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Original contribution

Effects of landiolol on QT interval and QT dispersion during induction of anesthesia using computerized measurement

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Abstract

Study Objective: To examine the effects of landiolol on the QT interval, rate-corrected QT (QTc) interval, QT dispersion (QTD), and rate-corrected QTD (QTcD) during tracheal intubation using computerized measurement.

Design: Randomized, double-blinded study.

Setting: Dokkyo Medical University Hospital operating room.

Patients: 30 ASA physical status I patients scheduled for elective surgery.

Inventions: Patients were randomized to receive either normal saline (saline group) or landiolol (landiolol group; one-min loading infusion of 0.125 mg/kg followed by 0.04 mg/kg/min infusion). Immediately after the start of administration of saline or landiolol, anesthesia was induced with intravenous (IV) fentanyl two μg/kg, propofol 1.5 mg/kg, and vecuronium 0.1 mg/kg. Six minutes after administration of saline or landiolol, tracheal intubation was performed within 20 seconds.

Measurements: Mean arterial pressure (MAP), RR interval, QT interval, QTc interval, QTD, and QTcD were consecutively recorded during the induction.

Main Results: There was no significant difference in MAP between groups during the study. RR interval in the landiolol group was significantly longer than in the saline group from two minutes after the start of the landiolol infusion to the end of the study. The QT interval in the landiolol group was significantly shorter than in the saline group from start of the infusion to 4 minutes after tracheal intubation. The QTc interval, QTD, and QTcD in the landiolol group were significantly shorter than those in the saline group from immediately after tracheal intubation to the end of study.

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Conclusion: A bolus of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min may reduce the risk of cardiac arrhythmias during induction of anesthesia.

1. Introduction

Laryngoscopy and tracheal intubation induce hypertension, tachycardia, cardiac arrhythmias, and coronary ischemia. Many studies have been performed to prevent hyperdynamic responses induced by tracheal intubation [1-8]. Of the various classes of drugs, β-adrenoceptor antagonists have frequently been used to prevent such detrimental events. Landiolol, an ultra-short acting β_1-adrenoceptor antagonist, has recently begun to be used in clinical anesthesia [1,2,9-12]. It is not only employed as a bolus dose to prevent cardiac events, but also used by continuous intravenous (IV) infusion because of its ultra-short duration [13].

Much attention has focused on variations of ventricular repolarization because of their relation to arrhythmias [14-17]. Dispersion of the QT interval (QTD), defined as maximal QT interval minus minimal QT interval on 12-lead of the surface electrocardiogram (ECG), reflects regional heterogeneity of ventricular repolarization [14], and is significantly greater in patients with arrhythmias than in those without [15-20]. The effects of landiolol on QT interval and QTD during tracheal intubation, which are associated with an increased risk of arrhythmias and cardiac events, are of considerable interest.

The purpose of this study was to examine the effects of landiolol on mean arterial pressure (MAP), RR interval, QT interval, rate-corrected QT (QTc) interval, QTD, and rate-corrected QTD (QTcD) during tracheal intubation using computerized measurement.

2. Materials and methods

After approval of the ethics committee of Dokkyo Medical University School of Medicine and written, informed consent, 30 ASA physical status I patients aged 20-62 years, within 15% of ideal body weight, who were scheduled to undergo elective otorhinolaryngological surgery during general anesthesia, were studied. All patients with cardiovascular, respiratory, metabolic, or cerebrovascular disease, were excluded from the study. Patients with predicted difficulty in tracheal intubation were also excluded from the study. No patients were receiving any medication.

A 10-mL syringe containing an equivalent volume of either normal saline or landiolol was prepared in advance by an anesthesiologist not involved in the data collection. Patients were prospectively randomized via sealed envelope assignment, to one of two groups.

No premedication was given. After patient arrival at the operation room, standard 12-lead ECGs (FDX-4521L; Fukuda Denshi Co. Ltd., Tokyo, Japan), mean invasive arterial blood pressure (BP), pulse oximetry (Satlite; Datex-Ohmeda, Madison, WI, USA) and capnography (Capnomac; Datex-Ohmeda) were monitored. The 30 patients were divided into two groups of 15 patients each to receive either 1) normal saline (saline group) or 2) a one-minute loading infusion of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min using an automated infusion pump during the study (landiolol group). One minute after the start of administration of saline or landiolol, anesthesia was induced with IV fentanyl two μg/kg and propofol 1.5 mg/kg. After loss of consciousness, vecuronium 0.1 mg/kg was given IV. During mask ventilation, 2% sevoflurane with 100% oxygen was added, and the trachea was intubated 6 minutes after the start of administration of saline or landiolol. Each intubation was performed by an experienced anesthesiologist, who was blinded to the drug, and was accomplished within 20 seconds. Anesthesia was maintained with 66% nitrous oxide in oxygen supplemented with sevoflurane 2%. The ventilator was adjusted initially to deliver a tidal volume of 9 mL/kg and respiratory rate of 12 breaths/min. End-tidal carbon dioxide tension ($P_{ET}CO_2$) was maintained at 35-40 mmHg during the study. All patients received a continuous infusion of acetate Ringer's solution at a rate of 5 mL/kg/h during the study.

From the ECG, consecutive beat-to-beat data were digitally recorded at a sample rate of two-milliseconds and stored on a 3.5-inch floppy disk. QT intervals were determined by the use of newly developed software (QTD-1; Fukuda Denshi Co. Ltd.), which detected the onset of the Q wave and the end of the T wave. The software used the differential threshold technique described elsewhere in detail [21,22]. In brief, this technique determines the onset of the Q wave as the intersection of a threshold level with the differential of the Q wave, and the end of the T wave as the intersection of a threshold level with the differential of the T wave, respectively. QT intervals were measured in all 12 leads and corrected for heart rate (HR; QTc) using Bazett's formula [23]. QTD was calculated as the difference between maximal and minimal QT intervals. The QTcD was defined as the difference between the maximum and minimum average QTc interval in the 12-lead ECG. The average value of data-derived from three successive beats for each lead was used for analysis. A cardiologist performed all measurements and analysis. Leads in which the end of the T wave could not be clearly discerned were excluded from the study.

Measurements of MAP, RR interval, QT interval, QTc interval, QTD, and QTcD were performed at every minute

from administration of saline or landiolol (baseline) to 10 minutes after intubation.

Data are presented as means ± SD. Intergroup differences were analyzed by two-way analysis of variance for the repeated-measures design. When a significant overall effect was detected, Scheffé's test was used for comparison of the mean values for the two variables. Comparison between both groups was made by applying Scheffé's test. The threshold for statistical significance was $P < 0.05$.

3. Results

There were no significant differences in age, gender, height, or body weight between the two groups (Table 1).

As shown in Fig. 1, significantly increased MAP was observed from immediately to two minutes after tracheal intubation in both groups. The RR interval in the landiolol group increased significantly from two minutes after the start of Landiolol administration through the end of study compared with that of the saline group (Fig. 2).

There was no significant change in QT interval or QTc interval after induction of anesthesia compared with the baseline value in both groups (Figs. 3 and 4). QT interval and QTc interval significantly increased after tracheal intubation in the saline group, but not in the landiolol group. There were significant differences in QT interval (from 6 to 10 min after induction of anesthesia) and QTc interval (from 6 to 16 min after induction of anesthesia) between the groups.

