Sevoflurane as a Pharmacological Probe to Explore the Genesis of the U Wave in the Electrocardiogram

Hsiang-Ning Luk[1,2,*] Chieh-hung Li[1] Chi-Tsung Chien[1] Chu-Pin Lo[2]

Juan-Ming Yuan[2] Chern-En Chiang[3]

[1]*Department of Anesthesiology, Taichung Veterans General Hospital, Taichung, Taiwan, 407 ROC*
[2]*Department of Applied Mathematics, Providence University, Taichung, Taiwan, 433 ROC*
[3]*Department of Cardiology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan, 112 ROC*

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Abstract

As one of the hypotheses, the presence of after-potentials might contribute to the genesis of U wave in ECG. Volatile anesthetics inhibit cardiac transmembrane ionic currents and intracellular calcium activity. Such pharmacological effects might explain their inhibitory actions on delayed afterdepolarizations and triggered activity. The aim of the present study was to evaluate the possible effect of sevoflurane on U wave in human beings. Perioperative ECG (lead II) were recorded and analyzed from 35 gynecologic patients (20 to 70 years old, ASA class I). All these 35 patients with sizable U waves were consecutively included in this observational study. Anesthesia was routinely induced with thiamylal, fentanyl and succinylcholine and maintained with sevoflurane and pure O_2. U wave amplitude (U_{Amp}) was manually measured from amplified ECG records. Discernible U wave in variable size could be identified in 35 patients (58 ± 29 μV). A negative correlation between RR interval and U_{Amp} (r = 0.471) supported the tachycardia-augmented nature of U wave in the presence of sympathetic stimulation. U_{Amp} was larger in extrasystolic beats (350 ± 217 % of the control, n = 11, $\boldsymbol{p} < 0.05$). Sevoflurane (1 to 1.5 MAC) significantly and reversibly suppressed U_{Amp} (a decrease by 53 ± 27 μV, n = 35, $\boldsymbol{p} < 0.05$). The suppressive effect of sevoflurane on U_{Amp} might suggest the role of intracellular calcium load and delayed afterdepolarizations as a possible origin of U wave in normal human beings.

Keywords: U wave, ECG, Sevoflurane, Volatile anesthetics

Introduction

U wave, an elusive inscription on the ECG, appeared in pathologic conditions (e.g., hypokalemia, hypocalcemia, cardiac ischemia, cardiac hypertrophy, subarachnoid hemorrhage, etc). Interestingly, U wave also exists in normal healthy subjects. The cellular mechanism for the origin of U wave, however, remains unclear [1]. Several hypotheses have been proposed to explain this late deflection immediately following T wave in the ECG. For instance, late repolarization of subendocardial Purkinje fibers was related to the generation of U wave [2]. Inhomogeneous dispersion of action potential duration in ventricular epicardium, endocardium, and middle layers (M-cell layers) might also contribute to the genesis of U wave [3]. Mechano-electrical feedback has been demonstrated to be related to U waves in ventricular hypertrophy [4]. Both delayed and early afterdepolarizations, due to the alteration in transmembrane ionic currents and intracellular calcium, have been proposed to play a plausible role in the formation of U wave [5,6]. Although several studies have already addressed this unsolved issue, direct evidence to fully support any of these hypotheses is still lacking.

Volatile anesthetics (e.g., isoflurane, desflurane, sevoflurane etc.) exert both antiarrhythmic and arrhythmogenic actions in the heart [7-9] and show inhibitory effects on various transmembrane ionic currents and intracellular sodium and calcium activities in cardiomyocytes [10-13]. It has been demonstrated that halothane and isoflurane could suppress digitalis or catecholamine-mediated triggered activity in canine Purkinje fibers and ventricular muscles in *in-vitro* condition [14-15]. These suppressive effects of halothane and isoflurane are demonstrated to be mediated by a reduction in the amplitude of afterdepolarizations. Therefore, it is plausible to hypothesize that volatile anesthetics could suppress U wave formation, under the assumption that the after-potentials do play an important role in the genesis of U wave. Recently, we have demonstrated that isoflurane and desflurane can suppress U wave in anesthetized female patients [16-17]. In the current study, the dynamic changes in T-U waves recorded by routine peri-operative ECG (lead II)

* Corresponding author: Hsiang-Ning Luk
Tel: +886-4-23592525 ext.4102; Fax: +886-4-2461-3371
E-mail: luk1015@vghtc.gov.tw

were analyzed in the anesthetized gynecologic patients receiving sevoflurane.

