Index of cardiac electrophysiological balance can better predict the risk of arrhythmia than QT and Tp-e interval in patients inhalating sevoflurane

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Research Article

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Abstract

Objective: To compare the value of ECG markers such as QT interval, Tp-e interval and index of cardiac electrophysiological balance (iCEB) in evaluating the effect of sevoflurane on cardiac electrophysiology.

Methods: Sixty patients undergoing elective gynecological surgery were randomly divided into group S₁, group S₂ and group S₃, 20 cases in each group. Patients were received 10ml/kg of hydroxyethyl starch, 0.1mg/kg of midazolam, 0.1 mg/kg of vecuronium, 3μg/kg of fentanyl and 0.3mg/kg of etomidate intravenously. Mechanical ventilation was performed after endotracheal intubation. Sevoflurane concentration was maintained at 0.6 MAC, 1.3 MAC and 2.0 MAC in group S₁, group S₂ and group S₃ respectively. The QT interval, QRS interval and Tp-e interval were measured before anesthesia induction (T₁), 5 minutes after tracheal intubation (T₂), and 20 minutes after rising to the set concentration of sevoflurane (T₃). The QTc interval, Tp-e/QT ratio and iCEB were measured and calculated. MAP and HR were recorded at the same time.

Results: Compared with T₁, MAP and HR decreased at T₃ in S₁-3 group (P < 0.05); Compared with T₁, iCEB increased at T₂-₃ in S₁-₃ groups, QTc interval prolonged at T₃ in S₁-₃ groups (P < 0.05). Compared with T₂, iCEB increased at T₃ in S₁-₃ groups. Compared with S₁ group, the Tp-e Shortened, iCEB increased in S₂-₃ groups. Compared with S₂ group, iCEB decreased in S₃ group at T₃.

Conclusion: iCEB is more sensitive and objective, and can better predict the risk of arrhythmia. iCEB can be used as the preferred index to evaluate the electrophysiological effects by anesthetics in clinic.

Background

QT interval, QTc interval and Tp-e interval are used to assess the risk of drug-induced arrhythmia on ECG. QT interval refers to the time from the start of QRS wave to the end of T wave. Because of the low sensitivity and specificity, it is not reliable to assess the risk of arrhythmia by QT (QTc) interval alone. Tp-e interval refers to the time interval between the peak of T wave and the end of T wave which reveals the heterogeneity of repolarization between ventricular subepicardial cardiomyocytes and M cell. Tp-e interval reflects the dispersion of repolarization, and can predict the arrhythmia caused by reentry especially. However it can not accurately predict the arrhythmia caused by other reasons. Sevoflurane, a classic inhaled anesthetic, is widely used for the induction and maintenance of anesthesia, but the conclusions of the effect of sevoflurane on these parameters are not consistent at the temporary. In previous studies, majority of experts consider that sevoflurane prolonged the QTc interval significantly and increased the risk of ventricular arrhythmia. It also has been reported that sevoflurane prolong the QT interval without affecting the Tp-e interval or QT interval. Therefore, finding an efficient biomarker that can correctly evaluate the effects of sevoflurane or other drugs on cardiac electrophysiology has a great importance in clinical. The index of cardiac electrophysiological balance (iCEB) is a new noninvasive biomarker that reflect the balance between myocardial electrophysiological depolarization...
and repolarization, it can predict the risk of drug-induced cardiac arrhythmias.\textsuperscript{11,12} In this study, we observed the effects of QT interval, Tp-e interval, Tp-e/QT and iCEB during inhalation of sevoflurane at different concentrations and compared the value of biomarkers, so as to provide reference for early assessment and intervention of perioperative arrhythmia risk.

**Methods**

The experiment was approved by Medical Ethics Committee in the college (Application Number: 20180141, Guizhou Medical University), and was registered at the Chinese Clinical Trial Registry (Registry name: Clinical study on the effects of intravenous anesthetics and inhaled anesthetics on cardiac electrophysiology, Registration Number: ChiCTR1900021967, 18/03/2019). All the subjects have given informed consent prior to participating in the study.

