Holter ECG monitoring of sympathovagal fluctuation during bronchoscopy

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Abstract

Background and Aims: The changes of autonomic nervous activity during bronchoscopic procedures are closely related to the development of cardiovascular complications. We aimed to evaluate the changes of autonomic nervous activity during bronchoscopic procedures using R-R interval variability from electrocardiograms (ECGs) obtained during diagnostic bronchoscopy.

Methods: Twenty-four patients who underwent bronchoscopy were included. Continuous ECG was recorded prior to, during and after the bronchoscopic procedure. Time and frequency domain analyses of heart rate variability were performed.

Results: Heart rate increased significantly after pre-medication compared with that before pre-medication and increased further during bronchoscopy. The coefficient of variation (CV_RR) values after pre-medication and during bronchoscopy were significantly higher than those before pre-medication (P = 0.031 and P = 0.041, respectively). The low frequency (LF) power decreased during bronchoscopy. LF powers obtained after bronchoscopy were significantly lower than those obtained before bronchoscopy (P < 0.041). The high-frequency (HF) power was found to be decreased during bronchoscopy. In particular, HF powers obtained after bronchoscopy were significantly lower than those obtained before bronchoscopy (P < 0.019). Although the LF/HF ratios increased after pre-medication, they decreased temporarily during the bronchoscope insertion.

Conclusions: This study shows for the first time that Holter ECG monitoring during diagnostic bronchoscopy was associated with activation of cardiac sympathetic and withdrawal of cardiac parasympathetic regulation, which may contribute to the occurrence of cardiac events during bronchoscopic procedures. So, Holter ECG monitoring during bronchoscopic procedures may confer reduction in cardiovascular events.

Key words
autonomic nervous system – bronchoscopy – heart rate variability – Holter ECG – pre-medications

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Introduction

Although generally regarded as a safe examination, diagnostic bronchoscopy is sometimes associated with serious adverse cardiovascular complications. Sixty percent of serious endoscopic complications and 50% of lethal complications during endoscopic procedures are associated with the presence of preexisting cardiopulmonary disorders (1). Furthermore, the incidence of endoscopic complications related to the use of
pre-medication has been reported to range from 0.068% to 5.4% (2, 3).

Hypoxemia and/or abnormal autonomic nervous activity during an endoscopic procedure are considered to be important risk factors for cardiovascular complications, including ventricular and atrial arrhythmias, bradyarrhythmias, myocardial ischemia, hypotension and hypertension (4, 5). It has been shown that the presence of autonomic nervous activity imbalance is associated with the development of lethal arrhythmias and sudden death (6, 7). Several studies have reported that enhanced sympathetic and/or decreased parasympathetic nervous activity induce cardiac arrhythmias (8, 9). It is well known that autonomic nervous activity imbalance following pre-medication and endoscopy is related to the development of cardiovascular complications (10).

Recently, the analysis of heart rate variability (HRV) has made it possible to evaluate the autonomic nervous system quantitatively, serially and non-invasively. Power spectral analysis of HRV, which measures sympathetic and parasympathetic activity, is useful in quantitatively evaluating autonomic nervous function. The changes in autonomic nervous activity during upper gastrointestinal endoscopy (11) and colonoscopy (12) have already been evaluated. However, no reports have evaluated autonomic activity during diagnostic bronchoscopy. Therefore, the aim of the present prospective study was to examine autonomic nervous activity during bronchoscopic procedures by analyzing HRV using time and frequency domain analyses.

Materials and methods

Subjects

After Institutional Ethics Committee approval and informed consent is obtained, 24 patients undergoing elective bronchoscopy at the Tokushima University Hospital, Japan, were prospectively included.

Flexible bronchoscopy and sedation

All flexible bronchoscopy were performed by physicians who had experience with bronchoscopic procedures and accreditation by the Japanese Endoscopic Society. Local anesthesia [nebulized lignocaine (4%)] of the upper airway tract and endobronchial local anesthetics was administered to all patients. The dose of midazolam was adjusted according to the patient’s age as follows: patients of 20–40 years of age received a dose of 0.05 mg/kg but no more than 5.0 mg; those of 41–60 years of age received 0.04 mg/kg but no more than 5.0 mg; those of 61–75 years of age received 0.03 mg/kg but no more than 2.0 mg. The patients received midazolam, intravenously and atropine (0.01 mg/kg body weight, intramuscular injection) exactly 10 min prior to bronchoscopy.