Methods

The study population consisted of 35 female patients receiving gynecological surgery. All patients were otherwise healthy (American Society of Anesthesiologists (ASA) class I, from 20 to 70 years old) and neither of them had arrhythmias, electrolytes 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 were taking medications. The investigation conformed with the principles outlined in the Declaration of Helsinki. This observational (non-randomized and non-invasive) clinical study was approved by the local institutional research board. Offline lead II ECG tracings showing sizable U waves from 35 patients receiving sevoflurane were analyzed.

ECG, as a standard monitoring, was routinely recorded in each patient before induction of anesthesia. The limb leads electrodes were located on the 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 or negative deflection immediately following the T wave. The amplitudes and the duration of intervals of ECG waveforms were manually measured using calipers and magnifying lens. 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 the T-U complex to the peak of the U wave. The ratio of U_{amp} / T_{amp} was also analyzed. The duration of QT interval was measured from start of the Q wave to the end of the T wave. If the descent of the T wave did not touch the baseline, the end of the T wave was determined by the intersection of slope of descent of the T wave and baseline. The duration of the QU interval was measured from the start of Q wave to the peak of the U wave. The preceding RR interval was measured and was used to correct QT and QU using Bazett's formula (QT_c and QU_c). All waveforms were recorded in lead II. For each ECG recording, measurement of waveforms was performed when the heart rate, baseline and configuration were stable.

In the study group of sevoflurane, standard peri-operative monitoring was routinely instituted (blood pressure, ECG, end-tidal CO_2, pulsed arterial saturation) in 35 patients. 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 sevoflurane (1 to 1.5 MAC) in the presence of pure oxygen (1 L / min). Both the inspiratory and end-expiratory concentrations of sevoflurane 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 in the round brackets. The association between the amplitudes of T-U waves and the preceding RR intervals was evaluated by linear regression analysis. Comparisons between T-U changes before and after the administration of sevoflurane were performed using paired samples ***t***-test. Numbers in parentheses indicate 95% confidence interval of difference. To test the difference, a ***p*** value < 0.05 was regarded as statistically significant.

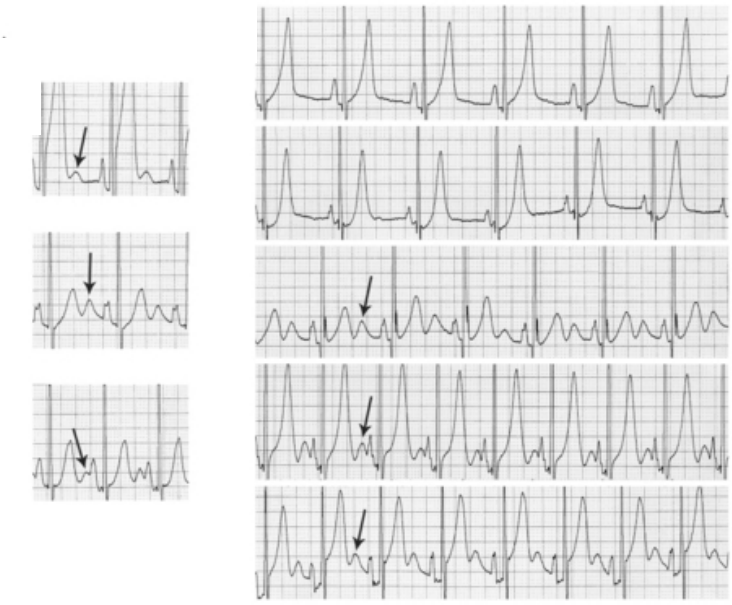
Table 1. Changes in ECG parameters by sevoflurane.