**Study populations**

There were 64 female patients enrolled (hysteromyomectomy, excision of ovarian cyst and excision of ovarian tumors), ASA ~, aged 20–50 years old, scheduled for elective surgery under general anesthesia. All patients with preoperative cardiac and pulmonary function tests were normal or within the scope of the compensation, Pulmonary function was normal, SpO\textsubscript{2} on fingers is more than 95%, ECG and electrolyte were normal, and heart rate corrected QT interval (QTc interval) < 440 ms, without diabetes and other endocrine diseases. All patients did not use drugs that prolonged QT drugs (such as antiarrhythmic drugs, beta blockers, antidepressants, phenothiazines, etc.). 4 patients were excluded due to declined to participate.

Patients were randomly divided into Group S\textsubscript{1} (0.6MAC)(n = 20), Group S\textsubscript{2} (1.3MAC)(n = 20) and Group S\textsubscript{3} (2.0MAC)(n = 20) using a random number table, 20 cases in each group.

**Procedure**

Patients were fasted strictly for 8 hours and drinking forbidden for 4 hours before surgery. Trials were performed in the morning (8:30 to 11:30 A.M.) to prevent the diurnal change of QT interval.\textsuperscript{13} On arrival in the operation room, each patient was monitored using a three-lead ECG, pulse oximetry, non-invasive arterial pressure continuously. After inserting an intravenous catheter, 130/0.4 sodium chloride injection (10 mL/kg) of hydroxyethyl starch (specification: 500 mL/bag, batch number: 81ME525, Beijing Fresenius Kabi Medical Group) was infused to the UEV within 30 min. 12-lead ECG electrode was obtained by using the ECG-1250C 12-lead electrocardiograph (Shanghai Photoelectric Medical Instrument Corporation) at a chart speed of 25 mm/s and gain amplification of 10 mm/mV. General anaesthesia was then induced with intravenous midazolam 0.1 mg/kg, vecuronium 0.1 mg/kg, fentanyl 3 ug/kg, and etomidate 0.3 mg/kg. Then the patients were accepted tracheal intubation and mechanical ventilation with tidal volume of 8ml/kg, ventilation frequency of 12 times/min, inspiration-expiration ratio of 1:2, oxygen flow rate of 2 L/min, while maintaining the airway pressure between 12–18 cmH2O, PETCO2 between 35–45 mmHg, SpO2 between 98%-100%. Then open the sevoflurane (240ml/bottle, batch...
number: 7X301, AbbVie Japan) evaporator. The concentrations of sevoflurane in groups S₁, S₂, S₃ were maintained at 0.6 MAC, 1.3 MAC, and 2.0 MAC respectively. 20 minutes after the concentration of sevoflurane rising to the maintained concentration, record the second 12-lead ECG.

12-lead ECG were obtained before induction(T₁), 20 minutes after rising to the maintenance concentration of sevoflurane (T₂), record the HR and MAP of patients in three groups at the same time. Then measure and calculate the QT interval, QTc interval, Tp-e interval, Tp-e /QT ratio and iCEB. The incidence of arrhythmia of patients during the trial was recorded.

**Electrocardiographic measurements**

All the ECG data were obtained from five consecutive averaging beats. An independent cardiologist who blindly analyzed ECG. Based on the literature¹⁴, V₄ leads were used to measure the QT interval and Tp-e interval. The QT interval was calculated as the time from the start of the QRS complex to the end of T wave, and the Tp-e interval was calculated as the interval between the peak and the end of T wave (The T peak is the highest point of T wave, and the T end point is the intersection of the descending branch tangent and the baseline. When U waves were present, the nadir between the T and U waves was regarded as the end of the QT interval). QT intervals and Tp-e intervals were measured on the V₄ lead from 3 consecutive beats, then calculate the mean values and Tp-e/QT ratio. The QTc interval was corrected for HR using Bazett's formula (QTc = QT / √RR).¹⁵ iCEB was calculated by the method according to literature¹²: iCEB = QT/QRS.

**Statistical analysis**

Statistical analysis was conducted by using SPSS 24.0 software. The ECG data and results are represented as mean ± SD (x ± s). Statistical analysis between groups was performed using a one-way analysis. Changes over time within each group were analysed with repeated measures analysis of variance. The enumeration data were analyzed with χ² test. P < 0.05 was considered statistically significant.

**RESULTS**

**Patients**

This study included 64 patients, 4 patients were excluded. There was no difference between the groups with respect to age, BMI, ASA class, other demographic characteristics and dose of midazolam, vecuronium, fentanyl and etomidate. (Table 1)
Table 1
Demographic of three groups ($\bar{x} \pm s$, $n = 20$).