Bronchoscopy was performed with a flexible bronchoscope (model 1T20; Olympus; Tokyo, Japan), with the patient in the supine position. The procedure was attempted transorally in all patients. Both bronchial trees were visualized sequentially. Biopsy (endobronchial or transbronchial) was performed whenever indicated and diagnostic specimens obtained. Patients were not intubated during the procedure.

Holter ECG recording

For each patient, a two-channel 24-h ambulant ECG (CM 5 and CC5 leads) was recorded using a Holter ECG recorder (SM-50, Fukuda Denshi Co. Ltd., Tokyo, Japan) from 30 min before bronchoscopy to 30 min after. Bronchoscopy was begun 10 min after pre-medication. Ambulant ECG was recorded in a fixed position throughout the procedure (supine position) to avoid the influence of positional changes on autonomic function.

Analysis of HRV

Ambulant ECG recorded on magnetic tapes was analyzed using an ambulant ECG analyzer workstation (DMW-9000H; Fukuda Denshi Corp., Tokyo, Japan). The R-R intervals data were sent to a personal computer (PC9801; NEC, Tokyo, Japan) via an RS232C cable, and the time and frequency domains for HRV were analyzed with a software program (Fukuda Denshi Corp.). Premature and missing beats were excluded from analysis of the R-R intervals.

HRV was analyzed by time and frequency domain methods. For the time domain analysis, the coefficient of variation (CV_{RR}) was determined. The CV_{RR} reflect parasympathetic nervous activity (13). Using the standard deviation (SD) and mean value of 100 consecutive R-R intervals, we calculated the CV_{RR} using the following equation: CV_{RR} (%) = (SD/mean R-R) × 100. Data regarding the R-R intervals of 256 consecutive heartbeats were analyzed for the power spectral analysis. The power spectrum comprised one peak in the low-frequency range (0.04–0.15 Hz) and another in the high-frequency range (0.15–0.40 Hz). They were designated the low-frequency (LF) power and high-frequency (HF) power, respectively. The HF power represents the fluctuation in heart rate caused by respiration, which is mediated by parasympathetic nervous activity during bronchoscopy.
activity (14, 15). The LF power reflects the balance of sympathetic and parasympathetic nervous system activities (14–17). The ratio of LF power to HF power (LF/HF) correlates with the level of sympathetic nervous activity (14, 18). Serial changes in LF power, HF power and LF/HF were assessed.

**Statistical analysis**

Data values are expressed as means ± SD. Values were compared between the two groups using the paired Student’s t-test (two-tailed). A level of \( P < 0.05 \) was regarded as statistically significant. SPSS package (SPSS 18 Inc., Chicago, IL, USA) was used for all statistics.

**Results**

**Patients’ characteristics**

Patients consisted of 21 males and three females between 55 and 87 years of age (mean age: 69.75 ± 7.92 years; Table 1).

**Changes in heart rate**

Heart rates before pre-medication, after pre-medication and during bronchoscopy are summarized in Fig. 1. Heart rate increased significantly after pre-medication compared with that before pre-medication \( (P < 0.013) \) and increased further during endoscopy \( (P < 0.001) \). Furthermore, heart rates after bronchoscopy completion were significantly higher than they were before bronchoscopy \( (P < 0.001) \). Although HR decreased after endoscopy, it did not recover to the basal level in any study group \( (P < 0.001 \) post-bronchoscopy vs baseline in all groups). No patient has been suffered from actual cardiac problem in this study.

**Time domain analysis of HRV**

Fig. 2 shows the time domain analysis of HRV before pre-medication, after pre-medication and during bronchoscopy. The \( CV_{RR} \) values after pre-medication \( (6.72 ± 3.90\%) \) and during bronchoscopy \( (6.21 ± 3.44\%) \) were significantly higher than those before pre-medication \( (4.74 ± 1.35\%; \ P = 0.031 \) and \( P = 0.041 \), respectively). However, the \( CV_{RR} \) values after bronchoscopy \( (3.92 ± 1.84\%) \) were significantly lower than those before pre-medication \( (4.74 ± 1.35\%; \ P = 0.041 \)).