	(n = 35)		
	Control	Sevoflurane	Difference
Age (yr)	41.1 ± 10.6 (20, 70)		
Weight (kg)	55.6 ± 4.8 (42, 63)		
Height (cm)	158.5 ± 5.4 (149, 173)		
RR interval (ms)	826 ± 121	1027 ± 158	201 ± 144* [152, 251]
T_{amp} (μV)	462 ± 180	457 ± 168	-5 ± 129 [-40, 49]
U_{amp} (μV)	58 ± 29	5 ± 9	- 53 ± 27* [-44, -63]
U_{Amp}/T_{Amp}	0.16 ± 0.17	0.01 ± 0.03	- 0.15 ± 0.17* [-0.09, -0.21]
QT (ms)	407 ± 26	460 ± 40	53 ± 35* [41, 65]
QT_c (ms)	450 ± 36	456 ± 39	6 ± 41 [-8, 20]
QU (ms)	507 ± 46	589 ± 66	82 ± 64* [33, 132]
QU_c (ms)	559 ± 46	563 ± 58	4 ± 72 [-51, 60]

Data are expressed as mean ± standard deviation. * denotes $p < 0.05$ Numbers in parentheses indicate 95% confidence interval of difference.

Results

In 35 gynecologic patients (ASA class I), visible U waves with variable sizes could be identified. The amplitude of U wave was 58 ± 29 μV on average (Table 1). Figure 1 shows examples of ECG recordings obtained from 8 patients. Note that U waves appeared in 3 of them and was not discernible in the other 2 patients (Fig. 1 B). Three different configurations of U wave in association with the T wave or P wave could be seen (Fig. 1 A). In addition to appear immediately after the end of the T wave, the U wave could either fuse with T wave or encroach into the P wave. Immediately after tracheal intubation during induction of anesthesia, the heart rate and blood pressure might increase due to residual adrenergic stimulation. Figure 2 shows such an example in a patient with



(a) (b)

Figure 1. Examples of U wave. (a) ECGs from 3 different patients. The U wave (indicated by arrow) was fused with the T wave (upper panel) or the P wave (lower panel). (b) The U wave was discernible in 3 patients (lower 3 panels) and not visible in 2 patients (upper two panels).

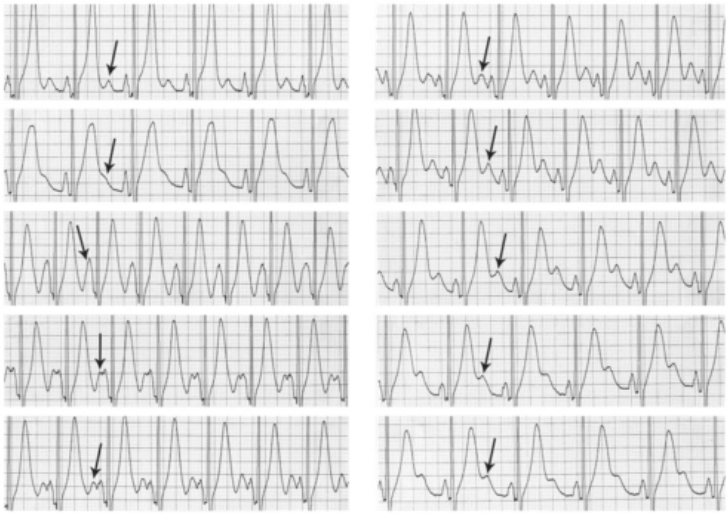


Figure 2. Sympathetic stimulation-augmented U wave. A series of ECGs changes from the pre-intubation resting state (left upper 2 panels) to those immediately after tracheal intubation (from left upper to right lower panels). Arrow indicates an example of the U wave. It is clear that U wave amplitude increased in the left 3rd and 4th panels.

a visible U wave. The amplitude of the U wave was larger at faster heart rates than at slower rates (from left upper to right lower panels). In 13 patients, the U wave amplitude is negatively correlated with the preceding RR interval (r = 0.471).

In certain patients, extrasystoles occurred immediately after tracheal intubation during induction of anesthesia. Figure 3 shows ECG tracings of such an example. It is noted that extrasystoles usually took off from near the peak of the U waves of the preceding beat. Under such a circumstance, the amplitude of U wave was much larger than those in the pre-induction resting state (Fig. 3 (c-d) versus (a)). Subsequently, the size of the extrasystole-augmented U waves decreased in sinus rhythm. In 11 patients displaying extrasystoles during induction of anesthesia, the U wave was augmented to 350 ± 217 % (150, 800) of the control during the sinus rhythm ($\boldsymbol{p} < 0.01$).