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>ASA grade (♀/♂)</th>
<th>Age (Year)</th>
<th>BMI (kg/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S$_1$</td>
<td>20</td>
<td>10/10</td>
<td>38 ± 9</td>
<td>22.12 ± 1.93</td>
</tr>
<tr>
<td>S$_2$</td>
<td>20</td>
<td>11/9</td>
<td>38 ± 8</td>
<td>22.51 ± 3.13</td>
</tr>
<tr>
<td>S$_3$</td>
<td>20</td>
<td>9/11</td>
<td>37 ± 9</td>
<td>22.45 ± 2.76</td>
</tr>
</tbody>
</table>

S$_1$: 0.6 MAC sevoflurane; S$_2$: 1.3 MAC sevoflurane; S$_3$: 2.0 MAC sevoflurane;

Circulation changes in three groups

Compared with T$_1$, MAP decreased at T$_2$, MAP and HR decreased at T$_3$ in S$_1$-3 groups ($P<0.05$). Compared with T$_2$, MAP and HR decreased at T$_3$ in S$_1$-3 groups ($P<0.05$) (Table 2).

Table 2
Comparison of MAP and HR of three groups at different times ($\bar{x} \pm s$, $n = 20$).

<table>
<thead>
<tr>
<th>Group</th>
<th>Index</th>
<th>T$_1$</th>
<th>T$_2$</th>
<th>T$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>S$_1$</td>
<td>MAP(mmHg)</td>
<td>83 ± 12</td>
<td>72 ± 11a</td>
<td>64 ± 10$^{ab}$</td>
</tr>
<tr>
<td></td>
<td>HR(/min)</td>
<td>74 ± 8</td>
<td>68 ± 9</td>
<td>73 ± 15$^{ab}$</td>
</tr>
<tr>
<td>S$_2$</td>
<td>MAP(mmHg)</td>
<td>82 ± 11</td>
<td>72 ± 8a</td>
<td>59 ± 5$^{ab}$</td>
</tr>
<tr>
<td></td>
<td>HR(/min)</td>
<td>74 ± 11</td>
<td>68 ± 10</td>
<td>62 ± 9$^{ab}$</td>
</tr>
<tr>
<td>S$_3$</td>
<td>MAP(mmHg)</td>
<td>83 ± 6</td>
<td>72 ± 7a</td>
<td>61 ± 6$^{ab}$</td>
</tr>
<tr>
<td></td>
<td>HR(/min)</td>
<td>74 ± 10</td>
<td>68 ± 9</td>
<td>57 ± 6$^{ab}$</td>
</tr>
</tbody>
</table>

S$_1$: 0.6 MAC sevoflurane; S$_2$: 1.3 MAC sevoflurane; S$_3$: 2.0 MAC sevoflurane; T$_1$: before induction; T$_2$: 5 min after tracheal intubation; T$_3$: 20 minutes after rising to the set concentration of sevoflurane;

Compared with T$_1$$^aP$ 0.05; Compared with T$_2$, $^bP$ 0.05

Changes of electrophysiological biomarkers in three groups
Compared with $T_1$, iCEB increased at $T_2-3$ in $S_1-3$ groups, QTc interval prolonged at $T_3$ in $S_1-3$ groups ($P < 0.05$). Compared with $T_2$, iCEB increased at $T_3$ in $S_1-3$ groups. Compared with $S_1$ group, the Tp-e Shortened, iCEB increased in $S_2-3$ groups. Compared with $S_2$ group, iCEB decreased in $S_3$ group at $T_3$ (Table 3).

### Table 3
Comparison of QTc,Tp-e intervals, the ratio of Tp-e/QT, and iCEB of the three groups at different times ($\bar{x} \pm s, n = 20$)

