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# An increasing electromechanical window is a predictive marker of ventricular fibrillation in anesthetized rabbit with ischemic heart

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**Abstract:** The QTc interval is widely used in Safety Pharmacological studies to predict arrhythmia risk, and the electromechanical window (EMW) and short-term variability of QT intervals ($STV_{QT}$) have been studied as new biomarkers for drug-induced Torsades de Pointes (TdP). However, the use of EMW and $STV_{QT}$ to predict ventricular fibrillation (VF) has not been elucidated. This study aimed to evaluate EMW and $STV_{QT}$ to predict VF in anesthetized rabbit model of VF. VF was induced by ligation of the left anterior descending and a descending branch of the left circumflex coronary arteries in a sample population of rabbits (n=18). VF was developed 55.6% (10/18). In rabbit with VF, the EMW was significantly higher than in rabbits without VF (96.3 ± 15.6 ms and 49.5 ± 5.6 ms, respectively, *P*<0.05). $STV_{QT}$ had significantly increased before the onset of VF in rabbits that experienced VF, but not in rabbits that did not experience VF (11.7 ± 1.8 ms and 3.7 ± 0.4 ms, respectively, *P*<0.05). The EMW and $STV_{QT}$ had better predictive power for VF with higher sensitivity and specificity than the QTc measure. The result suggested that the increasing of EMW, as well as the elevation of $STV_{QT}$, can potentially be used as biomarkers for predicting of VF.
**Key words:** electromechanical window, LAD ligation, rabbits, $STV_{QT}$, ventricular fibrillation

## Introduction

The QT interval (QT), the duration from the beginning of the Q wave to the end of T wave of electrocardiogram (ECG), and the QTc interval, the QT corrected for heart rate, have been used as surrogate markers to assess the risk of arrhythmia from new chemical entities (ICH harmonized tripartite guideline; safety pharmacology studies for human pharmaceuticals S7A and S7B). These tests have been performed by both pharmaceutical companies and regulatory agencies. Prolonged QT and QTc intervals reflected the retardation of ventricular depolarization and repolarization are associated with an increased risk of ventricular arrhythmias, particularly Torsades de Pointes (TdP) and sudden cardiac death. Interestingly, several investigators indicated that QT and

QTc intervals are poor predictor of drug-induced arrhythmias [18, 21, 27]. In male patients with idiopathic ventricular fibrillation (VF), the QT interval was found to be short [38]. In anesthetized rabbit infused with QT shortening drugs, it was shown that pinacidil shortened the QT interval and induced VF [22]. However, literatures have demonstrated that the QT interval alone is not sufficient to predict the occurrence of VF in the acute phase of myocardial infarction in rhesus monkeys and human [31, 35].

The electromechanical window (EMW), the interval between the end of T wave and the end of the left ventricular pressure (LVP), has been used to investigate the harmonization between the electrical signals and mechanical forces of the heart [37]. Several studies have demonstrated that a negative EMW is associated with the incidence of TdP [10, 11, 37]. Findings were observed in an anesthetized guinea pigs model of long QT syndrome type 2 [10, 11] and in a dog model of long QT syndrome type 1 [37]. It has also been determined that the EMW is a superior indicator to the QT and QTc intervals [37]. Therefore, the EMW appears to be a reliable biomarker for predicting TdP. Functional re-entry is the common mechanism of arrhythmia for both TdP and ventricular fibrillation (VF) [19], and yet the EMW has not been investigated in the rabbit model of ischemia/reperfusion arrhythmias.

Short-term variability of the QT intervals ($STV_{QT}$) quantifies the heterogeneity of the QT interval from one cycle to the next cycle [36]. In animal experiments, an increased $STV_{QT}$ is associated with ventricular arrhythmias in drug-induced TdP and in long QT syndrome [13, 32–34]. In humans with drug-induced long QT syndrome and non-ischemic heart disease, $STV_{QT}$ has been proven to be a useful index facilitating the identification of patients at risk of arrhythmias [13, 14]. Recently, the pro-arrhythmia nature of new chemical entities due to induced VF has gained interest, and $STV_{QT}$ has been investigated to predict the likelihood of VF in a rat model of ischemia-induced VF [28].

It is not clear whether QT or QTc intervals are reliable biomarkers for cardiac arrhythmias, and especially for fatal VF. Therefore, the present study aimed to assess changes in the EMW and $STV_{QT}$ in a rabbit model of VF induced by ligation of the coronary arteries. The hypothesis of the current study was that the EMW and $STV_{QT}$ increased in ischemic heart before the occurrence of VF.

## Materials and Methods

### Approvals

This study was approved by the Institutional Animal Care and Use Committee of Chulalongkorn University (protocol number 1673033). All experimental animal procedures were performed in compliance with the guidelines outlined in the Guide for the Care and Use of Laboratory Animals (2011).

### Animals

A total of eighteen healthy mature (3–4 months old) New Zealand White rabbits (*Oryctolagus cuniculus*), weighing between 2–3 kg of either gender were purchased from Department of Animal Husbandry, Faculty of Veterinary Science, Chulalongkorn University (Bangkok, Thailand). They were housed as group from the time of arrival until the end of the study in a rabbit caging system maintained at a temperature of $21 \pm 1°C$, a relative humidity of 50–70%, and a 12:12 h light:dark cycle. All animals were received commercial rabbit diet and water *ad libitum*.