As shown in Fig. 5, QTD in both groups significantly increased after induction of anesthesia. QTD significantly increased after tracheal intubation compared with before tracheal intubation in the saline group, but not in the landiolol group. There were significant differences in QTD after tracheal intubation between both groups (landiolol group: baseline, 40.5 ± 4.8 msec, peak at 15 min after start of administration of landiolol, 66.9 ± 4.0 msec, $P < 0.01$; saline group: baseline, 42.6 ± 5.8 msec, peak at 9 min after start of administration of saline, 76.3 ± 3.6 msec, $P < 0.01$).

As shown in Fig. 6, QTcD in both groups significantly increased after induction of anesthesia. QTcD significantly increased after tracheal intubation compared with before tracheal intubation in the saline group, but not in the landiolol group. There were significant differences in QTcD after tracheal intubation between the groups (landiolol group: baseline, 42.6 ± 3.8 msec, peak at 13 min after start of administration of landiolol, 65.7 ± 2.3 msec, $P < 0.01$; saline group: baseline, 41.7 ± 6.7 msec, peak at 6 min after start of administration of saline, 76.3 ± 3.6 msec, $P < 0.01$).

$P_{ET}CO_2$ was maintained at 35 and 39 mmHg during the study in both groups.

Table 1 Demographic data

	Saline (n = 15)	Landiolol (n = 15)
Age (yrs)	36 ± 13	34 ± 13
Gender (male/female)	8 ± 7	7 ± 8
Height (cm)	160 ± 10	161 ± 9
Weight (kg)	61 ± 11	59 ± 14

4. Discussion

β-adrenoceptor antagonists have been used in the treatment of hypertension, ischemic heart diseases, congestive heart failure, and ventricular or supraventricular arrhythmias. All β-adrenoceptor antagonists have potent effects when sympathetic nervous system activity is increased [24]. They attenuate the unexpected increase in HR. Therefore, β-adrenoceptor antagonists, such as esmolol or labetalol, have been used to prevent hyperdynamic responses induced by laryngoscopy and tracheal intubation [3-7,25]. Landiolol, a newer, ultra-short-acting β_1-adrenoceptor antagonist, has been proposed as an alternative drug to avoid adverse hemodynamic effects caused by intubation [1,8]. In the present study, QT interval, QTc interval, QTD, and QTcD in the landiolol group decreased significantly during and after tracheal intubation compared with the saline group. Since the increases of those values have been shown to predispose to arrhythmias, administration of landiolol during tracheal intubation may provide a decreased risk of arrhythmias. Since laryngoscopy and intubation increase the afterload of the heart by increased plasma concentrations of catecholamines [26], β-adrenoceptor antagonists such as landiolol may prevent hyperdynamic responses induced by the release of catecholamines.

Korpinen et al. [27] showed that relatively high doses of esmolol prevented the increase of QTc interval after induction of anesthesia, but not after laryngoscopy and intubation. However, in our study, QT and QTc interval were not increased after induction of anesthesia or laryngoscopy and tracheal intubation using continuous landiolol infusion. A one-minute loading infusion of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min may have a prophylactic effect for the increase of QT interval due to laryngoscopy and tracheal intubation. Larygoscopy and tracheal intubation also induce an adverse change in QT interval. Some agents were evaluated to prevent QT prolongation caused by tracheal intubation. Opioids, such as fentanyl, alfentanil, and remifentanil, attenuated the prolongation of QTc interval [28-30].

Anesthetic agents such as propofol and sevoflurane, when used for induction of anesthesia, affect QT interval, QTc interval, QTD, and QTcD. Induction of total IV anesthesia with propofol shortens QT interval [26,31], but not the QTc

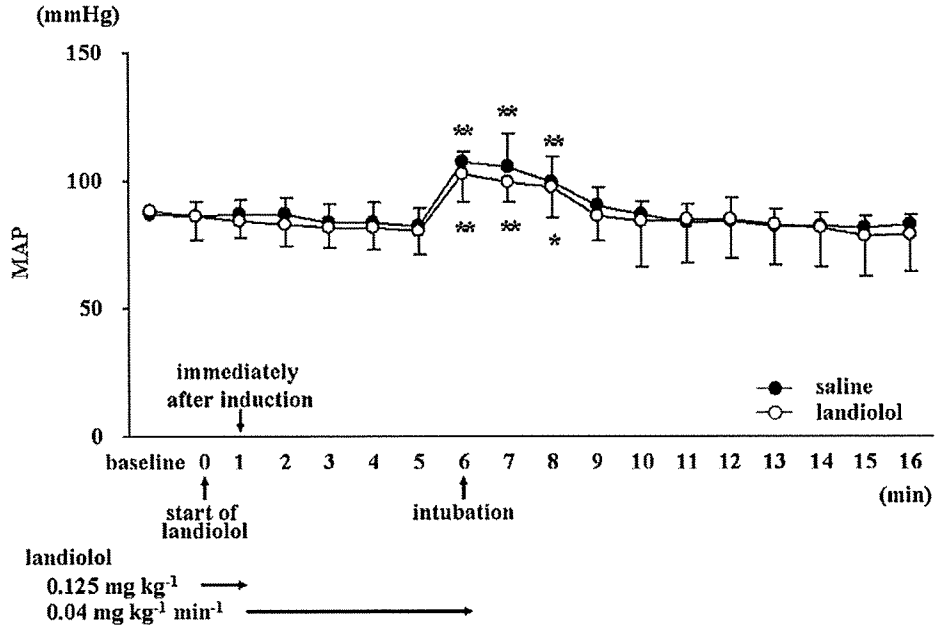

Fig. 1 Changes in mean arterial pressure (MAP). ●, saline group; ○, landiolol group. All values are expressed as means ± SD. * $P < 0.05$ vs baseline. ** $P < 0.01$ vs baseline.

interval [26]. Sevoflurane anesthesia increases the QT interval, QTc interval, QTD, and QTcD [31,32]. In clinical practice, the combination of IV propofol and inhaled sevoflurane is used during induction of anesthesia. The QTD and QTcD after induction of anesthesia increased significantly in both groups, and were lower in the landiolol group than the saline group. Therefore, landiolol may prevent increased QTD and QTcD caused by the induction of anesthesia.

Landiolol is rapidly hydrolyzed to an inactive metabolite M-1 by both pseudocholinesterase in the plasma and carboxylesterase in the liver, and excreted in the urine, resulting in an elimination half-life of approximately 3.5 minutes [13]. Its half-life is significantly shorter than

