



UNIVERSITÀ POLITECNICA DELLE MARCHE  
Repository ISTITUZIONALE

Electrocardiogram-based index for the assessment of drug-induced hERG potassium channel block

This is the peer reviewed version of the following article:

*Original*

Electrocardiogram-based index for the assessment of drug-induced hERG potassium channel block / Burattini, L.; Sbrollini, A.; Scinocca, L.; Peroni, C.; Marcantoni, I.; Morettini, M.. - In: JOURNAL OF ELECTROCARDIOLOGY. - ISSN 0022-0736. - ELETTRONICO. - 69:(2021), pp. 55-60. [10.1016/j.jelectrocard.2021.10.005]

*Availability:*

This version is available at: 11566/293722 since: 2024-05-09T14:30:36Z

*Publisher:*

*Published*

DOI:10.1016/j.jelectrocard.2021.10.005

*Terms of use:*

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. The use of copyrighted works requires the consent of the rights' holder (author or publisher). Works made available under a Creative Commons license or a Publisher's custom-made license can be used according to the terms and conditions contained therein. See editor's website for further information and terms and conditions.

This item was downloaded from IRIS Università Politecnica delle Marche (<https://iris.univpm.it>). When citing, please refer to the published version.

(Article begins on next page)

1 This is the accepted version of the following article, which has now been formally published  
2 in final form at Journal of Electrocardiology at  
3 <https://www.sciencedirect.com/science/article/pii/S0022073621002120?pes=vor>.

4 This version of the article may be used for non-commercial purposes in accordance with the  
5 Elsevier self-archiving terms and conditions.

6 [https://www.sciencedirect.com/journal/journal-of-electrocardiology/publish/open-access-](https://www.sciencedirect.com/journal/journal-of-electrocardiology/publish/open-access-options)  
7 [options](https://www.sciencedirect.com/journal/journal-of-electrocardiology/publish/open-access-options)

8  
9 TITLE - Electrocardiogram-based index for the assessment of drug-induced hERG potassium  
10 channel block

11 AUTHORS - Laura Burattini, Agnese Sbröllini, Laura Scinocca, Chiara Peroni, Ilaria  
12 Marcantoni, Micaela Morettini.

13 PUBLISHED: 24 Oct 2021

14 YEAR - 2021

15 DOI - <https://doi.org/10.1016/j.jelectrocard.2021.10.005>

16 JOURNAL - Journal of Electrocardiology

17 VOLUME 69

18 PAGES 55-60

19 PUBLISHER- Elsevier

20 Full text link –

21 <https://www.sciencedirect.com/science/article/pii/S0022073621002120?pes=vor>.

# **Electrocardiogram-Based Index for the Assessment of Drug-Induced hERG Potassium Channel Block**

**Laura Burattini, PhD, Agnese Sbrollini, PhD, Laura Scinocca, Chiara Peroni, MSc,  
Ilaria Marcantoni, PhD, Micaela Morettini, PhD**

Department of Information Engineering, Università Politecnica delle Marche, Ancona, Italy

Presenting and corresponding author:

Prof. Laura Burattini, PhD

Address: Via Breccie Bianche 12, 60131 Ancona, Italy

E-mail address: [l.burattini@univpm.it](mailto:l.burattini@univpm.it)

Phone: +39 071 2204461

Fax: +39 071 2204224

## Abstract

*Introduction:* Drug-induced block of the hERG potassium channel could predispose to torsade de pointes, depending on occurrence of concomitant blocks of the calcium and/or sodium channels. Since the hERG potassium channel block affects cardiac repolarization, the aim of this study was to propose a new reliable index for non-invasive assessment of drug-induced hERG potassium channel block based on electrocardiographic T-wave features.

*Methods:*  $ERD_{30\%}$  (early repolarization duration) and  $T_{S/A}$  (down-going T-wave slope to T-wave amplitude ratio) features were measured in 22 healthy subjects who received, in different days, doses of dofetilide, ranolazine, verapamil and quinidine (all being hERG potassium channel blockers and the latter three being also blockers of calcium and/or sodium channels) while undergoing continuous electrocardiographic acquisition from which  $ERD_{30\%}$  and  $T_{S/A}$  were evaluated in fifteen time points during the 24 hours following drug administration (“ECG Effects of Ranolazine, Dofetilide, Verapamil, and Quinidine in Healthy Subjects” database by Physionet). A total of 1320 pairs of  $ERD_{30\%}$  and  $T_{S/A}$  measurements, divided in training (50%) and testing (50%) datasets, were obtained. Drug-induced hERG potassium channel block was modelled by the regression equation  $B_{ECG}(\%) = a \cdot ERD_{30\%} + b \cdot T_{S/A} + c \cdot ERD_{30\%} \cdot T_{S/A} + d$ ;  $B_{ECG}(\%)$  values were compared to plasma-based measurements,  $B_{REF}(\%)$ .