### Experimental procedures

All rabbits were given tiletamine (50 mg/ml)/zolazepam (50 mg/ml) (Zoletil 100, Virbac, France) 25 mg/kg intramuscularly. After induction, the hair over the thoracic and the neck area was clipped. The rabbit was secured in a dorsal recumbency on water-circulating heating pad to maintain body temperature. The propofol (8–30 mg/kg/h) was administered intravenously to achieve an appropriate anesthetic plane.

A lead I electrocardiogram (ECG) was obtained by placing electrodes between the right (−) and left (+) front legs. The ground electrode was placed at right hind limb. Cutdown was performed to isolate the right carotid artery. A high-fidelity micromanometer catheter (Millar Instruments, Texas, USA) was placed retrograde in the left ventricle via right common carotid artery for recording the left ventricular pressure (LVP).

The process of ischemia-induced arrhythmia been described previously [2]. In brief, the thorax was opened via a midline sternotomy. After the pericardium was opened, the 4–0 monofilament polypropylene sutures with needle were placed around the left anterior descending (LAD) coronary artery and a descending branch of the left circumflex artery [20]. The rabbit was allowed to stabilize for at least 20 min. Thereafter, the animal

was subjected to an acute, ischemic insult for 30 min by tightening of the coronary arteries on PE-150. Myocardial ischemia was visually confirmed by color (i.e. cyanotic) changes in distal distributions of the ligation, and the ST elevation was observed using ECG. During the occlusion period, the experiment was stopped as soon as VF started, and rabbits were euthanized with 150 mg/kg pentobarbital sodium (Nembutal, Ceva Sante Animale, Libourne, France) administered intravenously. In case of no VF occurred during occlusion, rabbits were monitored until the end of 30 min occlusion period. At the end of the occlusion period, all rabbits were euthanized while they were under general anesthesia. Rabbits with or without VF during ischemia were allocated into the VF+ and VF− groups respectively. ECG and LVP were recorded from the beginning of the experiment and continue to monitor until the end of experiment. All parameters were obtained at baseline and a min before VF development (VF+) or at 30-min after coronary ligation (VF−).

*Data analysis*

Data were recorded and analyzed using Acq 3.9.1 acquisition systems (Biopac MP150, Santa Barbara, CA, USA). Standard ECG (RR, PQ, QRS, QT) and LVP (end-diastolic pressure, EDP; end-systolic pressure, ESP; the maximum rate of rise of the LVP, $dP/dt_{max}$; the maximum rate of fall of the LVP, $dP/dt_{min}$; relaxation time-constant, tau) parameters, and the EMW were manually measured. The values of the parameters in both groups of rabbits, i.e. those groups with and without VF, were averaged from baseline, a min just before the VF occurred, or at the end of 30th min of occlusion. An average of the 31 cardiac cycles per timepoint originated from the sinus node was reported. The QT was defined as the duration from the beginning of the Q wave to the end of T wave. QTcF was calculated according to Fridericia's equation [7]. $STV_{QT}$ was calculated using the formula: $STV_{QT} = \sum | Dn + 1 − Dn | / [30 \times \sqrt{2}]$ whereas D=the duration of QT (ms) without the occurred ventricular premature complex (VPC) [32]. The EMW was defined as the time difference between the duration of left ventricular pressure measured from the beginning of the Q wave to the end of left ventricular pressure (QLVPend) and the QT interval. The EMW was calculated using the following formula: EMW = QLVPend-QT [37]. The tau was calculated according to Glantz method [26]. The VF is characterized by ventricular complexes that are changing in frequency and amplitude in the ECG, resulting in the irregular patterns of ventricular excitation [25, 40]. The R-on-T was defined as the superimposition of an ectopic beat on the T wave of a preceding beat. The VF was defined as irregular unformed QRS complexes without any P waves, with 5 or more irregular beats on a row. The frequency of arrhythmic beats (i.e. VPC and R-on-T) that developed during occlusion was also reported.

Statistical analyses were performed with commercially available software (SPSS Statistics 17.0, IBM, NY, USA). All values were expressed as means ± SEM. The differences in incidences of VF were compared using Fisher's exact test. Values for ECG and LVP parameters were compared between groups (i.e. VF− versus VF+) and between timepoints (i.e. baseline vs occlusion) two-way ANOVA with repeated measures followed by Tukey post-hoc analyses. Frequencies of arrhythmic beats at occlusion period were compared between groups using *t*-test. Statistical significance was achieved when $P<0.05$. Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive power of EMW, $STV_{QT}$, QT and QTcF. Area under the ROC curve (AUC) and confidence intervals were calculated. Parameters that yielded an AUC that was greater than 0.8 were considered to have a validated predictive value for the occurrence of VF [24]. The optimal cut-off values were determined using Youden indexes.

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## Results

*Incidence of ventricular fibrillation*

Readable ECG and LVP data were obtained from all rabbits. After ligation of LAD and a descending branch of the left circumflex arteries, VF developed during the occlusion period in ten out of 18 rabbits (55.6%, $P<0.01$), no TdP was shown in any rabbits. The ST elevation was observed after occlusion of the coronary arteries in all rabbits. A representative tracing of the ECG (lead I) and of the LVP signals at baseline, during the development of VF (VF+) and during occlusion (VF−) in anesthetized rabbits were shown in Fig. 1.