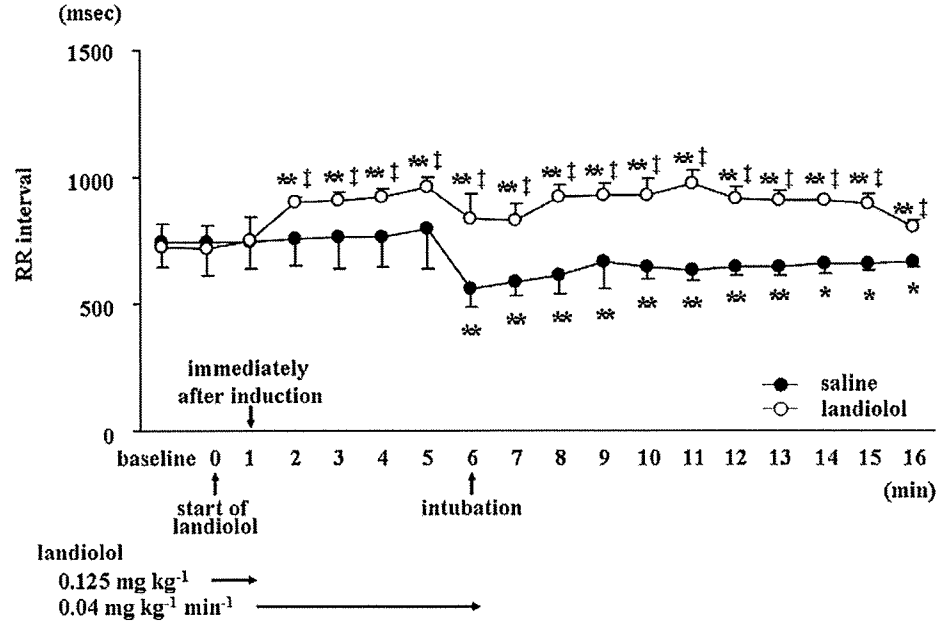

Fig. 2 Changes in RR interval. ●, saline group; ○, landiolol group. All values are expressed as means ± SD. * $P < 0.05$ vs baseline. ** $P < 0.01$ vs baseline. ‡ $P < 0.01$ vs landiolol.

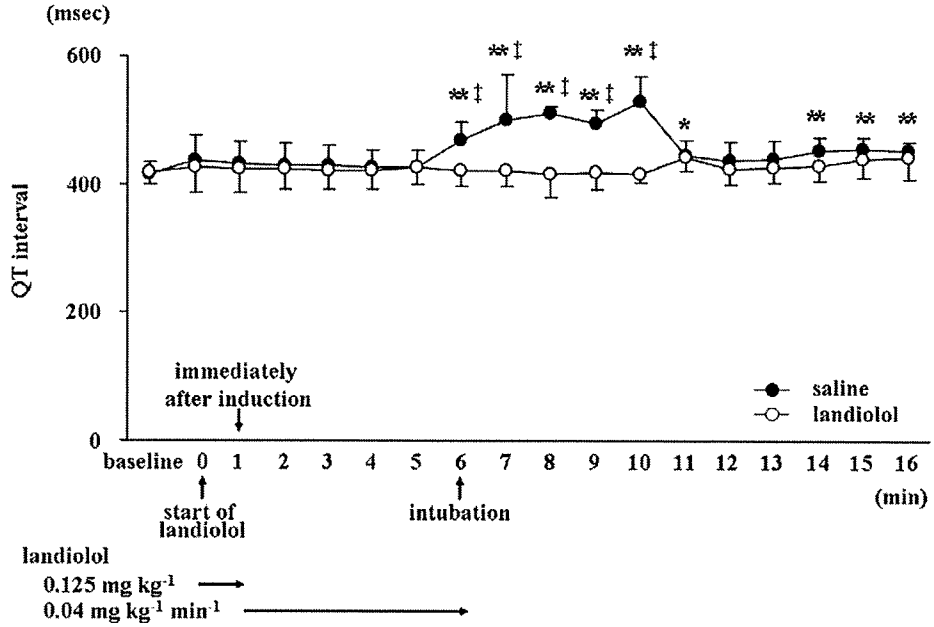

Fig. 3 Changes in QT interval. ●, saline group; ○, landiolol group. All values are expressed as means ± SD. * $P < 0.05$ vs baseline. ** $P < 0.01$ vs baseline. ‡ $P < 0.01$ vs landiolol.

that of esmolol, the first ultra-short-acting β_1-adrenoceptor antagonist, which has a half-life of 9.2 minutes [33]. The shorter half-life of landiolol is beneficial in avoiding side effects in clinical practice because it dissipates rapidly after discontinuation of the drug. Landiolol has much higher cardioselectivity ($\beta_1/\beta_2 = 255$) than esmolol ($\beta_1/\beta_2 = 33$) [34], and has more potent negative chronotropic effects than esmolol, with significantly fewer effects on BP [35]. Yamazaki et al. [1] reported that IV 0.1 or 0.3 mg/kg of landiolol inhibited increases in HR after tracheal intubation without decreasing BP. A one-minute loading infusion of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min was used because the dosage of landiolol was determined on the basis of its

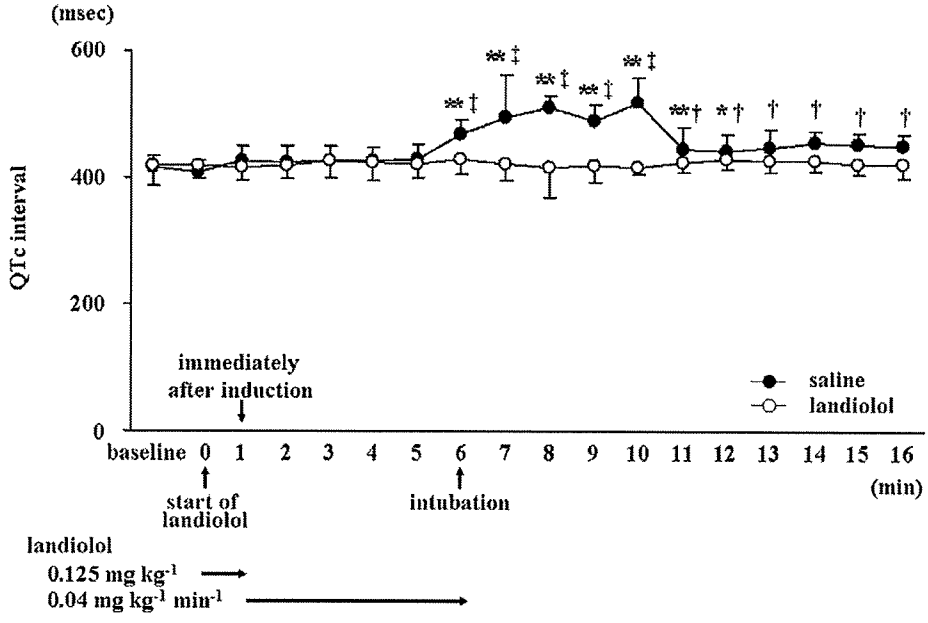

Fig. 4 Changes in rate-corrected QT (QTc) interval. ●, saline group; ○, landiolol group. All values are expressed as means ± SD. * $P < 0.05$ vs baseline. ** $P < 0.01$ vs baseline. † $P < 0.05$ vs landiolol. ‡ $P < 0.01$ vs landiolol.