The suppressive effect of sevoflurane (1 to 1.5 MAC) on the U wave was recorded in 35 patients with a discernible U wave. Figure 4 shows such an example. In comparison to that of the control (pre-induction resting state, Fig. 4 (a)), the amplitude of the U wave dramatically and progressively decreased by sevoflurane (Fig. 4 (d)). The overall suppressive effect of sevoflurane on the U wave is presented in Table 1. In addition to prolonging the QT interval (53 ± 35 ms, $\boldsymbol{p} < 0.05$), sevoflurane significantly decreased U_{amp} (53 ± 27 μV, $\boldsymbol{p} < 0.05$). It is noted that the suppressive effect of sevoflurane on U wave is reversible (for example, Fig. 4 (e)).

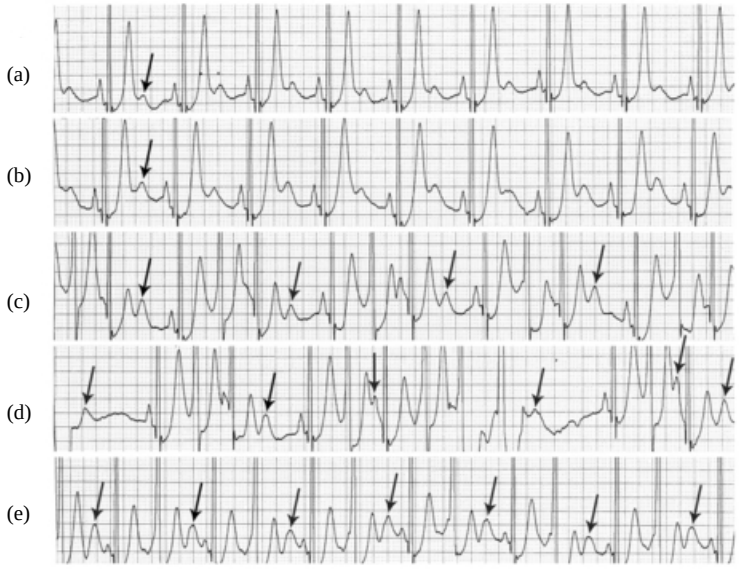


Figure 3. Extrasystoles-augmented U wave. (a) pre-intubation resting state; (b) after induction; (c-e) extrasystoles occurred immediately after tracheal intubation. U wave (arrows) size is increased during extrasystoles.

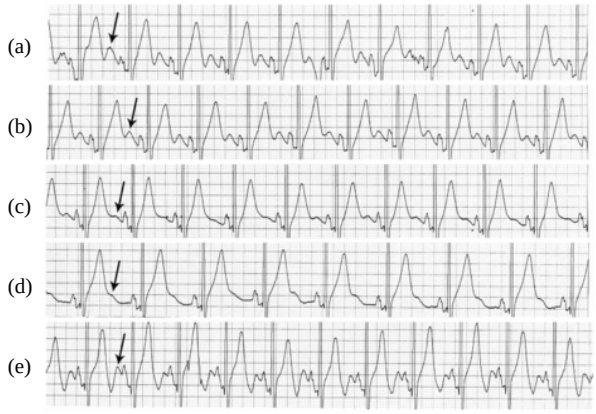


Figure 4. Reversible suppressive effect of sevoflurane on the U wave. (a) pre-induction resting state; (b-d) progressive inhibition of the U wave by sevoflurane during maintenance of anesthesia; (e) recovery of the U wave after emergence from anesthesia. Arrow indicates example of a U wave.