*Changes of EMW, $STV_{QT}$ and parameters of ECG and LVP*

At baseline, all parameters did not differ between VF+ and VF− rabbits (Fig. 2). The data of VF− obtained at the end of occlusion period were used to compare with the data obtained from the VF+ rabbits obtained a min
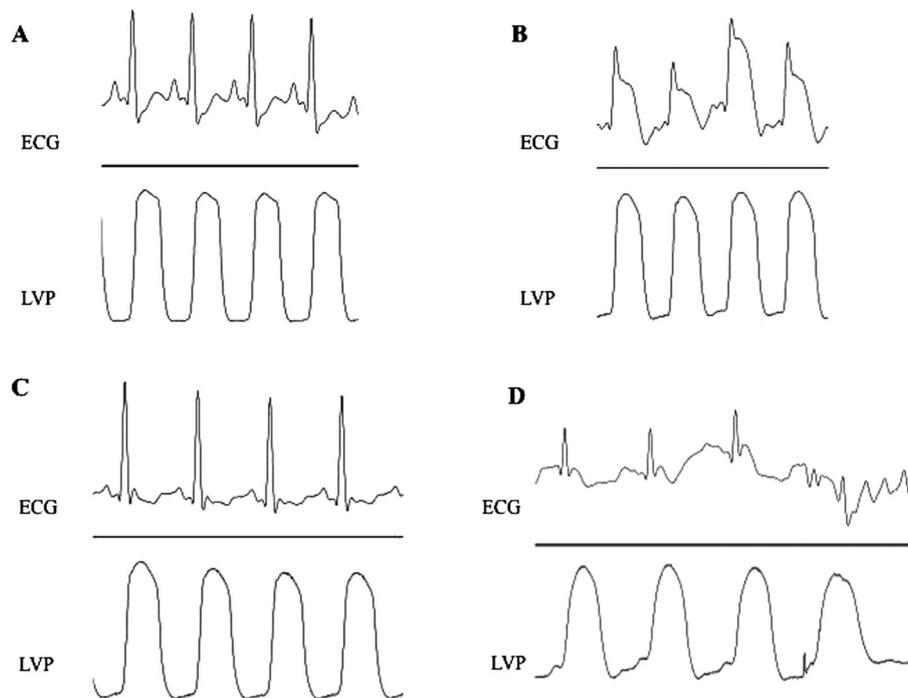
**Fig. 1.** Representatives of electrocardiogram (ECG) tracings (top) and left ventricular pressures (LVP) (bottom) obtained from anesthetized rabbits during baseline (A, C) and occlusion (B, D) periods. A=the ECG and LVP waveforms observed during the baseline in rabbit without VF (VF−). B=the ECG and LVP waveforms observed during the occlusion period in rabbit without VF. C=the ECG and LVP waveforms observed during the baseline in rabbit with VF (VF+). D=the ECG and LVP waveforms observed during the occlusion period in rabbit with VF notice the development of VF.

just before the development of VF. In VF+ rabbits, the EMW at occlusion ($96.3 \pm 15.6$ ms) was significantly higher than baseline value ($45.7 \pm 4.4$ ms) and value of VF− rabbits at occlusion ($49.5 \pm 5.6$ ms) ($P<0.05$, Fig. 2A). The $STV_{QT}$ (Fig. 2B) in VF+ rabbits at occlusion ($11.7 \pm 1.8$ ms) was significantly greater than the $STV_{QT}$ at baseline ($4.1 \pm 0.3$ ms) and that value in VF− rabbits obtained during occlusion ($3.7 \pm 0.4$ ms) ($P<0.05$). During occlusion, the QT interval (Fig. 2C), QTcF interval (Fig. 2D), EDP (Fig. 2E) and $dP/dt_{min}$ (Fig. 2F) were significantly increased from baseline in both groups ($P<0.05$) but these parameters did not differ between groups. During occlusion, the ESP (Fig. 2G) and $dP/dt_{max}$ (Fig. 2H) were significantly decreased from baseline in both groups ($P<0.05$) but these values were not differ between groups at occlusion. In VF+ rabbits during occlusion, the tau was significantly increased when compared with data obtained at baseline of the same group and at occlusion of the VF− rabbits ($P<0.05$) (Fig. 2I). In VF− rabbits at occlusion, tau was also significantly higher than tau at baseline of the same group

($P<0.05$). During occlusion, the HR of VF+ rabbits was significantly lower than the HR of VF− rabbits (HR: baseline $236 \pm 7.1$ bpm and $235 \pm 11$ bpm, respectively, and during occlusion $187 \pm 7.4$ bpm and $221 \pm 9.5$ bpm, $P<0.05$, respectively).

ROC analysis showed that both QT and QTcF intervals had AUC values less than 0.8 while the ROC analysis of the EMW and $STV_{QT}$ yield AUC values greater than 0.8 (Table 1). Therefore, the QT and QTcF intervals were not valid predictive values for the occurrence of VF. The sensitivities of the EMW and the $STV_{QT}$ were 0.67 and 0.9, respectively. The specificities of the EMW and the $STV_{QT}$ were 0.83 and 0.88, respectively (Fig. 3). Therefore, only these two parameters predicted VF with relatively high sensitivity and specificity. The AUC value of the EMW was lower than the value for the $STV_{QT}$, indicating a relatively lower predictive power. The optimal cut-off values of EMW and $STV_{QT}$ were 64 ms and 5.31 ms, respectively.