*Results:* Regression coefficients values, obtained on the training dataset, were:  $a = -561.0 \text{ s}^{-1}$ ,  $b = -9.7 \text{ s}$ ,  $c = 77.2$  and  $d = 138.9$ . In the testing dataset, correlation coefficient between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$  was 0.67 ( $p < 10^{-81}$ ); estimation error was  $-11.5 \pm 16.7\%$ .

*Conclusion:*  $B_{ECG}(\%)$  is a reliable non-invasive index for the assessment of drug-induced hERG potassium channel block, independently from concomitant blocks of other ions.

**Keywords:** Cardiac Repolarization; Drug safety; Electrocardiogram; Ion Channel Block; Prediction; T wave.

## Introduction

Drugs belonging to several therapeutic classes, among which antiarrhythmics, antibiotics, antipsychotics and anticancer agents, have side-effects which may cause serious ventricular tachyarrhythmias, such as torsade de pointes (TdP) [1]. Among antiarrhythmics drugs, dofetilide is the one with the highest risk of TdP, quantified in 1÷5% of exposed subjects [2]. By contrast, antibiotics, antipsychotics and other classes of ‘non-cardiovascular drugs’ provoke TdP less frequently [1]. All these drugs cause block of the human Ether-à-go-go-related gene (hERG) potassium channels, which conduct the rapid component of the delayed rectifier potassium current  $I_{Kr}$  (outward current), the major responsible of cardiac repolarization [3]; difference in TdP risk in drug-induced hERG potassium channel block can be ascribed to the presence of concurrent block of calcium and/or sodium channels (inward currents) [4].

All the drugs increasing the risk of TdP induce a prolongation of cardiac myocytes action potential which could result in a prolonged repolarization, and thus in a prolonged QT interval on the electrocardiogram (ECG) known as drug-induced long QT syndrome (diLQTS). The occurrence of diLQTS represents one of the most common reasons for drug withdrawal or relabeling, so that it is highly investigated in drug development [1,5]. However, the observation that some drugs block the hERG potassium channel and prolong QT with minimal TdP risk led to the conclusion that QT prolongation is not a specific clue of TdP risk [4]. Thus, further effects on cardiac repolarization (which will reflect on variations of the T-wave morphology on the ECG) are expected to occur.

ECG-based features describing T-wave morphology other than QT interval have been proven useful in characterizing drug-induced channel block. In particular, in a recent study on drug safety, an index based on T-wave down slope and T-wave amplitude has been proposed as an alternative metric for measuring the level of hERG potassium channel block, independent from concomitant calcium and/or sodium channels block [6]. However, previous studies

showed that hERG potassium channel block equally prolongs early (left T-wave half) and late repolarization (right T-wave half) [7], thus indicating that other ECG-based metrics should be considered in addition to the down-going T-wave slope and the T-wave amplitude to better quantify hERG potassium-channel block.

A recent study by our group [8] that used an approach based on artificial neural networks, confirmed that T-wave features on both right and left T-wave sides are necessary to provide a reliable classification of hERG potassium-channel block; in particular the features chosen as input of the artificial neural network were  $ERD_{30\%}$  (defined as the 30% early phase of repolarization duration and describing left T-wave side) and  $T_{S/A}$  (representing the down-going T-wave slope to T-wave amplitude ratio). Such approach has the advantage of providing a reliable and non-invasive classification of hERG potassium-channel block; however, it cannot determine the block level point estimate and requires specific expertise from the operator to be applied. Thus, the aim of this study was to propose a new index that can be computed through a simple formula and not requiring computational modelling techniques [9], for the reliable assessment of drug-induced hERG potassium channel block based on T-wave features on both right and left T-wave sides in condition of single-drug assumption.

## **Materials and Methods**

### *Study Population and Clinical Data*

Study population consisted of 22 healthy subjects who received, in different days separated by 7-day wash out periods, single doses of dofetilide (500 µg; Tikosyn, Pfizer, New York, NY), ranolazine (1500 mg; Ranexa, Gilead, Foster City, CA), verapamil hydrochloride (120 mg; Heritage Pharmaceuticals, Edison, NJ) and quinidine sulfate (400 mg; Watson Pharma, Corona, CA). While dofetilide blocks hERG potassium channel only, the other drugs also block calcium or sodium channels. Drug administration was performed under fasting conditions