Discussion

U wave inscribed in ECG has been observed for more than one hundred years, but its origin has not yet been fully identified. It is known that the QT or QTU interval is equivalent to the repolarization process of cardiac ventricular cells [18]. Decrease or increases in certain transmembrane ionic currents in cardiomyocytes from epicardium, endocardium or M-cell layers can change the early or late repolarization phase of the action potentials. Any inhomogeneous lengthening in action potential duration might cause a prolonging of the QT interval and provide substrates for torsade de pointes or ventricular tachycardia. In association with late ventricular repolarization, the pathophysiological role of U wave has been demonstrated in myocardial ischemia, cardiac hypertrophy or subarachnoid or intracerebral hemorrhage [4, 19, 20]. However, a definitive cellular mechanism of the genesis of the U wave is still lacking. Although several hypotheses have been proposed, none of them is sufficient to explain the elusive role of the U wave. For example, the proposed role of contribution of subendocardial Purkinje fiber to late repolarization has a shortcoming due to the small volume of Purkinje cells [2]. Although the inhomogeneous repolarization of cardiomyocytes from epicardium, endocardium and M-cell layers is a plausible hypothesis [3], the discrepancy of their electrophysiological characteristics have not been revealed in in-vivo experimental conditions. The role of mechano-electrical feedback on U wave formation also remains to be confirmed [4, 21]. Interestingly, a recent computational model study showed that the presence of after-potentials on the cardiac action potentials might explain the U wave features in normal subjects [5]. The role of after-potentials, however, has not been tested experimentally.

The size of the U wave has been demonstrated to be positively correlated with the preceding RR-interval in normal control subjects [22]. In contrast, our observation from female patients during induction of anesthesia shows a negative correlation between the preceding RR-interval and the amplitude of the U wave. When sympathetic activity was enhanced by tracheal intubation, the U wave became more prominent at faster heart rates (Fig. 2). This phenomenon could also be observed while the patient was extubated following emergence from anesthesia. These findings suggest a potential role of catecholamines in the facilitation of U wave magnitudes. Under stimulatory condition by catecholamines, intracellular calcium in ventricular myocytes could be expected to be much higher and delayed post-depolarizations might occur. This hypothesis could be further supported by the finding that the U wave magnitude was enhanced in those patients showing extrasystoles after tracheal intubation (Fig. 3). This phenomenon is quite similar to the finding that

post-extrasystole U wave augmentation is more prominent at faster preceding RR-intervals in patients with or without long QT and idiopathic ventricular tachycardia [23, 24]. The latter (e.g., right ventricular outflow tract-ventricular tachycardia) is correlated with the level of catecholamines, intracellular calcium activity and triggered activity [25]. Recently, it has been reported that the U wave can be enhanced by isoproterenol and inhibited by esmolol in normal healthy volunteers [26, 27]. Therefore, the U wave in ECG might reflect a dynamic increase in intracellular calcium activity and formation of the after-potentials (i.e., delayed afterdepolarizations, oscillatory potentials) modulated by the level of catecholamines. Prolonged QT interval, increasing dispersion and formation of early afterdepolarizations have been associated with U wave formation [6, 24]. In contrast, our study shows that the size of U wave did not increase when the heart rate decreased below 40 beats / min during the maintenance of anesthesia. This observation indicates that an extremely prolonged action potential duration is not required for the genesis of U wave in healthy subjects. This notion is also supported by the fact that all the female patients showing sizable U waves in our study had no prolonged QT interval. In the present study, we confirmed that a sevoflurane prolonged QT interval in clinical anesthetized patients was similar to the effect of other volatile anesthetics [28-31]. Interestingly, the U wave was not augmented, but suppressed by sevoflurane when the action potential duration was lengthened.

Volatile anesthetics inhibit various transmembrane ionic currents and therefore affect the configuration of the action potentials in the heart [10-13, 32, 33]. Previous studies also show that halothane and isoflurane could suppress digitalis- or catecholamine-induced triggered activity in canine Purkinje fiber and ventricular myocytes [14, 15, 34]. In such animal models, both volatile anesthetics could suppress the delayed afterdepolarizations and abolish repetitive triggered activity and aftercontractions. This antiarrhythmic action of volatile anesthetics can be explained by a reduction in transmembrane calcium influx and intracellular calcium load. It is known that volatile anesthetics inhibit transmembrane potassium currents, calcium current, Na-Ca exchanger activity and intracellular calcium transients [35-38]. Sevoflurane shared similar cardiac pharmacological actions with halothane and isoflurane [11, 12]. If the genesis of the U wave is associated with intracellular calcium load and delayed post-depolarizations [3, 5], then it is expected to observe that sevoflurane could suppress the U wave during late ventricular repolarization. Our results in the present study are in support of this hypothesis.