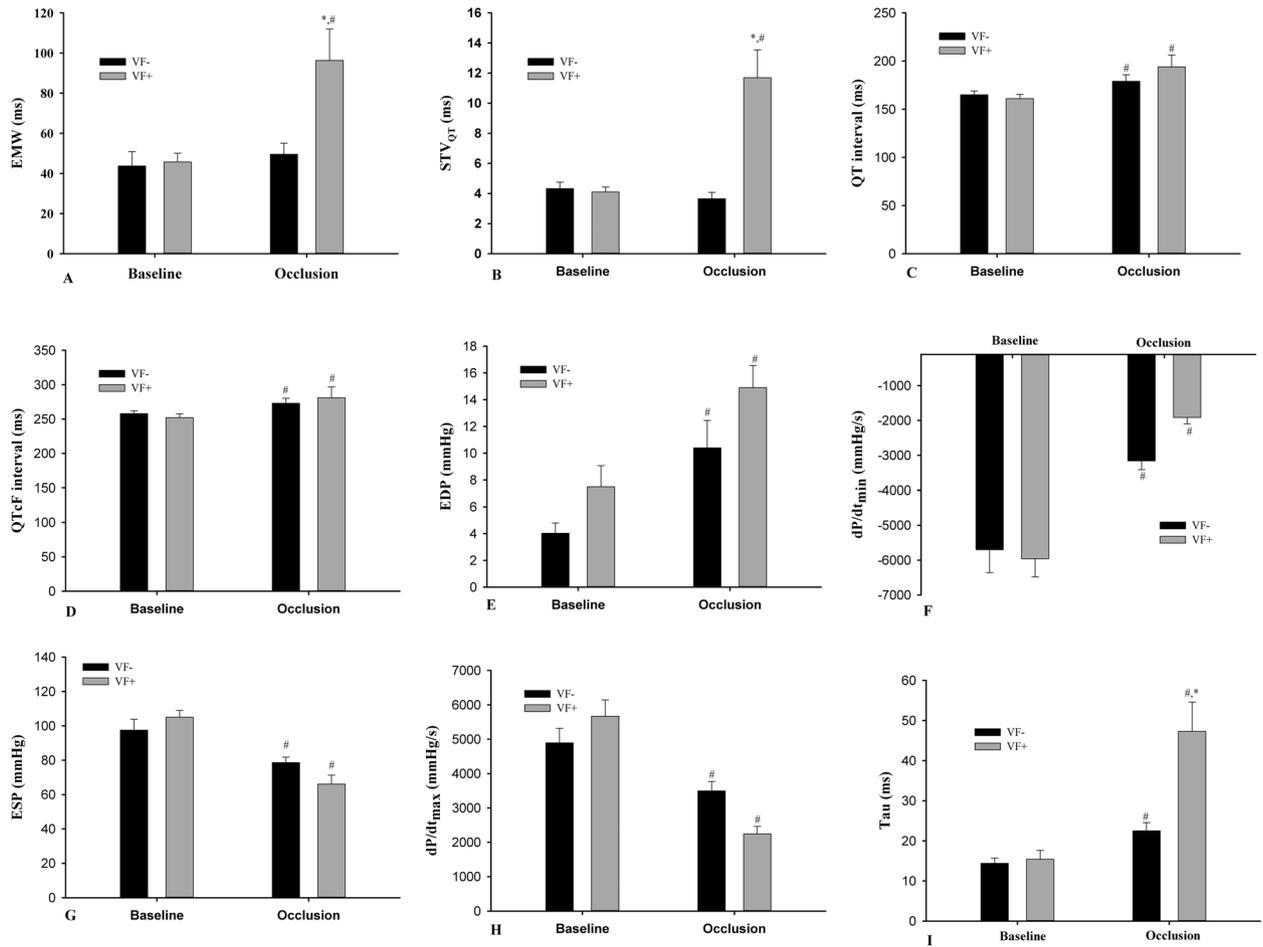In anesthetized rabbits with propofol, the EMW values at baseline were ranging from 23 to 78.8 ms. The current

**Fig. 2.** Plots of electromechanical window (EMW), short-term variability of QT interval (STV$_{QT}$), QT interval, QTcF interval, end-diastolic pressure (EDP), the maximum rate of fall of the left ventricular pressure (dP/dt$_{min}$), end-systolic pressure (ESP), the maximum rate of rise of the left ventricular pressure (dP/dt$_{max}$), relaxation time-constant (tau) at baseline and during occlusion. All values are expressed as mean ± SEM. # indicates $P<0.05$ compared with baseline, * indicates $P<0.05$ compared between groups (rabbits with ventricular fibrillation, VF+; rabbits without ventricular fibrillation VF−), QTcF=corrected QT interval by Fridericia's formula.