while undergoing continuous ECG acquisition (sampling frequency: 500 Hz; amplitude resolution: 2.5  $\mu$ V). From each continuous recording, triplicate 10-s 12-lead ECG segments were extracted at fifteen post-dose points (+0.5 h; +1.0 h; +1.5 h; +2.0 h; +2.5 h; +3.0 h; +3.5 h; +4.0 h; +5.0 h; +6.0 h; +7.0 h; +8.0 h; +12.0 h; +14.0 h; +24.0 h). The vectorcardiographic (VCG) median beat derived from each 10-s ECG segment was considered representative of the segment itself and used for features extraction. Therefore, 3960 (22 subjects by 3 ECG recordings by 15 time points by 4 drugs) VCG median beats were analyzed. Additionally, at the same fifteen time points a blood sample was drawn for pharmacokinetic analysis. All VCG and plasma data are available at the “ECG Effects of Ranolazine, Dofetilide, Verapamil, and Quinidine in Healthy Subjects” database by Physionet [7,10]. All Physionet data were fully de-identified and randomized, and can be used with no further independent ethics committee approval.

#### *ECG-based Index for Assessment of Drug-induced hERG Potassium Channel Block*

The new proposed ECG-based index of drug-induced hERG potassium channel block,  $B_{ECG}(\%)$ , is modelled by the following regression equation:

$$B_{ECG}(\%) = a \cdot ERD_{30\%} + b \cdot T_{S/A} + c \cdot ERD_{30\%} \cdot T_{S/A} + d \quad (1)$$

where:  $ERD_{30\%}$  (s) represents the 30% early repolarization duration [11];  $T_{S/A}$  ( $s^{-1}$ ) represents the ratio of down-going T-wave slope ( $T_{RS}$ ,  $mV \cdot s^{-1}$ ) and T-wave amplitude ( $T_A$ , mV) [6]; and a, b, c and d represent the model parameters to be estimated.  $T_{RS}$  is a downslope, thus being its sign negative, it was computed as the absolute value of the mean first derivative of the T wave in the interval from the T-wave peak to T-wave end ( $T_p T_e$ ; s).

Experimental values of  $ERD_{30\%}$  and  $T_{S/A}$  were obtained for all the 3960 VCG median beats. Specifically,  $ERD_{30\%}$  together with  $T_A$ , and  $T_p T_e$  values for each VCG median beat are reported

in the Physionet database [7,10]; the formers were used for calculation of  $T_{S/A}$  according to definition ( $T_{S/A}=I/T_pT_e$ ). Then, for each subject, the associated values of  $ERD_{30\%}$  and  $T_{S/A}$  for each of the fifteen time points relative to a drug administration were computed by averaging the values obtained from the VCG median values obtained from triplicate ECGs.

#### *Plasma-based Index for Assessment of Drug-induced hERG Potassium Channel Block*

The reference index of hERG potassium channel block,  $B_{REF}(\%)$ , at plasma drug concentration  $D$  (the values of which, for the fifteen post-dose time points, are available in the database) was obtained through the Hill equation [11]:

$$B_{REF}(\%) = 100 \cdot \frac{D^n}{IC_{50} + D^n} \quad (2)$$

where  $IC_{50}$  is the concentration of drug that causes 50% block, and  $n$  is the Hill coefficient.  $IC_{50}$  and  $n$  are equal to 1 nM and 0.6, 6490 nM and 0.8, 499 nM and 1.1, and 343 nM and 1.0, for dofetilide, ranolazine, verapamil, and quinidine, respectively [12].

#### *Statistical Analysis*

To determine the a, b, c, and d regression coefficients of Eq. (1), multiple regression analysis with interaction effects was performed between the two predictors,  $ERD_{30\%}$  and  $T_{S/A}$ , and  $B_{REF}(\%)$ ; coefficient of determination ( $R^2$ ) and statistical significance of the impact of each term on the prediction were computed.

The database was randomly divided in two datasets: 50% (corresponding to 660 pairs of  $ERD_{30\%}$  and  $T_{S/A}$  values from 11 subjects) was used as training dataset to build the model; the remaining 50% was used as testing dataset. Correlation between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$  in the training and testing datasets was performed by computation of the Pearson Product Moment correlation coefficient ( $r$ ); slope and intercept of the regression line, together with their corresponding 95% confidence intervals ( $CI$ ), was also computed. The Lilliefors test was used



to evaluate the hypothesis that each variable had a normal distribution with unspecified mean and variance. Normal distributions were described in terms of mean  $\pm$  standard deviation, while not-normal distributions were described in terms of 50<sup>th</sup> [25<sup>th</sup>; 75<sup>th</sup>] percentiles. Bland Altman plot was used to evaluate the degree of agreement between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$ .

