left pulmonary resection group	1.6 ± 0.3	1.5 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	0.9 ± 0.3	2.0 ± 0.4	2.1 ± 0.6

Data are mean ± SEM.

HRV = heart rate variability.

* $P < 0.05$ *versus* preoperative data.

pulmonary resection, with respect to perioperative HRV data.

Discussion

It is not uncommon for the ANS to be affected during surgery. In particular, upper mediastinal lymphadenectomy requires the surgical manipulation of the parasympathetic nerves, and the parasympathetic nerve is occasionally resected during esophagectomy.[20] Even though the autonomic nerves are not distinctly resected during surgery, the vagus trunks and recurrent nerves frequently are exposed and retracted for neck and thoracic lymphadenectomy, suggesting increased susceptibility of the cardiac parasympathetic nerves to injury from surgical manipulations.

The right cardiac parasympathetic branch mainly attenuates the pacemaker activity of the sinoatrial node and decreases atrioventricular conduction.[21] In addition, the right cardiac vagus nerve has greater influence on the sinoatrial node than does the left vagus nerve.[22] Surgical injury to the right cardiac vagus nerve increases heart rate as a result. Right radical lymph node dissection, for example, causes tachydysrhythmia probably because of surgical trauma to the ANS.[23] Increased heart rate in the esophagectomized patient, thus, might be partly related to surgical injury to the cardiac branches of the right vagus nerve. Decreased HRV in patients undergoing esophagectomy also suggests a loss of the role in the pulse rate control mediated by the cardiac parasympathetic branch because genesis of HRV in the supine position is mostly controlled by the parasympathetic nerve.[18]

An LF component of HRV less than 0.15 Hz partly contributed to the sympathetic nervous activity in addition to the vagal activity.[1,5] Some sympathetic fibers often are removed or injured during the neck surgery.[24] In addition to the vagal injury, alterations in the efferent sympathetic outflows to the heart caused by radical neck dissection might account for postoperative cardiac dysrhythmias.[23]

Patients undergoing right pulmonary resection showed increased heart rate and decreased LF and total-frequency components of HRV postoperatively. Injury to the right cardiac autonomic nerves during the course of the right pulmonary resection can be expected, resulting in postoperative dysrhythmias and alterations in HRV, as we observed. In the current study, we did not examine whether reduced postoperative HRV is prognostic of adverse postoperative dysrhythmias because measurement of HRV was limited to the short period of each postoperative day, and hence HRV as a tool for predicting postoperative dysrhythmia remains to be elucidated.

Resection of the thoracic esophagus requires right thoracotomy. In the esophagectomy group, prolonged decreases in HRV may arise, in part, from the right thoracotomy with thoracic lymphadenectomy, in addition to the surgical injury to the cardiac autonomic nerves in the course of esophagectomy. Neuroendocrinal and metabolic responses to surgical tissue trauma also might exert additional prolonged depressant effects on postoperative HRV.[7]

The heart rate of autonomically denervated hearts (called the intrinsic heart rate) is typically higher than the heart rate of innervated hearts.[25] Equal surgical trauma to both sympathetic and parasympathetic nerves elicits relative sympathotonic status, manifesting as an increase in heart rate, because cardiac parasympathetic tone predominates over cardiac sympathetic tone.[25] Thus, postoperative increases in heart rate and prolonged decreases in HRV could be explained by injury to the cardiac parasympathetic nerve and/or both cardiac parasympathetic and sympathetic nerves during esophagectomy.

Studies in patients with transplanted denervated human hearts demonstrated a high prevalence of dysrhythmia throughout the transplant period because of sinoatrial node dysfunction and autonomic denervation, which resembles that of esophagectomized patients.[26,27] In this study, esophagectomized patients showed a significant postoperative increase in heart rate and three esophagectomized patients showed atrial fibrillation, which might partly be explained by surgical denervation with loss of the ANS control of the heart. Furthermore, denervation supersensitivity elicits nonhomogeneous autonomic and electrophysiologic changes and makes the heart more dysrhythmogenic.[28]

Although postoperative HRV remained significantly reduced even at the end of the 30-day follow-up period, recovery of HRV was evident in some observed HRV data. Reversible injury to the autonomic nerves could be attributable to mechanisms of denervation supersensitivity and/or compensatory recovery of autonomic nerves.[29,30]

The significant difference of the mean ages between the esophagectomized patients and the patients undergoing left lung surgery did not influence the results of this study because the preoperative baseline HRV data in three groups were similar.

Respiration influences the HF region of HRV, particularly during positive pressure ventilation.[31,32] Positive pressure ventilation was converted to continuous positive airway pressure mode within 3 days after surgery. Respiratory rate remained unchanged throughout the study except for the first postoperative day in patients undergoing esophagectomy. Influence of respiration on postoperative HRV thus might have mostly affected through 3 days after surgery, and was considered to be minimal.

Calcium channel blockers that were preoperatively administered in four patients had been reported to have little effect on HRV.[33] One patient undergoing left lung surgery had been receiving angiotensin-converting enzyme inhibitors, which may increase HRV.[34] Other concomitant antiarrhythmic drug was aprindine. The effect of aprindine on autonomic nerves was reportedly minimal.[35]

Therapeutic doses of digitalis drugs, which were administered in three esophagectomized patients, diminish sympathetic outflows,[36–38] and increase parasympathetic outflows.[37,38] Thereby digitalis might alter HRV toward increase in HF region of HRV. This study showed that all frequency components of HRV in the esophagectomized group reduced throughout the study, indicating that the postoperative use of digitalis appears to have little influence on our results. Thus, perioperative administration of cardiovascular drugs cannot elucidate the characteristics of postoperative changes in HRV in the current study.

Epidural morphine or buprenorphine usually was administered twice a day for pain relief. Intravenous pentazocine and hydroxidine were sometimes given for sedation in the intubated patients. Heart rate variability measurements were performed more than 4 h after the intravenous or epidural administration of sedative or analgesic drugs to avoid residual effects of sedative or analgesic drugs on HRV.

Spectral analysis was determined for a short (less than 10 min) period each day. Circadian rhythm of HRV could influence postoperative alterations in observed HRV,[39] though Hayano *et al* reported diurnal variations in HRV were unaffected by the time of day except for after food intake.[40] We therefore measured HRV only in the afternoon to avoid influences of night-day differences in HRV data.

Control of heart rate is related to the interaction of multiple systems, including the integrity and balance of sympathetic and parasympathetic outflows, multiple autonomic reflexes, adrenergic receptor sensitivity, postsynaptic signal transduction, and electrochemical coupling. Analysis of a short epoch of HRV data provides information only about autonomic modulation of the heart, and not information about direct autonomic nerve activity.[41] Despite these limitations of interpretation of HRV data, analysis of HRV may provide a useful noninvasive probe of ANS activities during and after surgery. Severity of surgical involvement could be assessed by perioperative HRV analysis, which provides useful information of ANS control of pulse rate during postsurgical periods.

In summary, our findings suggest that esophagectomy and right pulmonary resection cause prolonged decreases in HRV arising from possible surgical injury to the cardiac autonomic nerves.

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