**Table 1.** Predictive power, sensitivity and specificity for QT, QTcF, EMW and STVQT

| Parameters | AUC | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| QT | 0.664 | 60 | 54 |
| QTcF | 0.54 | 60 | 58 |
| EMW | 0.829 | 67 | 83 |
| STV$_{QT}$ | 0.963 | 90 | 88 |

AUC; area under the curve; QT; the QT interval; QTcF; the corrected QT interval by Fridericia's formula; EWM; electromechanical window; STV$_{QT}$; short-term variability of QT interval.

study found that the EMW begins to increase just before the VF develops in VF+ rabbits. However, the EMW did not change throughout the experiment in VF− rabbits. Similarly, the value of STV$_{QT}$ in the current study was minimal during baseline (ranging from 2.29 to 6.6 ms) and this value was increased just before VF occurred.

*Frequency of arrhythmic beats*

The frequency of arrhythmic beats is presented in Fig. 4. At baseline and before coronary occlusion, the arrhythmic beats were zero. During occlusion, the frequencies of R-on-T and VPC in VF+ rabbits had increased significantly when compared with VF− rabbits ($P<0.05$). However, the predictive power, sensitivity and specificity of the arrhythmic frequencies for prediction of VF were lower than 0.8.
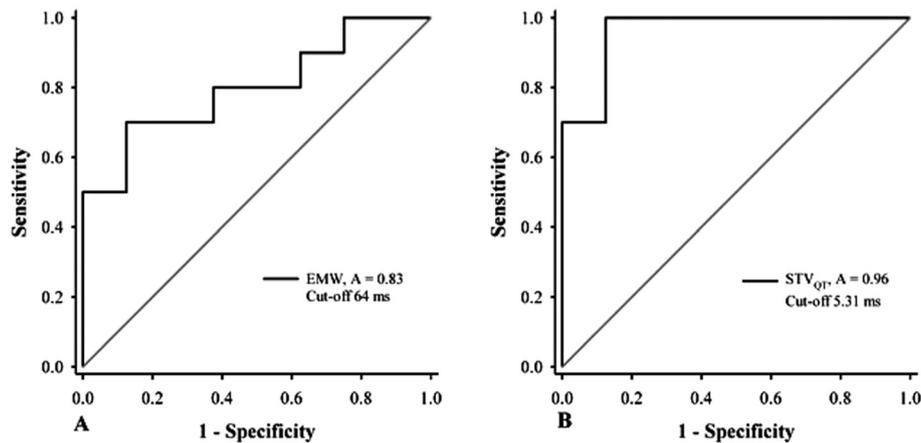
**Fig. 3.** Receiver operating characteristic (ROC) curve analysis of electromechanical window (EMW, A) and the short-term variability of QT interval (STV$_{QT}$) for the prediction of ventricular fibrillation in ischemic anesthetized rabbits. The area under curve (AUC) and cut-off value were shown in each graphs.
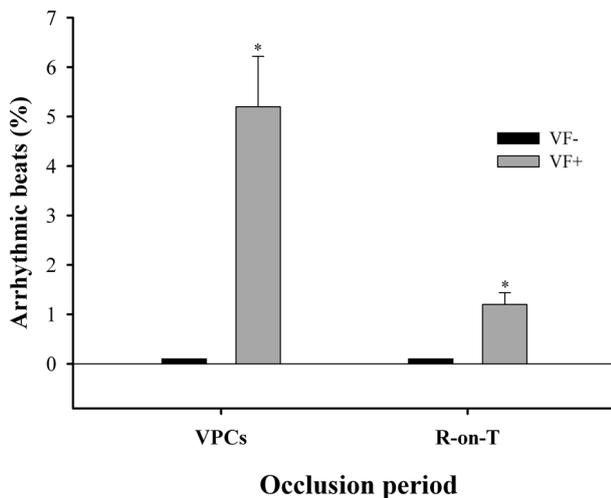


**Fig. 4.** Plot of the frequency of arrhythmic beats including ventricular premature complexes (VPCs) and R-on-T during occlusion period compared between rabbits with (VF+) and without (VF−) ventricular fibrillation. All values are shown as mean ± SEM. * indicates $P<0.05$ compared between groups (VF+ versus the VF−).

## Discussion

The main aim of the present study was to investigate whether the changes in the EMW and STV$_{QT}$ can be used to predict the risk of VF in an anesthetized rabbit model of ischemic-induced ventricular arrhythmias. The main findings were that increases of EMW and STV$_{QT}$ were observed just before the VF. These two indices had great predictive power with high sensitivity and specificity for

the occurrence of VF. In contrast, changes of the QT and QTcF intervals were not predictive of VF.

Prolonged duration of cardiac action potential duration and consequent lengthening of the QT intervals is proarrhythmic. However, it has been recognized that not all drugs that lengthen QT and QTc intervals possess proarrhythmic effects. The lengthening of QT and QTc intervals has been used as a surrogate marker for drug-induced TdP for decades [17]. Prior studies suggest that the QTc interval is an unreliable predictor of ventricular arrhythmia [15, 16]. While several novel biomarkers (i.e. iCEB, TRIaD, STV$_{QT}$ and EMW) have been established to predict drug-induced TdP, biomarkers for drug-induced shortening of the QT interval have been overlooked [23, 30, 33, 37]. Previous study has demonstrated that the absolute beat-to-beat variability and instability parameters of ECG intervals, otherwise known as BVI, have been validated for predicting ischemia-induced VF in an isolated heart preparation [28]. The study also demonstrated that QT and QTc intervals did not differ between 'VF+' and 'VF−' groups. However, absolute BVI could be used as a surrogate for VF in preclinical drug investigations.