Eventually, estimation error of hERG channel block provided by  $B_{ECG}(\%)$  in different block classes (<25%; 25%÷50%; >50%; defined according to  $B_{REF}(\%)$ ) was computed as signed difference between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$ . The statistical significance level was set at 5% ( $p<0.05$ ) in all cases.

## Results

$D$ ,  $B_{REF}(\%)$ ,  $ERD_{30\%}$  and  $T_{S/A}$  distributions over the 24 hours after the administration of the 4 drugs for all 22 subjects are depicted in Fig. 1. Overall,  $B_{REF}(\%)$  varied from 0.4% to 76.9% (36.4%[19.1%;53.5%]); similar distributions were observed in the training dataset, where  $B_{REF}(\%)$  varied from 0.4% to 76.9% (39.3%[20.9%;55.0%]), and in the testing dataset, where  $B_{REF}(\%)$  varied from 0.4% to 75.5% (34.3%[17.3%;49.2%]).

Proportion of variance explained by the two predictors in the training dataset was equal to 57% ( $R^2=0.57$ ). From the multiple regression analysis, regression coefficients (with their statistical significance) were found as  $a=-561.0 \text{ s}^{-1}$  ( $p=0.002$ ),  $b=-9.7$  ( $p<10^{-24}$ ) s,  $c=77.2$  ( $p=1.31\cdot10^{-5}$ ) and  $d=138.9$  ( $p<10^{-36}$ ), yielding:

$$B_{ECG}(\%) = -561.0 \cdot ERD_{30\%} - 9.7 \cdot T_{S/A} + 77.2 \cdot ERD_{30\%} \cdot T_{S/A} + 138.9 \quad (3)$$

A positive significant linear correlation was found between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$  in both training dataset ( $r=0.75$ ,  $p<10^{-119}$ ) and testing dataset ( $r=0.67$ ,  $p<10^{-81}$ ; Fig. 2). Regression-line slope and intercept were 1.0 ( $CI: 0.9\div1.1$ ) and 0.0 ( $CI: -2.8\div2.8$ ) in the training dataset, and 0.9 ( $CI: 0.8\div1.0$ ) and -6.1 ( $CI: -9.9\div-2.2$ ) in the testing dataset.

Figs. 3 and 4 show Bland Altman plots for the agreement evaluation of  $B_{ECG}(\%)$  and  $B_{REF}(\%)$  for the training and testing datasets considering all the drugs, and for the testing dataset considering each single drug separately. Eventually, estimation errors of  $B_{ECG}(\%)$  with respect to  $B_{REF}(\%)$  in various hERG-channel-block classes are reported in Table 1; estimation was more accurate for classes with higher hERG potassium channel block.

## Discussion

This study presented and validated a new index,  $B_{ECG}(\%)$ , based on  $ERD_{30\%}$  and  $T_{S/A}$  for the assessment of drug-induced hERG potassium channel block, possibly with concomitant block of other ions channels. Used drugs were: dofetilide, which is a strong pure hERG potassium channel blocker; ranolazine, which is a blocker of the hERG potassium channel as well as of the late sodium channel; verapamil, which is a blocker of the hERG potassium channel as well as of the calcium channel; and quinidine, which is a blocker of the hERG potassium channel as well as of the late sodium channel and of the calcium channel. To evaluate  $B_{ECG}(\%)$  reliability, results were compared against those obtained with a reference index,  $B_{REF}(\%)$ .  $B_{ECG}(\%)$  and  $B_{REF}(\%)$  were significantly correlated (Fig. 2) and showed very good agreement (Fig. 3), so that they can be considered substantially equivalent. Highest  $B_{ECG}(\%)$  performance was observed in the high percentage block class (Table 1), which is also the one possibly associated to higher cardiac risk.

Initially, all the features that correlate with hERG channel block were evaluated as possible predictors in the index formulation:  $ERD_{30\%}$ ,  $LRD_{30\%}$  (i.e. 30% late repolarization delay),  $T_{S/A}$  and  $T_pT_e$ . To these features, we added ECG features showing correlation with blood potassium concentration. Indeed, hERG channel block mimics hypokalemia (by reducing potassium outflow current), and both the hERG block and hypokalemia result in QT-interval prolongation and reduced T-wave amplitude [6,13]. In this regard, previous studies showed that blood