Under certain pathological conditions, such as myocardial ischemia, ventricular hypertrophy, subarachnoid hemorrhage, electrolytes imbalance, ventricular arrhythmias, U wave often appears and serves as a pathologic marker [19, 20, 39-42]. In a recent report, a larger U wave was found to be correlated with congenital arrhythmia (syndrome), in which an inward rectifier in cardiac cells was mutated [43]. In the present study, all these pathologic conditions were excluded. Since our patients did not take any medication and suffered no systemic diseases (ASA class I), the possible effect of drug interaction on the repolarization process is also excluded. Interestingly, our previous studies showed that both isoflurane and desflurane also suppressed the U wave [16-17]. The suppressive effects of volatile anesthetics on U waves in ECG seem to be universal. Since the U wave, together with the T wave, play a pivotal role in cardiac arrhythmogenesis [44], it is important to understand the cellular mechanism for the genesis of the U wave. In addition to a recent computer simulation modeling of the U wave [45], further mathematical modeling to support our hypothesis (i.e., the role of dynamic intracellular calcium load and delayed afterdepolarizations) is awaited.

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

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References

[1] B. Surawicz, “U wave: facts, hypotheses, misconceptions, and misnomers,” *J. Cardiovasc. Electrophysiol.,* 9: 1117-1128, 1998.

[2] Y. Watanabe, “Purkinje repolarization as a possible cause of the U wave in the electrocardiogram,” *Circulation,* 51: 1030-1037, 1975.

[3] C. Antzelevitch and S. Sicouri, “Clinical relevance of cardiac arrhythmias generated by afterdepolarizations. Role of M cells in the generation of U waves, triggered activity and torsade de pointes,” *J. Am. Coll. Cardiol.,* 23: 259-277, 1994.

[4] M. H. Choo and D. G. Gibson, “U waves in ventricular hypertrophy: possible demonstration of mechano-electrical feedback,” *Br. Heart J.,* 55: 428-433, 1986.

[5] D. Di Bernardo and A. Murray, “Origin on the electrocardiogram of U-waves and abnormal U-wave inversion,” *Cardiovasc. Res.,* 53: 202-208, 2002.

[6] J. Wu, J. Wu and D. P. Zipes, “Early afterdepolarizations, U waves, and torsades de pointes,” *Circulation,* 105: 675-676, 2002.

[7] E. Novalija, Q. H. Hogan, A. H. Kulier, L. H. Turner and Z. J. Bosnjak, “Effects of desflurane, sevoflurane and halothane on postinfarction spontaneous dysrhythmias in dogs,” *Acta Anaesthesiol. Scand.,* 42: 353-357, 1998.

[8] G. P. Johannesson, M. Floren and S. G. Lindahl, “Sevoflurane for ENT-surgery in children. A comparison with halothane,” *Acta Anaesthesiol. Scand.,* 39: 546-550, 1995.

[9] R. Navarro, R. B. Weiskopf and M. A. Moore, “Humans anesthetized with sevoflurane or isoflurane have similar arrhythmic response to epinephrine, *Anesthesiology,* 80: 545-549, 1994.

[10] R. Huneke, J. Fassl, R. Rossaint and A. Luckhoff, “Effects of volatile anesthetics on cardiac ion channels,” *Acta Anaesthesiol. Scand.,* 48: 547-561, 2004.

[11] A. Stadnicka, Z. J. Bosnjak, J. P. Kampine and W. M. Kwok, “Effects of sevoflurane on inward rectifier K+ current in guinea pig ventricular cardiomyocytes,” *Am. J. Physiol.,* 273: H324-332, 1997.

[12] N. Hatakeyama, Y. Momose and Y. Ito, “Effects of sevoflurane on contractile responses and electrophysiologic properties in

canine single cardiac myocytes," *Anesthesiology*, 82: 559-565, 1995.

[13] I. Seckin, G. C. Sieck and Y. S. Prakash, "Volatile anaesthetic effects on Na+-Ca2+ exchange in rat cardiac myocytes," *J. Physiol.*, 532: 91-104, 2001.