The present study showed that an increase EMW is associated with VF in the anesthetized rabbit model of ischemia. The EMW quantified the differences between the QT interval and the duration of the mechanical event. To the best of our knowledge, this is the first study designed to evaluate the EMW for predicting VF in anesthetized rabbits. Previous studies have found that a

negative EMW is associated with drug-induced TdP in several animal models [10, 11, 37]. Those authors also demonstrated that the EMW is not interfered by heart rate and body temperature. Therefore, the measure has been suggested for use as a biomarker in preclinical cardiovascular safety studies [37].

The present study also demonstrated that an increased $STV_{QT}$ is associated with VF in the model of ischemia. The $STV_{QT}$, known as beat-to-beat variability of repolarization or BVR, is used to quantify the temporal repolarization liability. Similar results to our findings have been demonstrated in the isolated rat heart, where the elevated $STV_{QT}$ had great predictive power for the occurrence of VF [28]. Previous studies have also found that the increase in $STV_{QT}$ caused by both cardiovascular and non-cardiovascular drugs can be used to predict drug-induced TdP [8, 32, 33]. Even as the detailed mechanisms of drug-induced TdP and VF are different, they share a broader common mechanism. Functional re-entry could explain the elevated $STV_{QT}$ in both types of arrhythmias [9].

An increased frequency of arrhythmic beats is associated with increase heterogeneity of repolarization, and has been suggested to be a substrate for the re-entry pathway, and a trigger for arrhythmias [1, 3]. Recently, the frequency of arrhythmic beats and R-on-T were found to be good predictors of the occurrence of VF in isolated rat hearts [28]. However, the complexity of arrhythmic beats was suggested to be more important for the mechanism of drug-induced TdP than the frequency of arrhythmic beats in an $\alpha_1$-adrenoceptor-stimulated, anesthetized rabbit model [6]. In the present study, the frequency of arrhythmic beats (i.e. R-on-T and VPC) in the VF+ rabbits was noticeably greater during coronary occlusion when compared with baseline or VF− rabbits.

Anesthetized rabbits were used because there is relatively similar profile between the potassium currents in rabbits and those in humans, although the heart rate is differs [5]. In the current study, coronary occlusion produced reductions in HR, ESP and $dP/dt_{max}$ whereas the QT, QTcF, EDP, $dP/dt_{min}$ and tau were increased. These results indicate that the model of acute myocardial ischemia performed by coronaries ligation was successfully established. Similar results were found in previous works of rabbits and other species [2, 4, 29, 39].

Rabbit models of ischemia are one of many other models of ventricular arrhythmias. Therefore, further studies should be performed in several animal models to confirm our findings. In addition, numerous factors (i.e. contractility, blood pressure and changes in preload) may affect the change of the EMW. Therefore, these factors must be evaluated before further investigations on the use of the EMW in humans. The potential limitation of this study is the quantity of infarcted area and area at risk since it may influence the outcome of arrhythmia. However, from our experience with this model, we have used the same procedure as our previous publications to produce the similar myocardial ischemia in every rabbits [2, 12, 20]. Therefore, the lack of measurements of infarcted area and area at risk in this study may not confound our results.

In conclusion, this study shows that, in comparison with the measure of QT/QTc intervals, changes in the EMW and $STV_{QT}$ are more sensitive to the development of VF in rabbit models, but these do not change in rabbits without VF. The present study is an early step in the validation of the EMW as a predictive measure, and illustrates the feasibility of using the EMW and $STV_{QT}$ in predicting the risk of VF created by the ligation of coronary arteries.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## Acknowledgments

## References

1. Boulaksil, M., Jungschleger, J.G., Antoons, G., Houtman, M.J., de Boer, T.P., Wilders, R., Beekman, J.D., Maessen, J.G., van der Hulst, F.F., van der Heyden, M.A., van Veen, T.A., van Rijen, H.V., de Bakker, J.M., and Vos, M.A. 2011. Drug-induced torsade de pointes arrhythmias in the chronic AV block dog are perpetuated by focal activity. *Circ Arrhythm Electrophysiol* 4: 566–576. [Medline] [CrossRef]

2. Brown, D.A., Hale, S.L., Baines, C.P., del Rio, C.L., Hamlin, R.L., Yueyama, Y., Kijtawornrat, A., Yeh, S.T., Frasier, C.R., Stewart, L.M., Moukdar, F., Shaikh, S.R., Fisher-Wellman, K.H., Neufer, P.D., and Kloner, R.A. 2014. Reduction of early reperfusion injury with the mitochondria-targeting peptide bendavia. *J. Cardiovasc. Pharmacol. Ther.* 19: 121–132. [Medline] [CrossRef]

3. Choi, B.R., Burton, F., and Salama, G. 2002. Cytosolic Ca2+ triggers early afterdepolarizations and Torsade de Pointes in rabbit hearts with type 2 long QT syndrome. *J. Physiol.* 543: 615–631. [Medline] [CrossRef]

4. Corr, P.B., Pearle, D.L., Hinton, J.R., Roberts, W.C., and Gillis, R.A. 1976. Site of myocardial infarction. A determinant of the cardiovascular changes induced in the cat by coronary occlusion. *Circ. Res.* 39: 840–847. [Medline] [CrossRef]