**Power spectral analysis of HRV**

Fig. 3 shows changes in LF powers, HF powers and LF/HF ratios obtained before, during and after bronchoscopy. Table 2 summarizes the results of spectral analysis of HRV fluctuation during bronchoscopy.

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>69.75 ± 7.92</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>21/3</td>
</tr>
<tr>
<td>Brinkman Index</td>
<td>(956.66 ± 606.24)</td>
</tr>
<tr>
<td>State of health</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
</tr>
<tr>
<td>Cardiovascular disease*</td>
<td>10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
</tr>
<tr>
<td>Duration of bronchoscopy (min)</td>
<td>61.04 ± 19.22</td>
</tr>
<tr>
<td>Examination</td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>13</td>
</tr>
<tr>
<td>TBTB</td>
<td>11</td>
</tr>
</tbody>
</table>

*One patient with hypertension and arrhythmia, and nine patients with hypertension.

TBTB, transbronchial tumor biopsy.

Figure 1. Patients display significantly increased heart rates at the pre-medication \( (P = 0.013) \), bronchoscopy \( (P < 0.001) \) and post-bronchoscopy phases \( (P < 0.001) \) compared with baseline phase.

Figure 2. Patients display significantly increased coefficient of variation \( (CV_{RR}) \) at the pre-medication \( (P = 0.013) \) and bronchoscopy phases \( (P = 0.031) \) and display significantly decreased \( CV_{RR} \) at post-bronchoscopy phase \( (P = 0.041) \) compared with baseline phase.
LF power, a marker of sympathovagal balance, was found to be decreased during bronchoscopy (from immediately after the insertion of the endoscope to its extubation). In particular, LF powers obtained after bronchoscopy were significantly lower than those obtained before bronchoscopy (103.79 ± 295.37 ms² vs 199.16 ± 261.02 ms²; \( P < 0.041 \) post-bronchoscopy phase vs baseline). After bronchoscopy, LF powers did not recover to basal levels.

The HF power in frequency domain analysis, which reflects parasympathetic activity, was found to be decreased. The changes in HF powers were similar to those in the LF powers. That is, HF powers continuously decreased during bronchoscopy. In particular, HF powers obtained after bronchoscopy were significantly lower than those obtained before bronchoscopy (35.89 ± 56.23 ms² vs 83.71 ± 81.53 ms²; \( P < 0.019 \) post-bronchoscopy phase vs baseline). After bronchoscopy, HF powers did not recover to the basal levels. Although the LF/HF ratios, an index of sympathetic activity, increased after pre-medication (3.78 ± 2.71 ms² vs 3.28 ± 2.33 ms²; pre-medication vs baseline), they decreased temporarily during the bronchoscope insertion. The LF/HF ratio did not differ significantly during any of the stages. As a result, the ratio between low and high frequency (LF/HF) values, which is a representative sympathetic activity, was increased. Bronchoscopy was associated with activation of cardiac sympathetic and withdrawal of cardiac parasympathetic regulation. This was mirrored by decrease of LF, HF and increased LF/HF ratio (Fig. 3). LF/HF ratio decrease significantly in cardiac patients compared with normal people (\( P = 0.004 \); Table 3).

![Figure 3. Power spectral analysis of heart rate variability.](image_url)

**Table 2.** Spectral analysis of heart rate variability during bronchoscopy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Baseline</th>
<th>Pre-medication</th>
<th>Bronchoscopy</th>
<th>Post-bronchoscopy</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (B/min)</td>
<td>74.52 ± 14.91</td>
<td>78.06 ± 16.67</td>
<td>88.78 ± 16.64</td>
<td>86.4 ± 14.54</td>
<td>0.000</td>
</tr>
<tr>
<td>CVRR (%)</td>
<td>4.74 ± 1.35</td>
<td>6.72 ± 3.90</td>
<td>6.21 ± 3.44</td>
<td>3.92 ± 1.84</td>
<td>0.003</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>199.16 ± 261.02</td>
<td>205.20 ± 240.26</td>
<td>128.87 ± 310.53</td>
<td>103.79 ± 295.37</td>
<td>0.499</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>83.71 ± 81.53</td>
<td>61.44 ± 58.71</td>
<td>57.69 ± 113.52</td>
<td>35.89 ± 56.23</td>
<td>0.245</td>
</tr>
<tr>
<td>LF/HF (ms²)</td>
<td>3.28 ± 2.33</td>
<td>3.78 ± 2.71</td>
<td>3.08 ± 2.33</td>
<td>3.32 ± 3.66</td>
<td>0.850</td>
</tr>
</tbody>
</table>

CVRR, coefficient of variation; HF, high frequency; HR, heart rate; LF, low frequency; LF/HF, ratio of LF power to HF power.