potassium concentration correlates with several T-wave features [14,15]. Eventually, only two independent (from multicollinearity testing) ECG features were selected here for the index formulation:  $ERD_{30\%}$  and  $T_{S/A}$ .  $T_{S/A}$  was chosen since conceptually similar indexes were found to be predictors of both hERG channel block and blood potassium level [6,14].  $ERD_{30\%}$  was chosen in addition to  $T_{S/A}$  because it is a feature related to early repolarization, differently from  $T_{S/A}$  which describes late repolarization. Adding  $ERD_{30\%}$  to  $T_{S/A}$  further improves the already reliable assessment of hERG channel block by  $T_{S/A}$  alone. Indeed, unreported results indicate that linear regression analysis performed using only  $T_{S/A}$  provides a coefficient of determination  $R^2=0.55$ , slightly lower than the one resulting from the model of this study ( $R^2=0.57$ ). This  $R^2$  improvement may appear limited but the statistical significance of the p-value related to  $ERD_{30\%}$  ( $p=0.002$ ) demonstrates that this ECG feature has a significant impact on the prediction of drug-induced hERG potassium channel block. Thus, although  $T_{S/A}$  represents the most important component, it is necessary to use both  $T_{S/A}$  and  $ERD_{30\%}$  features in order to optimize assessment of the hERG potassium channel block. All the other evaluated ECG features mentioned above were rejected because of their positive multicollinearity with  $ERD_{30\%}$  and/or  $T_{S/A}$ .

The two selected ECG features,  $ERD_{30\%}$  and  $T_{S/A}$ , have been previously used in the same context to provide a classification between “low” and “high” block values [8]. The method used in [8] was based on artificial neural networks, a typical non-linear data-driven model. Similarly, in this study, the  $B_{ECG}(\%)$  prediction obtained using only the sum of the  $ERD_{30\%}$  and  $T_{S/A}$  linear contributions ( $R^2=0.55$ ) was lower than that obtained using both the sum of  $ERD_{30\%}$  and  $T_{S/A}$  linear contributions and their bilinear contribution ( $R^2=0.57$ ), as in Eq. (1). Being the p-value associated to the bilinear contribution statistically significant ( $p=1.31 \times 10^{-5}$ ), the improvement of  $R^2$  is also statistically significant. Additionally,  $ERD_{30\%}$  and  $T_{S/A}$  direct values were used here, differently from what done in [8] and usually in clinical practice, where their

differential values with respect to the pre-dose values were used [8]. Indeed, use of serial electrocardiography [16] in Eq. (1) significantly reduces the predictive performances of the model ( $R^2=0.39$ ). However, the model here designed is meant to be simultaneously valid for different drugs with highly different effects (Fig. 1); ECG variations with respect to pre-dose values may be strongly dependent on the specific drug and may act as confounding factor. This fact, associated to the presence of an interaction (bilinear) term in our linear regression model, could explain the lower performance obtained with differential values and justify the use of absolute values which provide better results.

Goodness of our results can be discussed by comparing them with results obtained considering predictive quantitative structure–activity relationship (QSAR) models [9], which are computational modeling methods traditionally developed for revealing relationships between structural properties of chemical compounds and biological activities. We obtained  $R^2=0.57$  whereas QSAR regression models for hERG blockage in general exhibit predictive powers between  $R^2=0.5$  and  $R^2=0.7$  [9]. Thus, the value we obtained appears to be comparable to those traditionally achieved in QSAR models but we have to underline that the method proposed in the present study is based on an indirect measure of hERG blockage from ECG features. Indeed, use of this method may avoid complex, invasive and expensive experiments.

It has to be noted that heart rate may affect estimation of repolarization endpoints [17,18] and thus of  $ERD_{30\%}$  and/or  $T_pT_e$  and thus  $T_{S/A}$ . However, it was shown that neither  $ERD_{30\%}$  [11] nor  $T_pT_e$  [7] are heart rate dependent.

Other ECG biomarkers have been proposed to study drug effects on cardiac ventricular repolarization. For example, the recently proposed T-vector velocity [19,20] provides insights on the mechanistic link between drug effects on ionic currents and overall repolarization on the ECG. Differently, the here proposed approach is the first, to the best of our knowledge, to provide the point estimate of block level relating to the hERG potassium-channel. Future

studies on larger populations, possibly undergoing administration of other drugs are needed to confirm reliability of  $B_{ECG}(\%)$  index to assess hERG potassium channel block and its associated cardiovascular risk also with indexes different from the QT interval, such as T-wave alternans [21]. Finally, the index presented in this study was designed to predict hERG channel block only, thus it can be applied to investigate if a novel drug blocks the hERG potassium channel. Although it was shown that this index provides reliable results in case of drugs that are not pure hERG blockers (and thus characterized by lower values of block), in future studies the reliability of the proposed index should be also evaluated and possibly updated in known non-hERG blocker drugs to avoid the risk of detecting false condition of block. The index, by itself, cannot improve risk assessment since risk due to hERG channel block can be mitigated by other ion current change. However, the adopted methodology represents the first step for the development of a complete assessment of ion-specific indexes able to noninvasively predict ion channel blocks. When all these indexes will be available, they will provide detailed information on the drug effect on each ion channel and will support noninvasive assessment of proarrhythmia risk.