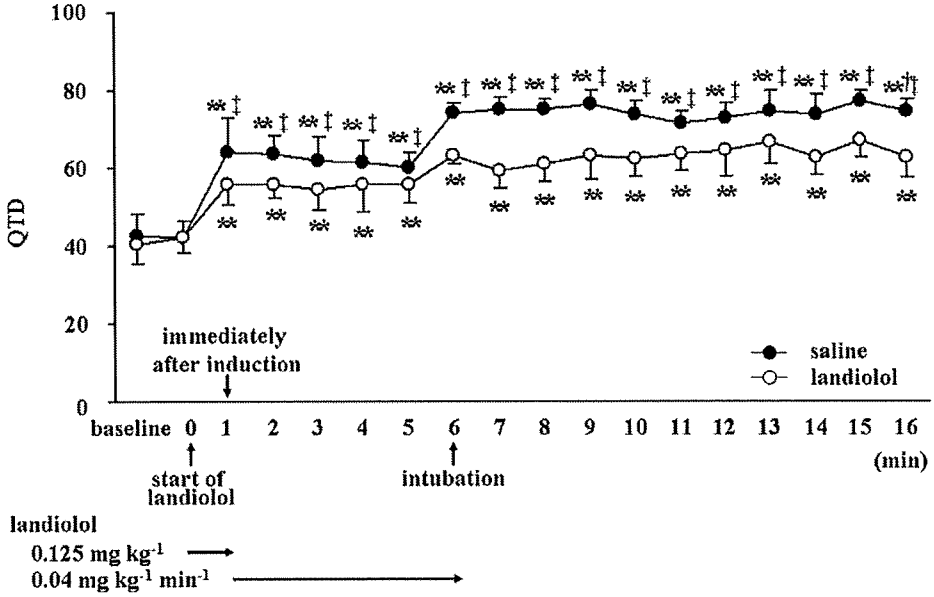

Fig. 5 Changes in QT dispersion (QTD). ●, saline group; ○, landiolol group. All values are expressed as means ± SD. ** $P < 0.01$ vs baseline. ‡ $P < 0.01$ vs landiolol.

effectiveness in reducing the hemodynamic response to tracheal intubation during sevoflurane anesthesia [8,36]. A one-minute loading infusion of landiolol 0.125 mg/kg followed by an infusion of landiolol 0.04 mg/kg/min did not exert an influence on BP during or after intubation in this study.

Previous studies, however, have demonstrated that QTD increases in patients with myocardial infarction [16-18], subarachnoid hemorrhage [37], or diabetes mellitus [38,39]. The administration of landiolol may be beneficial in avoiding cardiac arrhythmias caused by induction of anesthesia and tracheal intubation because landiolol has a lower frequency of adverse hemodynamic effects [40].

Landiolol, a newer, ultra-short-acting β_1-adrenoceptor antagonist, prevents increases in QT interval, QTc interval, QTD, and QTcD during and after tracheal intubation.

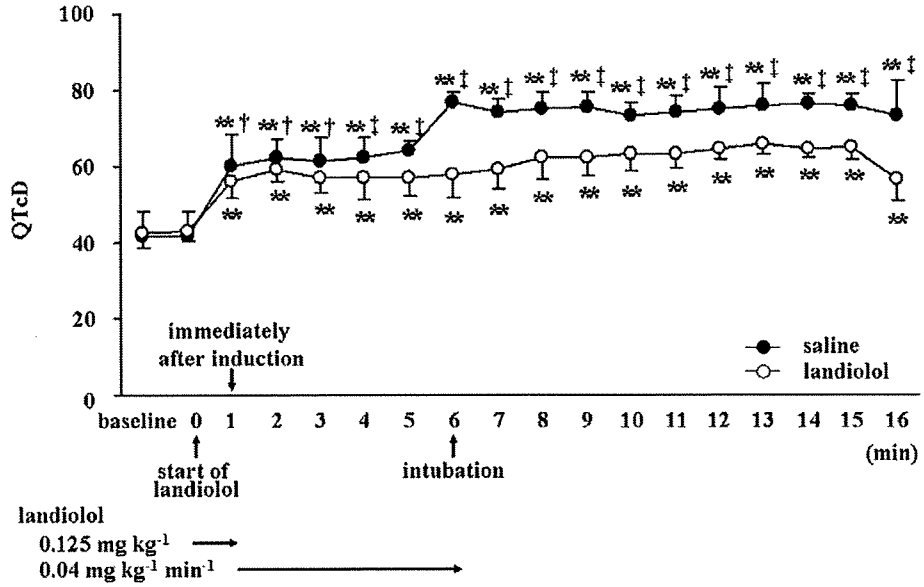

Fig. 6 Changes in rate-corrected QTD (QTcD). ●, saline group; ○, landiolol group. All values are expressed as means ± SD. ** $P < 0.01$ vs baseline. † $P < 0.05$ vs landiolol. ‡ $P < 0.01$ vs landiolol.

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Assessment of QT Interval and QT Dispersion During Electroconvulsive Therapy Using Computerized Measurements

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Background: Electroconvulsive therapy (ECT) used in the treatment of severe psychiatric disorders induces stimulation of the autonomic nervous system with initial parasympathetic outflow immediately followed by a sympathetic response. These responses induce an initial bradycardia, arrhythmias, and hypertension. QT dispersion (QTD), defined as maximal QT interval minus minimal QT interval on 12 leads of the surface electrocardiogram, reflects regional heterogeneity of ventricular repolarization. The effects of electrical stimulus due to ECT on QT interval and QTD are of considerable interest.

Objective: This study was designed to investigate the effects of electrical stimulation caused by ECT on RR interval, QT interval, the rate-corrected QT (QTc) interval, QTD, and the rate-corrected QTD (QTcD) under general anesthesia using computerized measurements.

Methods: Thirty psychiatric patients scheduled for ECT were studied under propofol anesthesia. A 12-lead electrocardiogram was monitored to measure parameters. Muscle paralysis was achieved by administering succinylcholine 1 mg/kg intravenously, and the efficacy of ECT was determined by the tourniquet technique.

Results: The RR interval and QT interval decreased significantly immediately after electrical stimulus, and returned to the baseline level 1 minute after electrical stimulus. In 25 out of 30 patients, the baseline value of QTc interval was higher than the normal limits, and the QTc interval decreased significantly for 2 minutes after electrical stimulus. In 27 out of 30 patients, the baseline values of QTD and QTcD were higher than the normal limits, and the QTD and QTcD increased significantly from immediately after electrical stimulus to 5 minutes after electrical stimulus.

Conclusions: The QTc interval, QTD, and QTcD, which were associated with increased risks of ventricular arrhythmias, increased significantly before anesthetic induction in patients with major depression. Electrical stimulus during ECT induced further increases of the QTD and QTcD.

Key Words: electroconvulsive therapy, QT interval, QT dispersion, propofol

(*J ECT* 2010;26: 41–46)

Dispersion of the QT interval (QTD), which is defined as maximal QT interval minus minimal QT interval, on 12 leads of the surface electrocardiogram (ECG) reflects regional heterogeneity of ventricular repolarization.[1] Prolongation of the QTD is associated with increased risk of ventricular arrhythmias and cardiovascular mortality.[2–9] It is well known that the QTD is regulated by not only heart rate but also autonomic tone.[10–14]

Although the exact mechanism of electroconvulsive therapy (ECT) is not elucidated, ECT has been widely used in the treatment of severe psychiatric disorders such as depression and schizophrenia. In the early days of ECT, complications such as trauma and fracture had been common. The use of intravenous anesthetics and neuromuscular blockades reduced such complications. Even if anesthesia management is appropriate, however, electrical current during ECT stimulates the autonomic nervous system and provokes acute cardiovascular response with initial parasympathetic outflow immediately followed by a sympathetic response.[15] These responses may induce arrhythmias or cardiac events. However, to our knowledge, QT interval and QTD during ECT have not been carefully measured using a computer. Computerized measurements enhance the accuracy and reproducibility compared with manual measurements. The purpose of this study was to investigate QT interval and QTD during ECT under propofol anesthesia using a computer.

