Electrophysiology

Desflurane Inhibits U Wave in Electrocardiogram

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Background: Volatile anesthetics inhibit cardiac transmembrane ionic currents and intracellular ionic activity and exert antiarrhythmic actions. Among electrocardiogram (ECG) waveforms, the effect of volatile anesthetics on U wave has never been studied. The aim of the present observational study was to evaluate the possible effect of desflurane on U wave in anesthetized patients.

Methods: Peri-operative ECG tracings (lead II) were recorded and analyzed from 24 gynecologic patients (American Society of Anesthesiologists (ASA), class I). Anesthesia was routinely induced with thiopental, fentanyl and succinylcholine and maintained with desflurane (1 to 1.5 minimal alveolar concentration (MAC)) and \( \text{O}_2 \). U wave amplitude (\( U_{\text{amp}} \)) was manually measured from amplified ECG records.

Results: Discernible U wave in 24 patients varied in amplitude (64 ± 24 \( \mu \text{V} \)). U wave was three times larger when heart rate increased to maximum during tracheal intubation. Similarly, \( U_{\text{amp}} \) was augmented (285% ± 58% of the control) in extrasystolic beats elicited by tracheal intubation. Desflurane (1 to 1.5 MAC) significantly and reversibly suppressed \( U_{\text{amp}} \) (a decrease by 60 ± 24 \( \mu \text{V} \), \( n = 24 \), \( p < 0.05 \)).

Conclusions: The suppressive effect of desflurane on \( U_{\text{amp}} \) might be explained by its inhibitory effects on transmembrane ionic currents, intracellular calcium load and delayed afterdepolarizations. Our results support a contributory role of afterpotentials in the genesis of U wave.

Key Words: U wave • ECG • Desflurane • Volatile anesthetics

INTRODUCTION

The origin of U wave has been explained by several hypotheses, although it remains is dispute up to now.1-4 For example, inhomogeneous prolongation of QT interval in epicardium, endocardium and M-cell layers may provide a substrate for TU complex in pathologic condition.5,6 In addition, in a computer simulation model, afterpotentials have been correlated with the occurrence of U wave.7 It should be mentioned that U wave can also be observed in normal healthy subjects. Therefore, U wave might be explained by a common cellular mechanism shared by both physiologic and pathologic conditions. Since volatile anesthetics are known for their cellular electropharmacological effects and antiarrhythmic actions,8,9 we therefore evaluated the possible effects of desflurane on U wave in anesthetized patients.

METHODS

From September 2004 to March 2005, 24 consecutive female patients receiving gynecologic surgery were included in this observational study. All patients were otherwise healthy (American Society of Anesthesiologists (ASA) class I, from 20 to 63 years old) and
neither of them had arrhythmia, electrolyte imbalance, myocardial ischemia and infarction, cardiac hypertrophy and cardiomyopathy, or cerebral hemorrhage. All subjects were in normal sinus rhythm and showed sizable U wave in their electrocardiogram (ECG). Medical history, physical examination, chest radiograph and biochemical data revealed no remarkable abnormalities. None of the patients was taking medications. The investigation conformed with the principles outlined in the Declaration of Helsinki. This prospective, non-randomized clinical study was approved by local institutional review committee. All patients gave their written informed consent. Peri-operative ECG (lead II) was recorded using a two-channel recorder and analyzed in all the patients during anesthesia (study protocol, see Figure 1). The limb lead electrodes were placed at left and right shoulders and the fifth intercostal space at the left axillary line. All ECG recordings were amplified (5 mm/0.1 mV) and all selected ECG strips were printed out at a paper speed of 25 mm/s. The U wave was defined as a positive deflection immediately following the T wave. The amplitudes and the duration of intervals of ECG waveforms were measured manually by using calipers and magnifying lens by two independent anesthesiologists in order to minimize the inter-observer variability. The amplitudes of T wave (T_{amp}) and U wave (U_{amp}) were defined as the absolute distance from the apex of the respective wave to the isoelectric baseline. If T and U waves fused, the U_{amp} was measured from the nadir of T-U complex to the peak of U wave. The ratio of U_{amp}/T_{amp} was also analyzed. The duration of QT interval was measured from start of Q wave to the end of T wave. If the descent of T wave did not touch the baseline, the end of T wave was determined by the intersection of slope of descent of T wave and baseline. The duration of QU interval was measured from the start of Q wave to the peak of U wave. The preceding RR interval was measured and was used to correct QT and QU using Bazett’s formula (QTc