## Conclusion

A novel ECG-based index for the assessment of drug-induced hERG potassium channel block, independently from concomitant blocks of other ions, has been proposed. This new index focuses on the characterization of both early and late ventricular repolarization changes and represents a step forward in the characterization of drug effects on human cardiac repolarization.

## Declaration of interest

None.

283    **Funding**

284    This research did not receive any specific grant from funding agencies in the public,  
285    commercial, or not-for-profit sectors.

## References

- [1] Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. *J Physiol* 2016;594:2459–68. <https://doi.org/10.1113/JP270526>.
- [2] Abraham JM, Saliba WI, Vekstein C, Lawrence D, Bhargava M, Bassiouny M, et al. Safety of oral dofetilide for rhythm control of atrial fibrillation and atrial flutter. *Circ Arrhythm Electrophysiol* 2015;8:772–6. <https://doi.org/10.1161/CIRCEP.114.002339>.
- [3] Mitcheson JS, Chen J, Lin M, Culberson C, Sanguinetti MC. A structural basis for drug-induced long QT syndrome. *Proc Natl Acad Sci U S A* 2000;97:12329–33. <https://doi.org/10.1073/pnas.210244497>.
- [4] Johannesen L, Vicente J, Gray RA, Galeotti L, Loring Z, Garnett CE, et al. Improving the assessment of heart toxicity for all new drugs through translational regulatory science. *Clin Pharmacol Ther* 2014;95:501–8. <https://doi.org/10.1038/clpt.2013.238>.
- [5] Sager PT, Gintant G, Turner JR, Pettit S, Stockbridge N. Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium. *Am Heart J* 2014;167:292–300. <https://doi.org/10.1016/j.ahj.2013.11.004>.
- [6] De Bie J, Chiu WB, Mortara DW, Corsi C, Severi S. Quantification of hERG potassium channel block from the ECG. *Comput. Cardiol.* (2010)., vol. 44, 2017, p. 1–4. <https://doi.org/10.22489/CinC.2017.239-123>.
- [7] Johannesen L, Vicente J, Mason JW, Sanabria C, Waite-Labott K, Hong M, et al. Differentiating drug-induced multichannel block on the electrocardiogram: Randomized study of dofetilide, quinidine, ranolazine, and verapamil. *Clin Pharmacol Ther* 2014;96:549–58. <https://doi.org/10.1038/clpt.2014.155>.
- [8] Morettini M, Peroni C, Sbröllini A, Marcantoni I, Burattini L. Classification of drug-induced hERG potassium-channel block from electrocardiographic T-wave features using artificial neural networks. *Ann Noninvasive Electrocardiol* 2019;24:1–7.

311 <https://doi.org/10.1111/anec.12679>.

312 [9] Hansen K, Rathke F, Schroeter T, Rast G, Fox T, Kriegl JM, et al. Bias-correction of  
313 regression models: a case study on hERG inhibition. *J Chem Inf Model* 2009;49:1486–  
314 96. <https://doi.org/10.1021/ci9000794>.

315 [10] Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PC, Mark RG, et al.  
316 PhysioBank, PhysioToolkit, and PhysioNet : Components of a New Research Resource  
317 for Complex Physiologic Signals. *Circulation* 2000;101:e215–20.  
318 <https://doi.org/10.1161/01.CIR.101.23.e215>.

319 [11] Vicente J, Johannesen L, Mason JW, Crumb WJ, Pueyo E, Stockbridge N, et al.  
320 Comprehensive T wave morphology assessment in a randomized clinical study of  
321 dofetilide, quinidine, ranolazine, and verapamil. *J Am Heart Assoc* 2015;4:1–13.  
322 <https://doi.org/10.1161/JAHA.114.001615>.

323 [12] Crumb WJ, Vicente J, Johannesen L, Strauss DG. An evaluation of 30 clinical drugs  
324 against the comprehensive in vitro proarrhythmia assay (CiPA) proposed ion channel  
325 panel. *J Pharmacol Toxicol Methods* 2016;81:251–62.  
326 <https://doi.org/10.1016/j.vascn.2016.03.009>.

327 [13] Diercks DB, Shumaik GM, Harrigan RA, Brady WJ, Chan TC. Electrocardiographic  
328 manifestations: Electrolyte abnormalities. *J Emerg Med* 2004;27:153–60.  
329 <https://doi.org/10.1016/j.jemermed.2004.04.006>.