[14] H. N. Luk, Suppressive effects of halothane and isoflurane on digitalis- and catecholamine-induced triggered activity. (Master Thesis) National Defense Medical Center, Taipei, Taiwan, 1985.

[15] J. D. Gallagher, "Effects of isoflurane on ouabain toxicity in canine Purkinje fibers. Comparison with halothane," *Anesthesiology*, 81: 1500-1510, 1994.

[16] C. E. Chiang, S. K. Peng, C. T. Chien, H. N. Luk, H. Z. Ren and T. H. Ye, "Suppressive effect of volatile anesthetics on U wave in anesthetized patients," *Int. J. Cardiol.*, 107: 417-418, 2006.

[17] C.E. Chiang, C. H. Li, S. K. Peng, C. P. Lo, J. M. Yuan and H. N. Luk, "Desflurane inhibits U wave in electrocardiogram," *Acta Cardiol. Sin.*, 21: 214-222, 2005.

[18] G. X. Yan, R. S. Lankipalli, J. F. Burke, S. Musco and P. R. Kowey, "Ventricular repolarization components on the electrocardiogram: cellular basis and clinical significance," *J. Am. Coll. Cardiol.*, 42: 401-409, 2003.

[19] K. Miwa, K. Nakagawa, T. Hirai and H. Inoue, "Exercise-induced U-wave alterations as a marker of well-developed and well-functioning collateral vessels in patients with effort angina," *J. Am. Coll. Cardiol.*, 35: 757-763, 2000.

[20] A. Lorsheyd, T. A. Simmers and E. O. Robles De Medina, "The relationship between electrocardiographic abnormalities and location of the intracranial aneurysm in subarachnoid hemorrhage," *Pacing Clin. Electrophysiol.*, 26: 1722-1728, 2003.

[21] M. R. Franz, D. Burkhoff, D. T. Yue and K. Sagawa, "Mechanically induced action potential changes and arrhythmia in isolated and in situ canine hearts," *Cardiovasc. Res.*, 23: 213-223, 1989.

[22] M. Nakagawa, T. Ooie, M. Hara, M. Ichinose, S. Nobe, H. Yonemochi and T. Saikawa, "Dynamics of T-U wave in patients with idiopathic ventricular tachycardia originating from the right ventricular outflow tract," *Pacing Clin. Electrophysiol*., 27: 148-155, 2004.

[23] S. Viskin, K. Heller, H. V. Barron, I. Kitzis, M. Hamdan, J. E. Olgin, M. J. Wong, S. E. Grant and M. D. Lesh, "Postextrasystolic U wave augmentation, a new marker of increased arrhythmic risk in patients without the long QT syndrome," *J. Am. Coll. Cardiol.*, 28: 1746-1752, 1996.

[24] N. El-Sherif, R. H. Zeiler, W. Craelius, W. B. Gough and R. Henkin, "QTU prolongation and polymorphic ventricular tachyarrhythmias due to bradycardia-dependent early afterdepolarizations. Afterdepolarizations and ventricular arrhythmias," *Circ. Res.*, 63: 286-305, 1988.

[25] B. B. Lerman, K. M. Stein and S. M. Markowitz, "Mechanisms of idiopathic left ventricular tachycardia," *J. Cardiovasc. Electrophysiol.*, 8: 571-583, 1997.

[26] A. R. Magnano, S. Holleran, R. Ramakrishnan, J. A. Reiffel and D. M. Bloomfield, "Autonomic modulation of the u wave during sympathomimetic stimulation and vagal inhibition in normal individuals, *Pacing Clin. Electrophysiol.*, 27: 1484-92, 2004.

[27] A. R. Magnano, S. Suleman, H. Garan and D. M. Bloomfield, "Autonomic modulation of the U wave during phenylephrine and esmolol infusions," *J. Electrocardiol.*, 38:152-156, 2005.

[28] D. Michaloudis, O. Fraidakis, T. Lefaki, I. Dede, F. Kanakoudes, H. Askitopoulou and B. J. Pollard, "Anaesthesia and the QT interval in humans. The effects of isoflurane and halothane," *Anaesthesia*, 51: 219-224, 1996.