**Table 3.** Heart Rate Variability in normal and cardiovascular patients

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular</th>
<th>Normal</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>79.6 ± 16.8</td>
<td>77.9 ± 17.8</td>
<td>0.727</td>
</tr>
<tr>
<td>CVRR (%)</td>
<td>5.8 ± 3.2</td>
<td>5.9 ± 3.3</td>
<td>0.910</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>126.7 ± 143.9</td>
<td>271.5 ± 406.4</td>
<td>0.132</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>63 ± 71.8</td>
<td>67.9 ± 105.9</td>
<td>0.857</td>
</tr>
<tr>
<td>LF/HF (ms²)</td>
<td>2.4 ± 1.5</td>
<td>4.6 ± 3</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CVRR, coefficient of variation; HF, high frequency; HR, heart rate; LF, low frequency; LF/HF, ratio of LF power to HF power.
Discussion

In recent years, bronchoscopy has contributed significantly not only to the diagnosis, but also to the therapy of respiratory disorders. Furthermore, bronchoscopy is being performed in an increasing number of elderly people. As a result, there is an increased possibility of the patients suffering cardiac arrest due to the appearance of arrhythmias or cardiac ischemia during bronchoscopy. The heart has rich innervation from the parasympathetic and sympathetic limbs of the autonomic nervous system. Autonomic nervous imbalance is believed to be an important factor responsible for these cardiac events. Measuring fluctuations in intervals between successive heartbeats (HRV) is widely used to evaluate the balance of the autonomic nervous system (15, 17). An assessment of HRV is performed from an analysis of intervals of successive QRS complexes from a continuous ECG recording. In the present study, alterations in autonomic nervous activity during diagnostic bronchoscopy were evaluated by time and frequency domain analyses of HRV.

Hemodynamics are tightly regulated by the autonomic nervous system. In the present study, HR increased significantly after pre-medication compared with that before pre-medication ($P < 0.001$) and increased further during bronchoscopy ($P < 0.001$). Furthermore, heart rates after bronchoscopy completion were significantly higher than they were before bronchoscopy ($P < 0.001$). Although HR decreased after bronchoscopy, it did not recover to the basal level in the study group ($P < 0.001$ post-bronchoscopy vs baseline in all groups). Raab reported that tachycardia, arrhythmia and ischemic changes in the myocardium are induced by catecholamines and cortisols released by emotional stress, suggesting the influence of changes in autonomic nervous activity (19).

Recent advances in micro-computer technology have facilitated the easy evaluation of spectral HRV, allowing serial evaluation of autonomic nervous activity (20). Measurement of autonomic nervous activity using power spectral analysis has been reported in patients with ischemic heart disease, arrhythmias, cardiomyopathy, heart failure and hypertension (21–24), but it has not been used in the field of bronchoscopy. As indices of parasympathetic activity, $CV_{RR}$ was used in time domain analysis, while HF power was used in spectral analysis. In the present study, The $CV_{RR}$ values after pre-medication ($6.72 \pm 3.90\%$) and during bronchoscopy ($6.21 \pm 3.44\%$) were significantly higher than those before pre-medication ($4.74 \pm 1.35\%$; $P = 0.031$ and $P = 0.041$, respectively). The values for $CV_{RR}$ differed from those for HF power. $CV_{RR}$ was not analyzed with respect to the temporal sequence of consecutive heart rates. Therefore, it is difficult to predict autonomic functions in subjects demonstrating a mixture of short and long periodic heart rate variabilities. Therefore, a discordance of $CV_{RR}$ and HF power was observed between Figs. 2 and 3A, based on the difference in analytical procedures (25).