330 [14] Corsi C, Cortesi M, Callisesi G, De Bie J, Napolitano C, Santoro A, et al. Noninvasive  
331 quantification of blood potassium concentration from ECG in hemodialysis patients. *Sci*  
332 *Rep* 2017;7:1–10. <https://doi.org/10.1038/srep42492>.

333 [15] Dillon JJ, Desimone C V., Sapir Y, Somers VK, Dugan JL, Bruce CJ, et al. Noninvasive  
334 potassium determination using a mathematically processed ECG: Proof of concept for a  
335 novel “blood-less, blood test.” *J Electrocardiol* 2015;48:12–8.



<https://doi.org/10.1016/j.jelectrocard.2014.10.002>.

- [16] Sbröllini A, De Jongh MC, Ter Haar CC, Treskes RW, Man S, Burattini L, et al. Serial electrocardiography to detect newly emerging or aggravating cardiac pathology: a deep-learning approach. *Biomed Eng Online* 2019;18:15. <https://doi.org/10.1186/s12938-019-0630-9>.
- [17] Malik M. The imprecision in heart rate correction may lead to artificial observations of drug induced QT interval changes. *Pacing Clin Electrophysiol* 2002;25:209–16. <https://doi.org/10.1046/j.1460-9592.2002.00209.x>.
- [18] Desai M, Li L, Desta Z, Malik M, Flockhart D. Variability of heart rate correction methods for the QT interval. *Br J Clin Pharmacol* 2003;55:511–7. <https://doi.org/10.1046/j.1365-2125.2003.01791.x>.
- [19] Bystricky W, Maier C, Gintant G, Bergau D, Carter D. Identification of Drug-Induced Multichannel Block and Proarrhythmic Risk in Humans Using Continuous T Vector Velocity Effect Profiles Derived From Surface Electrocardiograms. *Front Physiol* 2020;11. <https://doi.org/10.3389/fphys.2020.567383>.
- [20] Bystricky W, Maier C, Gintant G, Bergau D, Kamradt K, Welsh P, et al. T vector velocity: A new ECG biomarker for identifying drug effects on cardiac ventricular repolarization. *PLoS One* 2019. <https://doi.org/10.1371/journal.pone.0204712>.
- [21] Marcantoni I, Laratta R, Mascia G, Ricciardi L, Sbröllini A, Nasim A, et al. Dofetilide-Induced Microvolt T-Wave Alternans. 2019 41st Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., IEEE; 2019, p. 95–8. <https://doi.org/10.1109/EMBC.2019.8857486>.

## FIGURE LEGENDS

**Figure 1.**  $D$ ,  $B_{REF}(\%)$ ,  $ERD_{30\%}$  and  $T_{S/A}$  distributions over the 24 hours after the administration of the dofetilide, ranolazine, verapamil and quinidine for all 22 subjects (grey lines; black bold line represents the mean trend over population).

**Figure 2.** Linear regression plots between  $B_{REF}(\%)$  and  $B_{ECG}(\%)$  in the training and testing datasets. Regression line ( $x=B_{ECG}(\%)$ ;  $y=B_{REF}(\%)$ ) and correlation coefficient ( $r$ ) are also reported.

**Figure 3.** Bland-Altman plots for the testing and training datasets. Mean: mean value of  $B_{ECG}(\%)$  and  $B_{REF}(\%)$ ; estimation error: difference between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$ . Continuous lines represent mean estimation errors; dotted lines represent  $\text{mean} \pm 1.96 \cdot \text{standard deviation}$  values of estimation errors.

**Figure 4.** Bland-Altman plots for the testing dataset considering each single drug separately: A) Dofetilide, B) Ranolazine, C) Verapamil, D) Quinidine. Mean: mean value of  $B_{ECG}(\%)$  and  $B_{REF}(\%)$ ; estimation error: difference between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$ . Continuous lines represent mean estimation errors; dotted lines represent  $\text{mean} \pm 1.96 \cdot \text{standard deviation}$  values of estimation errors.

**Table 1.** Errors in the estimation of hERG channel block, computes as difference between  $B_{ECG}(\%)$  and  $B_{REF}(\%)$ .