METHODS

Thirty patients with major depression (22 women, 8 men; age, 40–64 years), American Society of Anesthesiologists 1 or 2, who were scheduled to undergo elective ECT under propofol anesthesia, were studied after approval of the hospital ethics committee had been obtained, and the patients or their family had given informed consent. All patients with cardiovascular or respiratory diseases were excluded from the study. To avoid enrollment of patients with cardiac diseases, all patients received echocardiography and ECG before the study. All patients received antidepressants, benzodiazepines, and/or major tranquilizers (Table 1). They received the usual long-term medication in the morning before ECT session.

No patients received premedication before entry to the operating room. After arriving at the operating room, standard 12-lead ECGs (FDX-4521L; Fukuda Denshi Co Ltd, Tokyo, Japan), indirect arterial blood pressure, pulse oximetry (Satlite; Datex, Finland), and capnography (Capnomac; Datex, Finland) were monitored. A tourniquet was applied above the right ankle. Anesthesia was induced with intravenous injection of propofol 1 mg/kg by a trained anesthesiologist. After loss of consciousness, ventilation was controlled using a face mask with 100% oxygen, and the end-tidal carbon dioxide partial pressure measured at nostril was maintained between 35 and 40 mm Hg. The tourniquet was simultaneously inflated to 300 mm Hg to isolate the circulation to the foot and permit accurate motor seizure assessment. Then, succinylcholine 1 mg/kg was administered intravenously. Immediately after fasciculation caused by succinylcholine injection disappeared from the left leg, the electrical stimulus was delivered via bitemporal electrodes by a single psychiatrist using an ECT stimulator (Thymatron System;

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TABLE 1. List of All Medications

Antidepressants	
Clomipramine	n = 6
Amitriptyline	n = 2
Nortriptyline	n = 1
Amoxapine	n = 1
Mianserin	n = 9
Setiptiline	n = 1
Milnacipran	n = 11
Fluvoxamine	n = 3
Paroxetine	n = 5
Trazodone	n = 3
Lithium	n = 4
Benzodiazepines	
Etizolam	n = 2
Lorazepan	n = 3
Alprazolam	n = 6
Cloxazolam	n = 3
Triazolam	n = 2
Lormetazepan	n = 1
Brotizolam	n = 7
Flunitrazepan	n = 18
Estazolam	n = 4
Nitrazepan	n = 5
Quazepan	n = 1
Major Tranquilizers	
Aripiprazole	n = 2
Risperidone	n = 2
Quetiapine	n = 6
Chlorpromazine	n = 5
Levomepromazine	n = 2
Perphenazine	n = 1

Somatics LLC, Lake Bluff, Ill). The magnitude of the energy setting for ECT stimulus was predetermined by age. The efficacy of ECT was determined by the tourniquet technique. That was by observation of convulsive movements of the distal leg, around which an inflated tourniquet was set to block the distribution of succinylcholine. Electroencephalogram (EEG) seizure was also measured by an EEG monitor set in the electrical stimulator. The criteria for adequacy of electrical stimulus were more than 15 seconds of EEG seizures.

From each ECG, consecutive beat-to-beat data were digitally recorded at a sample rate of 2 milliseconds and stored on a 3.5-in. floppy disk. QT intervals were determined by the use of newly developed software (QTD-1; Fukuda Denshi Co Ltd.) that detected the onset of the Q wave and the end of the T wave. The software used the differential threshold technique described elsewhere in detail.[16,17] In brief, this technique determines the onset of the Q wave as the intersection of a threshold level with the differential of the Q wave and the end of the T wave as the intersection of a threshold level with the differential of the T wave, respectively. QT intervals were measured in all 12 leads and corrected for heart rate (QTc) with Bazett's formula.[18] QTD was calculated as the difference between maximal and minimal QT intervals. The corrected QT dispersion (QTcD) was defined as the difference between the maximum and minimum average QTc interval in the 12-lead ECG. The average value of data derived 3 successive beats for each lead was used for analysis. A cardiologist performed all measurements and analysis. Leads in which the end of the T wave could not be clearly discerned were excluded from the study.

Measurements of the RR interval, QT interval, QTc interval, QTD, and QTcD were performed before anesthetic induction (baseline), immediately after anesthetic induction, immediately after electrical stimulus, and every 1 minute for 10 minutes after electrical stimulus.

Data are presented as mean ± SD. Differences were analyzed by 2-way repeated-measures analysis of variance. Scheffe's tests were used as determined by the analysis of variance results. The threshold for statistical significance was $P < 0.05$.

RESULTS

All data were available in this study.

The RR interval did not change significantly after anesthetic induction. However, it shortened significantly immediately after electrical stimulus, and recovered the baseline value 1 minute after electrical stimulus (Fig. 1).

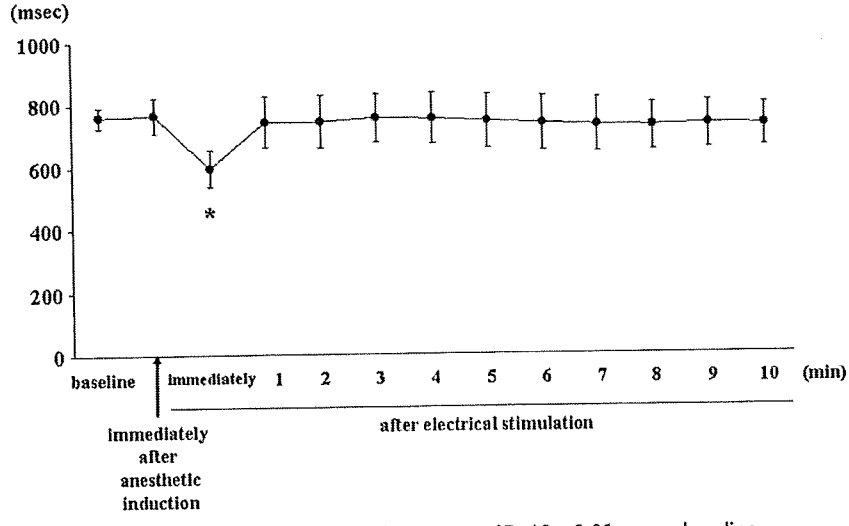

FIGURE 1. Changes in the RR interval. All values are expressed as mean ± SD. *$P < 0.01$ versus baseline.

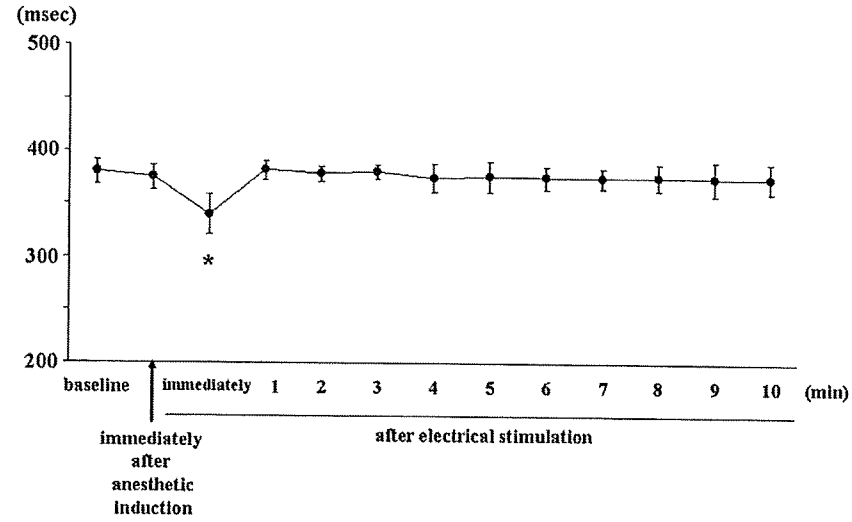

FIGURE 2. Changes in the QT interval. All values are expressed as mean ± SD. *$P < 0.01$ versus baseline.