[29] R. Owczuk, M. A. Wujtewicz, W. Sawicka, M. Wujtewicz and M. Swierblewski, "Is prolongation of the QTc interval during isoflurane anaesthesia more prominent in women pretreated with anthracyclines for breast cancer?," *Br. J. Anaesth.*, 92: 658-661, 2004.

[30] W. T. Schmeling, D. C. Warltier, D. J. McDonald, K. E. Madsen, J. L. Atlee and J. P. Kampine, "Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans," *Anesth. Analg.*, 72: 137-144, 1991.

[31] E. Kuenszberg, A. Loeckinger, A. Kleinsasser, K. H. Lindner, F. Puehringer and C. Hoermann, "Sevoflurane progressively prolongs the QT interval in unpremedicated female adults," *Eur. J. Anaesthesiol.*, 17: 662-664, 2000.

[32] W. K. Park, J. J. Pancrazio, C. K. Suh and C. Lynch 3rd, "Myocardial depressant effects of sevoflurane. Mechanical and electrophysiologic actions in vitro," *Anesthesiology*, 84: 1166-1176, 1996.

[33] E. Niggli, A. Rudisuli, P. Maurer and R. Weingart, "Effects of general anesthetics on current flow across membranes in guinea pig myocytes," *Am. J. Physiol.*, 256: C273-281, 1989.

[34] L. C. Freeman and Q. Li, "Effects of halothane on delayed afterdepolarization and calcium transients in dog ventricular myocytes exposed to isoproterenol," *Anesthesiology*, 74: 146-154, 1991.

[35] A. Suzuki, Z. J. Bosnjak and W. M. Kwok, "The effects of isoflurane on the cardiac slowly activating delayed-rectifier potassium channel in guinea pig ventricular myocytes," *Anesth. Analg.*, 96: 1308-1315, 2003.

[36] J. J. Pancrazio and C. Lynch 3rd, "Differential anesthetic-induced opening of calcium-dependent large conductance channels in isolated ventricular myocytes," *Pflugers Arch – Eur. J. Physiol.*, 429: 134-136, 1994.

[37] R. A. Haworth and A. B. Goknur, "Inhibition of sodium/calcium exchange and calcium channels of heart cells by volatile anesthetics," *Anesthesiology*, 82: 1255-1265, 1995.

[38] V. C. Baum and G. T. Wetzel, "Sodium-calcium exchange in neonatal myocardium: reversible inhibition by halothane," *Anesth. Analg.*, 78: 1105-1109, 1994.

[39] K. Miwa, Y. Miyagi, M. Fujita, A. Fujiki and S. Sasayama, "Transient terminal U wave inversion as a more specific marker for myocardial ischemia," *Am. Heart J.*, 125: 981-986, 1993.

[40] H. Kataoka and S. Yano, "Associations between different status of myocardial ischemia and ischemia-related negative or positive epicardial U-waves: observations during coronary angioplasty," *J. Electrocardiol*., 32: 293-303, 1999.

[41] E. Watanabe, I. Kodama, M. Ohono and H. Hishida, "Electrocardiographic prediction of the development and site of acute myocardial infarction in patients with unstable angina," *Int. J. Cardiol.*, 89: 231-237, 2003.

[42] T. Maruyama, T. Ohe, T. Kurita, N. Aihara and W. Shimizu, "Physiological and pathological responses of TU waves to class Ia antiarrhythmic drugs," *Eur. Heart J.*, 16: 667-673, 1995.

[43] L. Zhang, D. W. Benson, M. Tristani-Firouzi, L. J. Ptacek, R. Tawil, P. J. Schwartz, A. L. George, M. Horie, G. Andelfinger, G. L. Snow, Y. H. Fu, M. J. Ackerman and G. M. Vincent, "Electrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations: characteristic T-U-wave patterns predict the KCNJ2 genotype," *Circulation*, 111: 2720-2726, 2005.

[44] T. Hlaing, T. DiMino, P. R. Kowey and G. X. Yan, "ECG repolarization waves: their genesis and clinical implications," *Ann. Noninvasive Electrocardiol.*, 10: 211-223, 2005.

[45] H. J. Ritsema van Eck, J. A. Kors and G. van Herpen, "The U wave in the electrocardiogram: a solution for a 100-year-old riddle," *Cardiovasc. Res.*, 67: 256-262, 2005.