In the present study, HF power decreased (reduced parasympathetic nervous function) after pre-medication with atropine and decreased further during bronchoscopy. Because atropine exhibits a parasympathetic blockade effect, the influence of this drug on autonomic activity cannot be neglected. Myers et al. (26) have reported a close relationship between reduced HF power and sudden cardiac death. Furthermore, several studies have reported that enhanced sympathetic activity induces arrhythmias, while enhanced parasympathetic nervous activity has an anti-arrhythmic effect (7–9). However, Hayashi et al. reported that the development of arrhythmia could be predicted if the value for HF power was below $160$ ms$^2$ before gastrointestinal endoscopy (sensitivity, 88.9%; specificity, 44.4%) (25). The decrease in HF powers observed during bronchoscopy might constitute a developmental factor in cardiovascular complications. Therefore, we concluded that HF power should be measured prior to bronchoscopy to predict ‘high-risk’ subjects in order to prevent cardiovascular complications related to pre-medication and insertion of the bronchoscope.

LF power, a marker of sympathovagal balance, was found to be decreased during bronchoscopy (from immediately after the insertion of the endoscope to its extubation). In particular, LF powers obtained after bronchoscopy were significantly lower than those obtained before bronchoscopy ($P < 0.041$ post-bronchoscopy phase vs baseline). After bronchoscopy, LF powers did not recover to basal levels. Although the LF/HF ratios, an index of sympathetic activity, increased after pre-medication, they decreased temporarily during the bronchoscope insertion. As a result, bronchoscopy was associated with activation of cardiac sympathetic and withdrawal of cardiac parasympathetic regulation. This was mirrored by decrease of LF, HF and increased LF/HF ratio (Fig. 3). Paralleling our results, Saijyo et al. (27) reported an increase in LF/HF ratio during gastroscopy indicative of enhanced sympathetic tone. In addition, they reported increased parasympathetic tone at the very beginning of insertion of the endoscope. However, the vagal tone decreased rapidly to preprocedural level during the
endoscopic procedure. In another Japanese study (25) on 54 subjects pre-medicated with scopolamine butyl bromide, both LF and HF powers decreased after pre-medication and further during gastroscopy. LF/HF ratio increased after pre-medication, but no further changes appeared during endoscopy. Also, Ochi et al. (28) reported that endoscopic retrograde cholangiopancreatography (ERCP) decreased both LF and HF powers. LF/HF ratio tended to increase immediately after insertion of the endoscope but, differing from our findings, decreased continuously thereafter. However, ERCP is a more complex procedure than a diagnostic bronchoscopy including cannulation of the common bile and/or pancreatic duct following injection of a radio contrast.

In the present study, midazolam seemed to potentiate the dominance of the sympathetic nervous system induced by the bronchoscopic procedure. In fact, the same phenomenon has been reported during colonoscopy as well (29). This interesting controversy derives probably from the complex action of midazolam on the cardiovascular system, which includes both direct and indirect effects. Midazolam induces anxiolysis and sleep but decreases systemic vascular resistance and causes venodilatation resulting in reduction of arterial pressure and decreased venous return (30). It also decreases myocardial contractility and cardiac output. In response to these, baroreflexes are deactivated, resulting in increased heart rate and contractility with splanchnic and other blood volumes mobilized to the central circulation. In accordance with this, Yazawa et al. (31) reported no reduction of cardiac stress in a study on eight healthy volunteers given midazolam (0.1 mg/kg) and evaluated by electrocardiogram, blood pressure, oxygen saturation and Doppler echocardiography. Thus, the data on the effect of midazolam on HRV are somewhat conflicting. Although midazolam is generally considered as a sympatholytic drug enhancing parasympathetic dominance (32), many studies on line with us report sympathetic dominance at least when midazolam is given in smaller doses (33, 34). We are aware of the potential limitations of our study. Continuous blood pressure was not measured. Hence, the effect of blood pressure on the results could not be evaluated. A sudden rise in blood pressure activates baroreceptors followed by parasympathetic activation, inducing a decrease in heart rate. Similarly, although various patient characteristics including cardiac medication and diabetes certainly influence HRV, the numbers of patients on cardiac medication or having diabetes were rather high and equally distributed between the study group.

Conclusion

In conclusion, bronchoscopic procedures are performed frequently in elderly people and in patients with serious underlying disease, and thus the effect of bronchoscopy on the cardiovascular system should not be neglected. Power spectral analysis offers a non-invasive and quantitative evaluation of autonomic nervous activity. This new method may be useful for predicting and preventing arrhythmia during bronchoscopy.

References