![Diagram](image_url)

**Figure 1.** Study protocol. Lead II ECG tracings were recorded at different stages of anesthesia.

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and QUc).

Standard peri-operative monitoring was routinely instituted (blood pressure, ECG, end-tidal CO₂, pulsed arterial saturation). The induction of anesthesia was performed with fentanyl (1 to 2 µg/kg), thiamylal (4 to 6 mg/kg), and succinylcholine (1 to 2 mg/kg). After tracheal intubation was completed, anesthesia was maintained with desflurane (1 to 1.5 MAC) in the presence of pure oxygen (0.5 L/min). Both the inspiratory and end-expiratory concentrations of desflurane were on-line monitored with an agent analyzer. Muscle relaxation was maintained with either atracurium or rocuronium. The depth of anesthesia was monitored and adjusted by bispectral analysis, auditory evoked potential or autonomic parameters. The results are expressed as the mean ± standard deviation. Minimal and maximal values are indicated. Comparison of T-U changes before and after the administration of desflurane were performed using paired samples t-test. Numbers in parentheses indicate 95% confidence interval of difference (Table 1). To test the difference, a p value < 0.05 was regarded as statistically significant.

RESULTS

Typical examples of U wave from 7 different patients are shown in Figure 2. In addition to appearing immediately after the end of T wave, U wave sometimes fused with T wave during bradycardia or encroached into P wave during tachycardia. The demographic data and ECG parameters of 24 gynecologic patients in this observational study are summarized in Table 1. The size of U wave was variable (64 ± 24 µV). Since U wave was previously regarded as bradycardia-dependent, the size of U wave was therefore compared at maximal and minimal values of heart rate during tracheal intubation. In 4 patients, the size of U waves was three times larger at maximal heart rate than that at minimal one (300% ± 156%).

In 7 out of 24 patients, ventricular extrasystoles were elicited by tracheal intubation during induction of anesthesia. Figure 3 shows ECG tracings of such an example. The size of the U wave of the extrasystoles could be augmented to 285% ± 58% of the control value before induction of anesthesia (n = 7). The suppressive effect of desflurane (1 to 1.5 MAC) on U wave was recorded in 24 patients with discernible U wave. Figure 4 shows such an example. In comparison to that of control (pre-induction resting state), the amplitude of U wave was dramatically and progressively decreased by desflurane. The overall suppressive effect of desflurane on U wave is presented in Table 1. In addition to prolonging the QT interval (54 ± 36 ms, p < 0.05), desflurane significantly decreased Uamp (60 ± 24 µV, p < 0.05). It is noted that suppressive effect of desflurane on U wave was reversible when desflurane was gradually washed out from the patient during emergence from anesthesia (Figure 5).