<table>
<thead>
<tr>
<th>Group</th>
<th>Index</th>
<th>$T_1$</th>
<th>$T_2$</th>
<th>$T_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>QTc(ms)</td>
<td>416.65 ± 14.94</td>
<td>422.85 ± 13.46</td>
<td>433.00 ± 13.17$^a$</td>
</tr>
<tr>
<td></td>
<td>Tp-e</td>
<td>81.05 ± 6.01</td>
<td>85.10 ± 7.44</td>
<td>82.35 ± 7.72</td>
</tr>
<tr>
<td></td>
<td>Tp-e/QT</td>
<td>0.20 ± 0.01</td>
<td>0.21 ± 0.02</td>
<td>0.20 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>iCEB</td>
<td>4.76 ± 0.34</td>
<td>4.93 ± 0.48$^a$</td>
<td>5.35 ± 0.52$^{ab}$</td>
</tr>
<tr>
<td>$S_2$</td>
<td>QTc(ms)</td>
<td>415.15 ± 15.54</td>
<td>420.25 ± 16.53</td>
<td>432.10 ± 14.70$^a$</td>
</tr>
<tr>
<td></td>
<td>Tp-e</td>
<td>80.00 ± 7.51</td>
<td>85.15 ± 6.24</td>
<td>78.56 ± 7.14$^{bc}$</td>
</tr>
<tr>
<td></td>
<td>Tp-e/QT</td>
<td>0.21 ± 0.02</td>
<td>0.20 ± 0.02</td>
<td>0.20 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>iCEB</td>
<td>4.87 ± 0.55</td>
<td>5.06 ± 0.60$^a$</td>
<td>5.39 ± 0.55$^{ab}$</td>
</tr>
<tr>
<td>$S_3$</td>
<td>QTc(ms)</td>
<td>414.50 ± 16.13</td>
<td>423.80 ± 19.12</td>
<td>432.25 ± 24.64$^a$</td>
</tr>
<tr>
<td></td>
<td>Tp-e</td>
<td>82.00 ± 5.47</td>
<td>84.80 ± 4.76</td>
<td>79.35 ± 4.05$^{bc}$</td>
</tr>
<tr>
<td></td>
<td>Tp-e/QT</td>
<td>0.21 ± 0.01</td>
<td>0.21 ± 0.01</td>
<td>0.21 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>iCEB</td>
<td>4.84 ± 0.47</td>
<td>4.98 ± 0.44$^a$</td>
<td>5.54 ± 0.53$^{abcd}$</td>
</tr>
</tbody>
</table>

$S_1$: 0.6 MAC sevoflurane; $S_2$: 1.3 MAC sevoflurane; $S_3$: 2.0 MAC sevoflurane; $T_1$: before induction; $T_2$: 5 min after tracheal intubation; $T_3$: 20 minutes after rising to the set concentration of sevoflurane; Compared with $T_1$, $^aP<0.05$; Compared with $T_2$, $^bP<0.05$; Compared with $S_1$, $^cP<0.05$; Compared with $S_2$, $^dP<0.05$

### Discussion

The effect of drugs on cardiac electrophysiology is important while evaluating the safety of drug. The action potential produced by cardiac myocytes is the basis of cardiac electrical activity. The balance between depolarization and repolarization ion currents in cardiac membrane maintains the stability of
cardiac electrophysiology. When the balance of ion currents is broken, it affects the stability of cardiac electrophysiology and leads to arrhythmia\textsuperscript{16,17}. While the mechanism of drug-induced arrhythmias is complex, it is significant to find sensitive markers to predict the risk of arrhythmia on ECG.

Drug cardiotoxicity has been characterized by prolonged QT interval as a risk marker for a long time\textsuperscript{18–19}. The QT interval refers to the time from the beginning of QRS wave to the end of T wave, including the process of ventricular depolarization and repolarization. With the further understanding of long Q-T syndrome (LQTS), it was found that the correlation between prolonged QT interval and the occurrence of torsade de pointes (TdP) was not close. It was not sufficient to evaluate the potential arrhythmic risk of drugs by using QTc interval alone\textsuperscript{19,20}. The ventricle is composed of endocardium, epicardial myocytes and M cells. The different electrophysiological characteristics of myocardial cells in three layers cause the transmural dispersion of repolarization (TDR). Tp-e interval is defined as the time from T-wave peak to T-wave end to a point where it reaches the baseline, which is the typical reflection of the repolarization dispersion across ventricular walls on ECG\textsuperscript{21}. Previous studies showed that Tp-e interval can predict the risk of arrhythmia caused by I\textsubscript{ks} blockade, and Tp-e/QT ratio can predict the risk of arrhythmia caused by hERG channel blockade\textsuperscript{22,23}.