A significant decrease of the QT interval occurred immediately after electrical stimulus, and recovered the baseline value 1 minute after electrical stimulus (Fig. 2). In 25 out of 30 patients, the baseline value of QTc interval was higher than the normal limits (320–440 milliseconds). Significant decreases of the QTc interval were observed from immediately after electrical stimulus to 2 minutes after electrical stimulus (Fig. 3).

In 27 out of 30 patients, the baseline values of QTD and QTcD were higher than the normal limits (20–50 milliseconds) in Figures 4 and 5. The QTD increased significantly from immediately after electrical stimulus to 5 minutes after electrical stimulus (baseline, 65.0 ± 8.5 milliseconds; peak at immediately after electrical stimulus, 95.9 ± 3.7 milliseconds; $P < 0.01$). The QTcD also increased significantly from immediately electrical stimulus to 5 minutes after the electrical stimulus (baseline, 73.8 ± 8.8 milliseconds; peak at immediately after the electrical stimulus, 125.2 ± 7.2 milliseconds; $P < 0.01$).

We observed temporary ventricular premature complexes (VPC) in 2 patients and sinus tachycardia in 24 patients after electrical stimulus.

DISCUSSION

The present study focused on computerized measurements of RR interval, QT interval, QTc interval, QTD, and QTcD during ECT under propofol anesthesia. QT interval is the time interval from the first recognizable part of QRS complex to the final recognizable part of the T wave. The QT interval is easy to measure because QT deflections are usually sharp. However, the terminal part of the T wave is often a rather gentle slope, and the precise position of the final part of T wave may be difficult or even impossible to determine.[19] Therefore, the accuracy and reproducibility of the QT interval and QTD in manual measurements have been limited. Use of computerized detection of T wave offset enhances more accuracy and reproducibility.

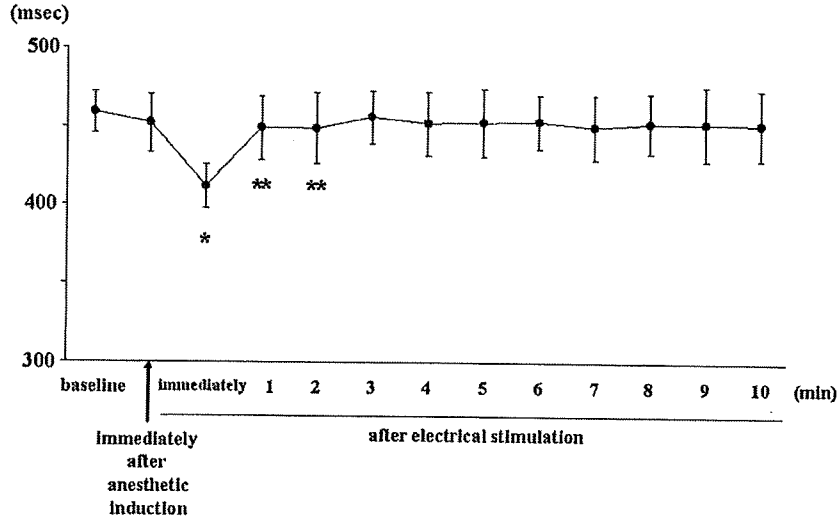

FIGURE 3. Changes in the QTc interval. All values are expressed as mean ± SD. *$P < 0.01$ versus baseline, **$P < 0.05$ versus baseline.

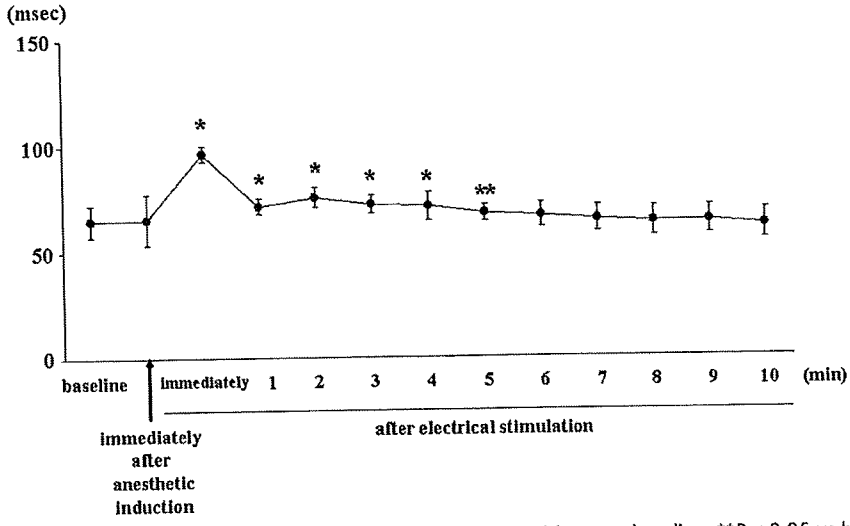

FIGURE 4. Changes in the QTD. All values are expressed as mean ± SD. *$P < 0.01$ versus baseline, **$P < 0.05$ vs baseline.

This is the first study to examine how ECT affects the ECG findings using computerized measurements. In the present study, the QT interval and QTc interval decreased significantly immediately after electrical stimulus. Because temporary predominance of parasympathetic nerve activity occurs during electrical stimulus, withdrawal of parasympathetic nerve activity may shorten the QT interval and QTc interval. This finding appears to be in agreement with earlier observation that withdrawal of parasympathetic nerve activity shortens the QT interval.[20] We also found that electrical stimulus during ECT caused increases of the QTD and QTcD in patients with major depression. Because the QTD and the QTcD have been shown to predispose to ventricular arrhythmia, our finding of changes in QTD and QTcD during ECT may explain the occasional emergence of ventricular arrhythmia during ECT. Temporary ventricular premature complexes or sinus tachycardia occurred after electrical stimulus in 26 of the 30 patients.

Interestingly, the baseline values of the QTc interval in 83% of patients in this study were already higher than the upper normal limit of 440 milliseconds. Tricyclic antidepressants are known to induce prolongation of the QT interval.[21] In the previous studies, use of tricyclic antidepressants, thioridazine, droperidol, or butyrophenone, is a robust predictor of QTc prolongation in a dose-dependent manner.[22,23] The baseline values of the QTD and QTcD in 90% of patients were also higher than the upper normal limits of 50 milliseconds. Rasmussen et al[24] reported that QTcD as measured on the baseline ECG positively correlated with number of arrhythmias during ECT. Although electrical stimulus during ECT caused further increases of the QTD and QTcD, these values returned to the baseline value 6 minutes after electrical stimulus in this study.