Block class	Estimation error (%)
<25%	-23.3±12.0
25-50%	-11.0±14.8
>50%	5.3±9.4
0-100%	-11.5±16.7

Figure 1

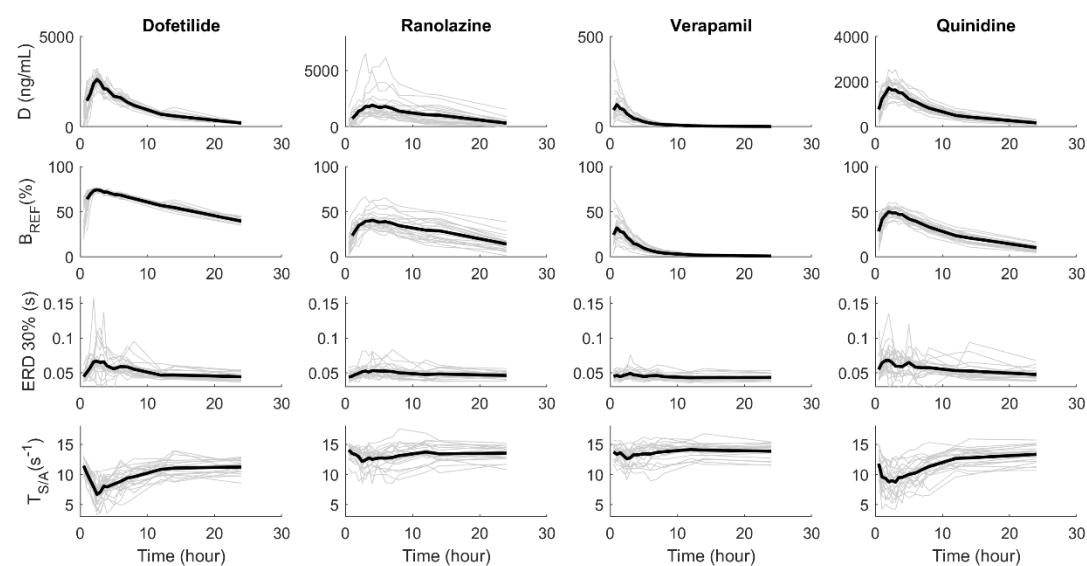


Figure 2

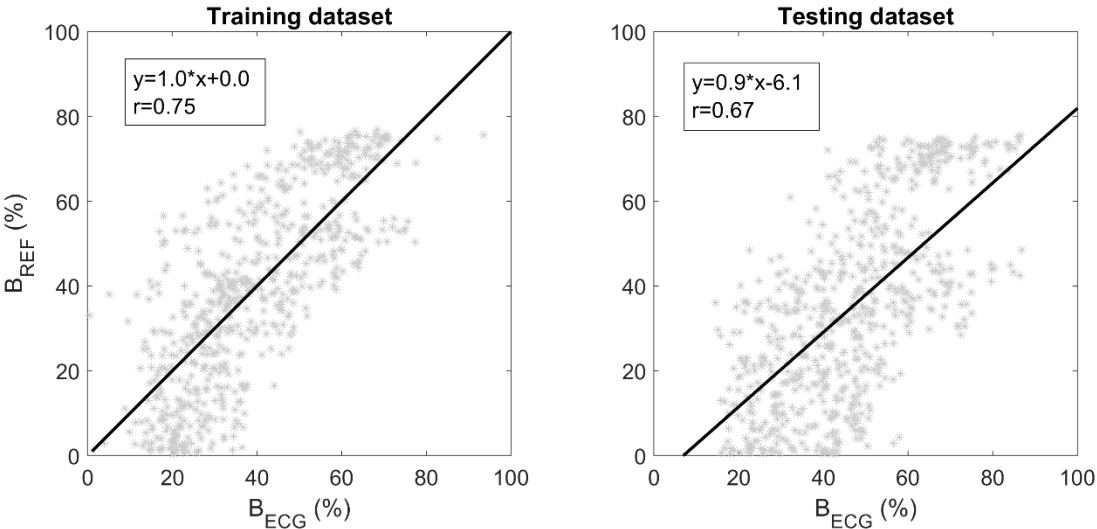


Figure 3

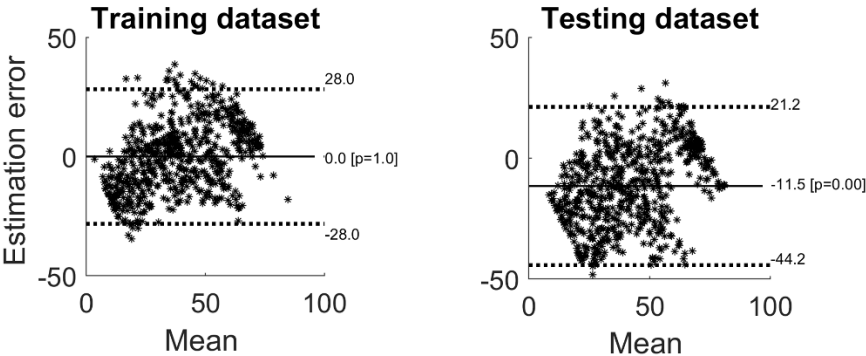


Figure 4