DISCUSSION

U wave in ECG is known to appear in certain
pathologic conditions, such as electrolyte imbalance, subarachnoid hemorrhage, myocardial ischemia, left ventricular hypertrophy and cardiomyopathy.\textsuperscript{10-14} It should be mentioned, however, that U wave can also appear in normal healthy subjects (up to 70% of prevalence). Thus, the genesis of U wave might be explained by a common cellular mechanism in both pathologic and physiologic conditions. A few hypotheses have been proposed up to now, but none of them is overwhelmingly persuasive. For example, inhomogeneous prolongation of action potentials in ventricular myocytes might provide a substrate for abnormal TU complex, prolonged QT interval, and possibly the ventricular arrhythmias.\textsuperscript{5,6} Such theory might explain the large U wave in patients with hypokalemia and ventricular hypertrophy, because both conditions caused prolongation of the action potential duration in cardiomyocytes. But this theory cannot explain the ischemia-related U wave because both ischemia and hypoxia are expected to shorten the action potential. Above all, the U wave can even become negative in polarity under the condition of myocardial ischemia. Such change of inverted U wave cannot fully be explained by

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{Discernible U wave in ASA class 1 female patients. Lead II ECG tracings were recorded from 7 patients before anesthesia. Sizable U wave was fused with T wave (panels A, F, G) or P wave (panel B). ECG waveforms were amplified (5 mm/0.1 mV), and all selected ECG strips were printed out at a paper speed of 25 mm/s. In each panel, a representative U wave is indicated by an arrow.}
\end{figure}
the inhomogeneous prolongation of the action potential. In the present study, we demonstrated that desflurane suppressed U wave (Figures 4, 5) but did not shorten the QT or QTc (Table 1). Instead, desflurane significantly prolonged QT and QU intervals during anesthesia. In vitro experiments, volatile anesthetics depressed variable cardiac ionic channels and delayed the late repolarization phase of the action potentials. Clinical studies also confirmed that volatile anesthetics, such as desflurane, increased QT interval. Therefore, it seems that prolongation of the action potentials is not prerequisite for the genesis of U wave in normal healthy subjects, and the antagonizing action of desflurane on U wave is not likely via reversing the prolongation of QT interval.

In a computer simulation model, U wave was correlated with the afterpotentials. It is well known that afterpotentials or delayed afterdepolarizations are related to intracellular calcium overload and activation of sodium-calcium exchange and transient inward current. Thus, it is plausible to hypothesize that the size of U wave might be reflected by the status of intracellular calcium load on a beat-by-beat basis. In in-vitro studies, volatile anesthetics inhibit transmembrane calcium current, reduce intracellular calcium activity and suppress delayed afterdepolarizations. Our results favor this hypothesis because desflurane could significantly decrease U wave size in the present study (Figures 4, 5). Other volatile anesthetics (e.g., isoflurane and sevoflurane), with shared similar cardiac cellular electropharmacological actions, also suppress U wave. Therefore, the links between intracellular calcium load, delayed afterdepolarizations, and U wave can be made.

Such link can be further supported by the fact that sympathomimetics can increase U wave size in normal healthy subjects. In addition, post-extrasystole U wave augmentation has been demonstrated in patients with right ventricular outlet-ventricular tachycardia which is correlated with catecholamine, intracellular calcium and triggered activity. Our results also show that U wave

Figure 3. Extrasystoles-augmented U wave during tracheal intubation. In this patient with sizable U wave, ventricular extrasystoles occurred immediately after tracheal intubation (panels A-D). The amplitudes of U wave following the extrasystoles (arrows) were much larger than those in pre-anesthesia state and progressively decreased when the extrasystoles were replaced by sinus rhythm (panel E). Voltage scale: 5 mm/0.1 mV. Speed scale: 25 mm/s.
amplitude was increased at faster heart rate during tracheal intubation when sympathetic tone was enhanced. We also demonstrated that high sympathetic tone elicited ventricular extrasystoles during tracheal intubation while amplitude of U wave was increased (Figure 3). Whether a protein kinase A-dependent signal transduction pathway is involved in the modulation of U wave needs to be further studied.