Selection and determination of dosage of anesthetic agents may be crucial in ECT management. Anesthetic requirements

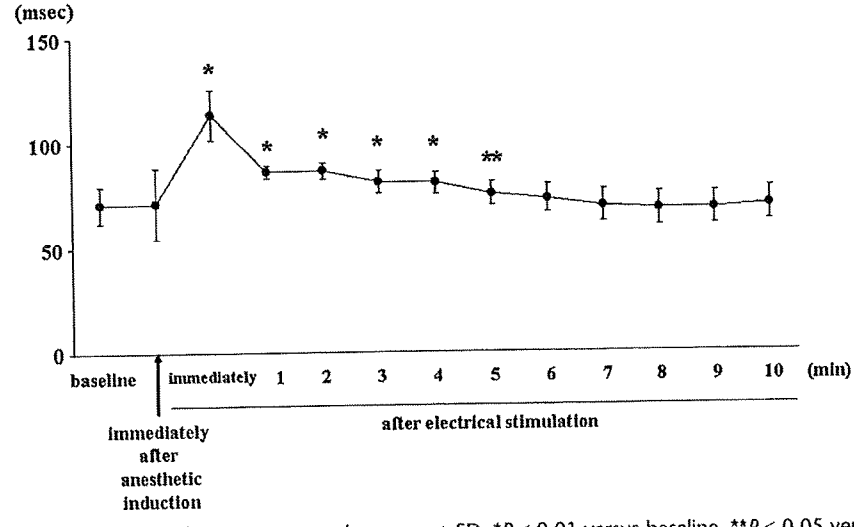

FIGURE 5. Changes in the QTcD. All values are expressed as mean ± SD. *$P < 0.01$ versus baseline, **$P < 0.05$ versus baseline.

for successful ECT are rapid induction, rapid recovery after the seizure, and minimization of any antagonistic effects on seizure activity by anesthetic agents.[15] We recommend intravenous ultra-short-acting anesthetics for ECT. Methohexital is recommended as the first choice anesthetic for ECT by the American Psychiatric Association.[15,25] Propofol is also used in ECT because systemic and cerebrovascular hemodynamic changes under propofol anesthesia are more stable than under barbiturate anesthesia. Kleinsasser et al[26] demonstrated that propofol using by 2.5 mg/kg shortened the QT interval but did not change the QTc interval. In the present study, however, the QT interval, QTc interval, QTD, and QTcD did not change after intravenous injection of propofol 1 mg/kg. The difference between the 2 studies may be because of the dosage of propofol. Volatile anesthetics such as sevofulurane are a suitable alternative treatment option to intravenous anesthetics.[27–31] Rasmussen et al[27] suggest that sevoflurane is useful for patients in whom intravenous access is problematic or in whom intravenous anesthetics cause severe on injection. As to neuromuscular blockade, succinylcholine 0.5 to 1.0 mg/kg has usually been used in ECT because of its short duration of action. It has to be deep enough to suppress abdominal muscle contraction to avoid aspiration of stomach contents, and to avoid trauma.[15]

In the present study, we excluded patients with cardiovascular diseases. Previous studies, however, have demonstrated that the QTD increases in patients with myocardial infarction, subarachnoid hemorrhage, or diabetes mellitus.[7,8,32–34] It is suggested that ECT may induce further increased risks of ventricular arrhythmias and cardiovascular events in such patients. Further examination is needed in such patients.

In conclusion, significant increases of the QTc interval, QTD, and QTcD, which are associated with increased risks of arrhythmias, were observed before anesthetic induction in patients with major depression. Electrical stimulus during ECT may induce further increases of the QTD and QTcD.

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下咽頭癌治療における化学放射線治療の役割

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宮崎眞和　斉川雅久　海老原　敏

要旨：下咽頭癌は初診時既に進行していることが多く，予後不良の疾患である。患者のQOLを考え，進行度に応じて機能温存を考慮した治療が必要である。当院では喉頭温存手術が困難な症例に対しては手術とCRTの両者を提示している。化学放射線療法（CRT）では胃瘻や気管切開への長期依存を余儀なくされることがあり，機能温存が達成されないこともある。治療後の機能や合併症，再発時の対応，重複癌に対する治療などを十分考慮して手術，CRTの適応を検討する必要がある。CRTでは胃瘻を用いた栄養管理とオピオイドを用いた疼痛対策などをはじめとする支持療法によって治療完遂率を高め，粘膜炎の遷延や腎障害を予防している。

キーワード：化学放射線療法，喉頭機能温存，支持療法

はじめに

下咽頭癌は頭頸部扁平上皮癌の中でも予後不良な疾患であり，初診時に既に進行していることが多い。治療にあたっては手術であれ，化学放射線療法（CRT）であれ，根治性と同時に機能温存を考えた治療が必要である。CRTでは形態的に喉頭・咽頭は残るが胃瘻や気管切開への長期依存を余儀なくされることがあり，機能温存が達成されないこともある。口腔内乾燥・嚥下障害などの放射線治療による障害，再発時の救済手術の困難性，重複癌に対する治療，なども十分に考慮して治療の適応を検討する必要がある。本稿では切除可能症例に対するCRTの役割とCRT完遂のための支持療法について述べる。

当院における下咽頭癌の治療方針

当院では下咽頭扁平上皮癌に対するCRTを次のような症例に対して行っている。初回治療として喉頭温存手術が困難な症例のうち喉頭摘出を拒否する症例，手術切除不能症例，術後治療として手術切除標本で切除断端陽性やリンパ節の節外浸潤を認める症例，これらの症例に対して進行度及び全身状態を評価し適応を判断している（図1）。

早期の症例に対しては放射線治療と同時に喉頭温存下咽頭部分切除術の適応も考慮する。切除範囲が一側の梨状陥凹＋披裂喉頭蓋ヒダ＋喉頭蓋の患側基部，もしくは後壁の欠損が2～3 cm径で限局するものについては切除後の一次縫縮が可能である。切除範囲がそれ以上で披裂および披裂喉頭蓋ヒダに及ぶものに対しては遊離空腸や前腕皮弁によって再建を行っている。さらにこれらを超える病変に対する手術治療としては下咽頭喉頭全摘出術もしくは喉頭摘出・下咽頭部分切除術を選択している。

患者へは手術治療，CRTの両者について，根治性，有害事象，治療後の機能，再発・多発時の治療について説明を行っている。甲状軟骨破壊や咽頭収縮筋への浸潤がある症例に対してはCRTで治癒が得られたとしても気道狭窄や咽頭狭窄，嚥下困難，誤嚥などによって喉頭機能が温存出来ないことが多いため，十分に治療後の機能を説明している。さらに，CRT後に残存・再発が認められた場合は頸部の瘢痕形成により手術が困難となる場合があることも説明している。

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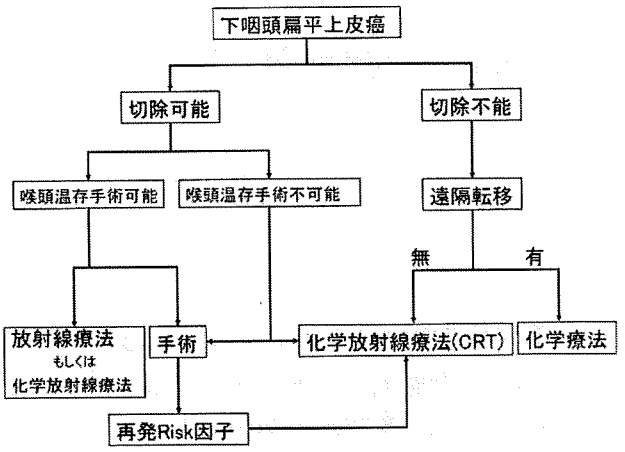