5. Dumaine, R., and Cordeiro, J.M. 2007. Comparison of K+ currents in cardiac Purkinje cells isolated from rabbit and dog. *J. Mol. Cell. Cardiol.* 42: 378–389. [Medline] [CrossRef]

6. Farkas, A.S., Rudas, L., Makra, P., Csík, N., Leprán, I., Forster, T., Csanády, M., Papp, J.G., Varró, A., and Farkas, A. 2010. Biomarkers and endogenous determinants of dofetilide-induced torsades de pointes in α(1) -adrenoceptor-stimulated, anaesthetized rabbits. *Br. J. Pharmacol.* 161: 1477–1495. [Medline] [CrossRef]

7. Fridericia, L.S. 1920. Die systolendauer im elektrokardiogramm bei normalen menschen und bei herzkranken. *Acta Med. Scand.* 53: 469–486. [CrossRef]

8. Gallacher, D.J., Van de Water, A., van der Linde, H., Hermans, A.N., Lu, H.R., Towart, R., and Volders, P.G. 2007. In vivo mechanisms precipitating torsades de pointes in a canine model of drug-induced long-QT1 syndrome. *Cardiovasc. Res.* 76: 247–256. [Medline] [CrossRef]

9. Gaztañaga, L., Marchlinski, F.E., and Betensky, B.P. 2012. Mechanisms of cardiac arrhythmias. *Rev. Esp. Cardiol. (Engl. Ed.)* 65: 174–185. [Medline] [CrossRef]

10. Guns, P.J., Johnson, D.M., Van Op den Bosch, J., Weltens, E., and Lissens, J. 2012. The electro-mechanical window in anaesthetized guinea pigs: a new marker in screening for Torsade de Pointes risk. *Br. J. Pharmacol.* 166: 689–701. [Medline] [CrossRef]

11. Guns, P.J., Johnson, D.M., Weltens, E., and Lissens, J. 2012. Negative electro-mechanical windows are required for drug-induced Torsades de Pointes in the anesthetized guinea pig. *J. Pharmacol. Toxicol. Methods* 66: 125–134. [Medline] [CrossRef]

12. Hamlin, R.L. and Kijtawornrat, A. 2008. Use of the rabbit with a failing heart to test for torsadogenicity. *Pharmacol. Ther.* 119: 179–185. [Medline] [CrossRef]

13. Hinterseer, M., Thomsen, M.B., Beckmann, B.M., Pfeufer, A., Schimpf, R., Wichmann, H.E., Steinbeck, G., Vos, M.A., and Kaab, S. 2008. Beat-to-beat variability of QT intervals is increased in patients with drug-induced long-QT syndrome: a case control pilot study. *Eur. Heart J.* 29: 185–190. [Medline] [CrossRef]

14. Hinterseer, M., Beckmann, B.M., Thomsen, M.B., Pfeufer, A., Ulbrich, M., Sinner, M.F., Perz, S., Wichmann, H.E., Lengyel, C., Schimpf, R., Maier, S.K., Varró, A., Vos, M.A., Steinbeck, G., and Kääb, S. 2010. Usefulness of short-term variability of QT intervals as a predictor for electrical remodeling and proarrhythmia in patients with nonischemic heart failure. *Am. J. Cardiol.* 106: 216–220. [Medline] [CrossRef]

15. Hondeghem, L.M. 2008. QT and TdP. QT: an unreliable predictor of proarrhythmia. *Acta Cardiol.* 63: 1–7. [Medline] [CrossRef]

16. Hondeghem, L.M. 2008. QT prolongation is an unreliable predictor of ventricular arrhythmia. *Heart Rhythm* 5: 1210–1212. [Medline] [CrossRef]

17. Hondeghem, L.M. 2011. QTc prolongation as a surrogate for drug-induced arrhythmias: fact or fallacy? *Acta Cardiol.* 66: 685–689. [Medline] [CrossRef]

18. Jacobson, I., Carlsson, L., and Duker, G. 2011. Beat-by-beat QT interval variability, but not QT prolongation per se, predicts drug-induced torsades de pointes in the anaesthetised methoxamine-sensitized rabbit. *J. Pharmacol. Toxicol. Methods* 63: 40–46. [Medline] [CrossRef]

19. Jalife, J. and Berenfeld, O. 2004. Molecular mechanisms and global dynamics of fibrillation: an integrative approach to the underlying basis of vortex-like reentry. *J. Theor. Biol.* 230: 475–487. [Medline] [CrossRef]

20. Kijtawornrat, A., Nishijima, Y., Roche, B.M., Keene, B.W., and Hamlin, R.L. 2006. Use of a failing rabbit heart as a model to predict torsadogenicity. *Toxicol. Sci.* 93: 205–212. [Medline] [CrossRef]

21. Kijtawornrat, A., Panyasing, Y., Del Rio, C., and Hamlin, R.L. 2010. Assessment of ECG interval and restitution parameters in the canine model of short QT syndrome. *J. Pharmacol. Toxicol. Methods* 61: 231–237. [Medline] [CrossRef]

22. Limprasutr, V., Saengklub, N., Meedech, P., Kijtawornrat, A., and Hamlin, R.L. 2017. Characteristics of electromechanical window in anesthetized rabbit models of short QT and long QT syndromes. *J. Toxicol. Sci.* 42: 579–587. [Medline] [CrossRef]