It is surprising that such high prevalence of visible U wave could be observed in female patients in our study and in other normal healthy subjects (up to 70%). Since our patients were categorized into ASA class I, the common causes of pathologic U wave can be excluded. The role of U wave in healthy subjects is not known so far. However, our preliminary results show that patients with sizable U wave are prone to develop ventricular extrasystoles during induction of anesthesia (manuscript in preparation). The arrhythmogenic role of sizable U wave in patients during induction of anesthesia remains to be explored. On the other hand, lack of ventricular extrasystoles in such patients during maintenance of anesthesia might be explained by the antiarrhythmic ac-

Figure 4. Suppressive effects of desflurane on U wave. A series of U wave changes from pre-anesthesia state (panel A) to those immediately after tracheal intubation (panels B-D) and during maintenance of anesthesia (panels E-G). Arrow indicates an example of U wave in each tracing. It is noted that U wave was completely suppressed by desflurane (panel G). Voltage scale: 5 mm/0.1 mV. Speed scale: 25 mm/s.
tions of volatile anesthetics via suppressing U waves. So far, the potential clinical implication of the antiarrhythmic action of desflurane on U wave is not clear yet.

Several limitations of the present study should be noted. Due to practical limitation, lead II was used for routine peri-operative ECG monitoring, which might not reflect the real changes of U wave. U wave usually can be best observed in precordial leads V2, V3 and V4 from a complete 12-lead ECG. The confounding factors (such as age, body weight, hemodynamic changes, duration of anesthesia) were not analyzed in the present study due to the small sample size.

In conclusion, desflurane could suppress U wave in healthy anesthetized female patients and might serve as a pharmacological tool to further understand the origin of U wave.

ACKNOWLEDGEMENTS

The grant for this research from Taichung (TCVGH-946304C) and Taipei Veterans General Hospitals and Providence University is highly appreciated. The authors thank Miss Mindy Lin for her devoted secretarial work.

![Figure 5. Reversible inhibitory effects of desflurane on U wave. (A): pre-anesthesia state; (B-D): progressive inhibition of U wave by desflurane during maintenance of anesthesia; (E-F): recovery of suppressed U wave during emergence from anesthesia. Arrows indicate examples of U wave in each tracing. Voltage scale: 5 mm/0.1 mV. Speed scale: 25 mm/s.](image-url)
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REFERENCES

Desflurane 抑制心電圖的 U 波

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背景 揮發性麻醉劑可抑制心臟細胞細胞膜上的各種離子流及細胞內的離子活性，同時也表現出其抗心律不整的藥理作用。然而，在心電圖所有的波型當中，唯有 U 波從未被研究是否受到此類麻醉劑的影響。本觀察型的臨床研究就是要探討，在婦科病患的麻醉過程當中，desflurane 對 U 波的影響。

方法 在 24 位健康的婦科病患 (美國麻醉學會分類的第一級)，於麻醉過程當中記錄並分析其第二導程的心電圖。麻醉誘導的方式採用常規的藥物，包括 thiopental, fentanyl, succinylcholine 三種藥物。麻醉維持期則以 desflurane (1 至 1.5 最小肺泡濃度) 及氧氣為主。U 波幅度的大小是從放大的心電圖記錄紙以手工目視量取。

結果 在 24 位呈現 U 波的婦科病患當中，其平均幅度為 64 ± 24 μV。當進行氣管插管的動作時，若病患的心跳因此而有明顯的增速，U 波的幅度可以隨心跳變快而增大 3 倍左右。若病患此時出現短暫的心室性早期收縮，U 波的幅度也會變大，是麻醉前的 285% ± 58%。在 24 位病患當中，desflurane (1 至 1.5 最小肺泡濃度) 會顯著且可逆地抑制 U 波幅度的大小 (減少 60 ± 24 μV, p < 0.05)。

結論 心電圖的 U 波會受到 desflurane 的抑制，可能是與其抑制心臟細胞膜的離子流、細胞內的鈣離子活性及延遲性後去極化有關。本研究結果顯示，U 波的生成可能與後膜電位的假說較有關聯。

關鍵詞：U 波、心電圖、desflurane、揮發性麻醉劑。