図 1　下咽頭癌に対する治療選択のシェーマ

下咽頭癌に対する化学放射線治療の報告

当院での下咽頭癌に対するCRTの報告[1]では，喉頭摘出を要する切除可能下咽頭癌70例に対して化学放射線治療もしくは放射線治療を行い，過分割照射群で3年生存率83%，通常照射群で3年生存率66%と良好な成績を得ている。合併症，機能障害としてはシスプラチン・5FUを併用した3例にのみ胃瘻依存・気管切開依存などが認められたが，永続的な障害は1例のみであった。この検討には甲状軟骨破壊例と気道狭窄例は含まれておらず，症例の選択によっては機能温存と根治が両立できると言える。

海外の報告では，切除可能進行下咽頭癌について下咽頭喉頭全摘出術を先行したほうが放射線治療よりも制御率，5年生存率ともに良いとする報告がある[2]。その一方，梨状陥凹原発扁平上皮癌について，導入化学療法および放射線治療は患者の生命予後を危険にさらすことなく喉頭を温存し得るとする報告もある[3]。Sooら[4]はStage Ⅲ-Ⅳの転移のない頭頸部癌に対して手術＋術後照射60Gy群と化学放射線治療（CDDP＋5FU＋66Gy）をランダム化し，生存率に差はなかったが，臓器温存については下顎放射線治療群が優れていたと報告している。

現時点では進行下咽頭癌に対する治療方法は検討の積み重ねが行われている状態といえる。

放射線単独と化学放射線治療の比較ではBrowmanら[5]はプラチナ製剤ベースの同時放射線化学療法は，放射線単独療法に比べ，生存率を改善させるとしている。術後治療としても，Cooper[6]やBernier[7]は高リスク患者において，術後放射線療法に化学療法を同時併用すると，術後放射線療法を単独で実施した場合に比べ，生存率を改善させると報告している。進行度，浸潤に応じて放射線治療に化学療法の併用を考慮すべきである。

救済手術について

切除可能症例に対して化学放射線治療を行った場合，再発時に救済手術が安全に行えるかが問題となる。国立がんセンター東病院で下咽頭喉頭全摘出術を行った下咽頭・頸部食道癌の放射線治療後再発症例34例について過去報告したが[8]，救済手術としての下咽頭喉頭全摘出術の場合は通常の下咽頭喉頭全摘出術とは異なり，次のような工夫をして合併症の予防を図っている。皮弁は広頸筋直下ではなく，前頸筋膜の下から厚めに挙上する。リンパ節は残存部分のみ部分郭清。死腔充填のために腸間膜を多く付けて空腸を採取する。腸間膜で吻合血管を被覆する。これらの工夫によって放射線照射を行っていない症例と同程度の合併症の頻度であったが，CRT後の症例では気管孔周囲の感染が比較的高率であり，注意が必要である（表1）。救済手術として行った下咽頭喉頭全摘出術症例の術後1年生存率は65%であった。手術可能であれば救済手術を考慮すべきだが，CRT後の手術は瘢痕形成や手術操作が困難となることが明らかであり，治療前に十分に説明することが必要である。

支持療法

CRTにおいては有害事象，特に疼痛や感染，低栄養によって完遂が困難になりがちである。特に低栄養は粘膜炎の遷延をもたらし，さらに経口摂取困難となるため悪循環となりえる。結果として治療の休止・延長につながってしまい，十分な治療効果が得られないことがあり，これらを改善するために支持療法が必要となる（図2）。

当院ではCRT症例に対してはほぼ全例に内視鏡的に胃瘻を造設している。造設はCRT開始前に消化器内科で1週間程度の入院でおこなっている。胃瘻は治療中のみならず，腫瘍の再発や残存によって経口摂取困難となった場合にも有用な投

表 1　救済手術として行った咽喉食摘術の合併症

	RT（n＝15）	CRT（n＝19）
	例数（%）	例数（%）
腸管全壊死	0　(0)	0　(0)
血栓形成・血流障害	1　(6.6)	1　(5.2)
瘻孔形成	1　(6.6)	1　(5.2)
頚部皮弁壊死	0　(0)	1　(5.2)
創部感染	1　(6.6)	0　(0)
狭窄	0　(0)	1　(5.2)
気管孔周囲感染	2（13.3）	7（36.8）

CRT術後では気管孔周囲の感染が高率となっている。

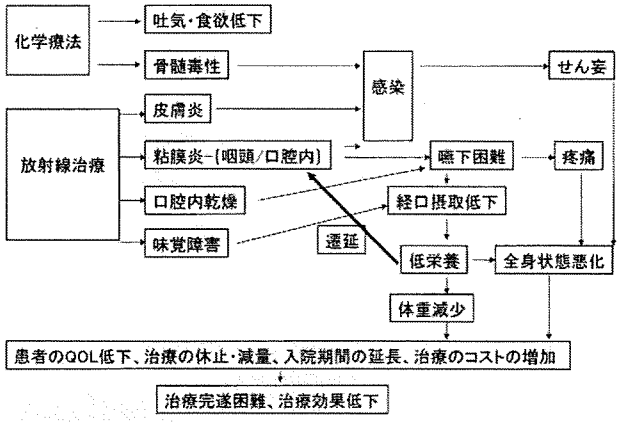

図 2　頭頸部癌に対する化学放射線療法における有害事象
化学放射線治療においては有害事象，特に疼痛や感染，低栄養によって完遂が困難になりがちである。
特に低栄養は粘膜炎の遷延をもたらし，さらに経口摂取困難となるため悪循環となる。

薬・栄養経路となるため，QOLの保持に役立つ。

経皮的胃瘻造設に伴う急性期有害事象のために化学放射線治療の開始が延期となった症例は経験していない。胃瘻造設によるCRTのコンプライアンスを表2に示す。胃瘻を造設することによって放射線休止割合は14％と低く，放射線及び化学放射線治療完遂割合91～95％と非常に良好であった。総治療期間も中央値51日と治療期間の延長も抑えられている。治療終了から退院までの期間は中央値7日間と短期間であった。化学放射線治療に伴う粘膜炎の痛みに対しては早期からオピオイドを併用し，良好な鎮痛効果を得ている。オピオイドはモルヒネ液のみでなく，モルヒネ徐

表 2　胃瘻造設によるCRTのコンプライアンス（n＝100）

放射線照射休止割合		14％(14/100)
放射線照射完遂割合		95％(95/100)
CRT完遂割合		91％(91/100)
総治療期間	中央値 (range)	51日 (3～70)
治療終了 ～退院までの期間	中央値 (range)	7日 (－13～67)

胃瘻造設によって良好な完遂率が得られている。

放細粒やオキシコドンを胃瘻から投与することが可能である。支持療法は治療完遂および治療効果改善のために不可欠なものである。

結　語

・国立がんセンター東病院における下咽頭癌に対する化学放射線治療について述べた。

・喉頭摘出拒否例に対しては喉頭温存治療として一定の成績を得ている。

・化学放射線治療を行うにあたっては，胃瘻及び麻薬の使用などの支持療法によって良好な完遂率を得ることが可能である。

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