23. Lu, H.R., Yan, G.X., and Gallacher, D.J. 2013. A new biomarker--index of cardiac electrophysiological balance (iCEB)--plays an important role in drug-induced cardiac arrhythmias: beyond QT-prolongation and Torsades de Pointes (TdPs). *J. Pharmacol. Toxicol. Methods* 68: 250–259. [Medline] [CrossRef]

24. Mandrekar, J.N. 2010. Receiver operating characteristic curve in diagnostic test assessment. *J. Thorac. Oncol.* 5: 1315–1316. [Medline] [CrossRef]

25. Moe, G.K. and Abildskov, J.A. 1964. Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart. *Circ. Res.* 14: 447–460. [Medline] [CrossRef]

26. Raff, G.L. and Glantz, S.A. 1981. Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load-

dependent relaxation in the intact dog heart. *Circ. Res.* 48: 813–824. [Medline] [CrossRef]

27. Redfern, W.S., Carlsson, L., Davis, A.S., Lynch, W.G., MacKenzie, I., Palethorpe, S., Siegl, P.K., Strang, I., Sullivan, A.T., Wallis, R., Camm, A.J., and Hammond, T.G. 2003. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc. Res.* 58: 32–45. [Medline] [CrossRef]

28. Sarusi, A., Rárosi, F., Szűcs, M., Csík, N., Farkas, A.S., Papp, J.G., Varró, A., Forster, T., Curtis, M.J., and Farkas, A. 2014. Absolute beat-to-beat variability and instability parameters of ECG intervals: biomarkers for predicting ischaemia-induced ventricular fibrillation. *Br. J. Pharmacol.* 171: 1772–1782. [Medline] [CrossRef]

29. Scherlag, B.J., Kabell, G., Harrison, L., and Lazzara, R. 1982. Mechanisms of bradycardia-induced ventricular arrhythmias in myocardial ischemia and infarction. *Circulation* 65: 1429–1434. [Medline] [CrossRef]

30. Shah, R.R. and Hondeghem, L.M. 2005. Refining detection of drug-induced proarrhythmia: QT interval and TRIaD. *Heart Rhythm* 2: 758–772. [Medline] [CrossRef]

31. Sun, X., Cai, J., Fan, X., Han, P., Xie, Y., Chen, J., Xiao, Y., and Kang, Y.J. 2013. Decreases in electrocardiographic R-wave amplitude and QT interval predict myocardial ischemic infarction in Rhesus monkeys with left anterior descending artery ligation. *PLoS One* 8: e71876. [Medline] [CrossRef]

32. Thomsen, M.B., Verduyn, S.C., Stengl, M., Beekman, J.D., de Pater, G., van Opstal, J., Volders, P.G., and Vos, M.A. 2004. Increased short-term variability of repolarization predicts d-sotalol-induced torsades de pointes in dogs. *Circulation* 110: 2453–2459. [Medline] [CrossRef]

33. Thomsen, M.B., Volders, P.G., Beekman, J.D., Matz, J., and Vos, M.A. 2006. Beat-to-Beat variability of repolarization determines proarrhythmic outcome in dogs susceptible to drug-induced torsades de pointes. *J. Am. Coll. Cardiol.* 48: 1268–1276. [Medline] [CrossRef]

34. Thomsen, M.B., Oros, A., Schoenmakers, M., van Opstal, J.M., Maas, J.N., Beekman, J.D., and Vos, M.A. 2007. Proarrhythmic electrical remodelling is associated with increased beat-to-beat variability of repolarisation. *Cardiovasc. Res.* 73: 521–530. [Medline] [CrossRef]

35. Tomassoni, G., Pisanó, E., Gardner, L., Krucoff, M.W., and Natale, A. 1998. QT prolongation and dispersion in myocardial ischemia and infarction. *J. Electrocardiol.* 30:(Suppl): 187–190. [Medline] [CrossRef]

36. van der Linde, H., Van de Water, A., Loots, W., Van Deuren, B., Lu, H.R., Van Ammel, K., Peeters, M., and Gallacher, D.J. 2005. A new method to calculate the beat-to-beat instability of QT duration in drug-induced long QT in anesthetized dogs. *J. Pharmacol. Toxicol. Methods* 52: 168–177. [Medline] [CrossRef]

37. van der Linde, H.J., Van Deuren, B., Somers, Y., Loenders, B., Towart, R., and Gallacher, D.J. 2010. The Electro-Mechanical window: a risk marker for Torsade de Pointes in a canine model of drug induced arrhythmias. *Br. J. Pharmacol.* 161: 1444–1454. [Medline] [CrossRef]

38. Viskin, S., Zeltser, D., Ish-Shalom, M., Katz, A., Glikson, M., Justo, D., Tekes-Manova, D., and Belhassen, B. 2004. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. *Heart Rhythm* 1: 587–591. [Medline] [CrossRef]

39. Wang, Y., Qi, X., Wang, C., Zhao, D., Wang, H., and Zhang, J. 2017. Effects of propofol on myocardial ischemia-reperfusion injury in rats with type-2 diabetes mellitus. *Biomed. Rep.* 6: 69–74. [Medline] [CrossRef]

40. Witkowski, F.X. and Penkoske, P.A. 1990. Activation patterns during ventricular fibrillation. *Ann. N. Y. Acad. Sci.* 591: 219–231. [Medline] [CrossRef]