Index of cardiac electrophysiological balance (iCEB), a new noninvasive biomarker which is measured from electrocardiogram (ECG), is more practical than long QT interval to predict torsades de pointes (TdP), and more effective than transmural dispersion of repolarization to evaluate the risk of drug-induced arrhythmia\textsuperscript{24,25}. iCEB is calculating using a formula QT/QRS which can be very easy and practical, and replace the classical value $\lambda$ ($\lambda = CV \times ERP$). QRS duration is inversely proportional to CV while the QT interval is proportional to ERP, thus replacing $\lambda$ with iCEB can not only avoid traumatic invase, but also predict the occurrence of Tdp and non-TdP ventricular tachycardia/fibrillation\textsuperscript{11,26}. Thus, under normal heart rhythm and conduction velocity, iCEB can predict the incidence and susceptibility of arrhythmia. iCEB reflects the slight deviation and dynamic balance between depolarization and repolarization. The tiny change of duration from depolarization and repolarization is harmless or even can be anti-arrhythmic, but the excessive change may lead to the severe arrhythmia\textsuperscript{25}.

The results also showed that inhalation of sevoflurane at different concentrations prolonged the QTc interval, suggesting that sevoflurane prolonged ventricular repolarization by blocking the inward rectification potassium channel (I\textsubscript{Kr}) on myocardial cell membranes\textsuperscript{26}. The QT interval corresponds to the total ventricular refractory period and the Tp-e interval corresponds to the relative ventricular refractory period\textsuperscript{27,28}. After the inhalation of sevoflurane at three different concentrations, the Tp-e interval was not prolonged and the ratio of Tp-e/QT remained unchanged, which indicated that inhalation of sevoflurane prolonged action potential duration (APD) of three layers of ventricular myocytes at the same degree and did not increase the heterogeneity of repolarization. Inhalation of sevoflurane did not develop the probability of cardiomyocyte electrical reentry because the ratio of relative ventricular refractory period to total ventricular refractory period remained unchanged.
The maintenance of electrophysiological stability of heart depends on the dynamic balance between depolarization and repolarization of action potential in cardiac myocytes. The depolarization is formed by inward sodium ion current, while the repolarization is formed by inward calcium current and outward potassium current. Some previous studies suggested that using sevoflurane at clinical concentration only prolonged the QTc interval but not the Tp-e interval. While blockade of potassium channel increases the risk of drug-induced arrhythmia, the Tp-e interval can not represent the change of cardiac repolarization dispersion, and can not predict arrhythmias caused by delayed depolarization. Therefore, it is limited to evaluate the effects of sevoflurane on cardiac electrophysiology only by using QTc interval and Tp-e interval. Lu et al. found that iCEB can objectively reflect the dynamic balance between cardiac depolarization and repolarization, and has more advantages in predicting the potential risk of drug-induced malignant arrhythmia by observing the effect of seven drugs on cardiac electrophysiology in isolated rabbit heart. Our results also showed that compared with before inhalation, iCEB increases significantly after inhalation of different concentrations sevoflurane. The more concentration of sevoflurane, the more iCEB increased, suggesting that the balance between depolarization and repolarization was interrupted by sevoflurane while it prolonged the ventricular repolarization duration. iCEB changed and electrical stability decreased when we used sevoflurane. After inhalation of sevoflurane at 2.0 MAC for 20 minutes, the balance between myocardial depolarization and repolarization was affected seriously. While the QTc interval, Tp-e interval and Tp-e/QT ratio did not reflect the change of cardiac electrical activity significantly, iCEB did, suggesting the stability of ECG was affected and there was a risk of arrhythmia.

Conclusions

In conclusion, among the effects of sevoflurane on QT interval, Tp-e interval and iCEB in patients undergoing gynecological surgery, iCEB is more sensitive and objective, and can be used as the preferred index in evaluating the electrical effects caused by sevoflurane in clinical. iCEB can reflect the cardiac electrical changes earlier and provide further clues on the treatment of arrhythmias caused by inhalation of anesthetics.

Declarations

Ethics approval and Consent to Participate

This study was approved by the ethics committee of Guizhou medical university (Application Number: 20180141). We certify that the study was performed in accordance with the 1964 declaration of HELSINKI and later amendments. Informed consent was obtained from all subjects and/or their legal guardian(s).

Availability of Data and Materials
The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

**Consent for Publication**

Not applicable

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**Competing Interests**

The authors declare that they have no conflict of interest.

**Authors’ contributions**

Yanqiu Liu contributed to the conception of the study. Xiaokui Fu performed the experiment and contributed significantly to analysis and wrote the manuscript. Xiaoling Yan performed the data analyses and helped perform the analysis with constructive discussions. All authors reviewed the manuscript.

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**References**


