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

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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 $B_{ECG}(\%)=a\cdot ERD_{30\%}+b\cdot T_{S/A}+ c\cdot ERD_{30\%}\cdot T_{S/A}\cdot+d$; $B_{ECG}(\%)$ values were compared to plasma-based measurements, $B_{REF}(\%)$.

Results: Regression coefficients values, obtained on the training dataset, were: a=-561.0 s^{-1}, b=-9.7 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±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

115 while undergoing continuous ECG acquisition (sampling frequency: 500 Hz; amplitude
116 resolution: 2.5 μV). From each continuous recording, triplicate 10-s 12-lead ECG segments
117 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
118 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
119 (VCG) median beat derived from each 10-s ECG segment was considered representative of the
120 segment itself and used for features extraction. Therefore, 3960 (22 subjects by 3 ECG
121 recordings by 15 time points by 4 drugs) VCG median beats were analyzed. Additionally, at
122 the same fifteen time points a blood sample was drawn for pharmacokinetic analysis. All VCG
123 and plasma data are available at the "ECG Effects of Ranolazine, Dofetilide, Verapamil, and
124 Quinidine in Healthy Subjects" database by Physionet [7,10]. All Physionet data were fully de-
125 identified and randomized, and can be used with no further independent ethics committee
126 approval.
127

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

129 The new proposed ECG-based index of drug-induced hERG potassium channel block,
130 $B_{ECG}(\%)$, is modelled by the following regression equation:

131 $$B_{ECG}(\%) = \mathrm{a} \cdot ERD_{30\%} + \mathrm{b} \cdot T_{S/A} + \mathrm{c} \cdot ERD_{30\%} \cdot T_{S/A} + \mathrm{d} \qquad (1)$$

132 where: $ERD_{30\%}$ (s) represents the 30% early repolarization duration [11]; $T_{S/A}$ (s^{-1}) represents
133 the ratio of down-going T-wave slope (T_{RS}, $mV \cdot s^{-1}$) and T-wave amplitude (T_A, mV) [6]; and
134 a, b, c and d represent the model parameters to be estimated. T_{RS} is a downslope, thus being its
135 sign negative, it was computed as the absolute value of the mean first derivative of the T wave
136 in the interval from the T-wave peak to T-wave end (T_pT_e; s).
137 Experimental values of $ERD_{30\%}$ and $T_{S/A}$ were obtained for all the 3960 VCG median beats.
138 Specifically, $ERD_{30\%}$ together with T_A, and T_pT_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 ($T_{S/A}=1/T_pT_e$). 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]:

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

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 ± standard deviation, while not-normal distributions were described in terms of 50^{th} [25^{th}; 75^{th}] 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 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:

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

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÷1.1) and 0.0 (*CI*: -2.8÷2.8) in the training dataset, and 0.9 (*CI*: 0.8÷1.0) and -6.1 (*CI*: -9.9÷-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=1.31our $\cdot 10^{-5}$), 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 ERD30% [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.

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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 mean ± 1.96 · standard deviation values of estimation errors.

Figure 4. Bland-Altman plots for the testing dataset considering each single drug separately: A) Dofetilide, B) Ranolazione, 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 mean ± 1.96 · 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

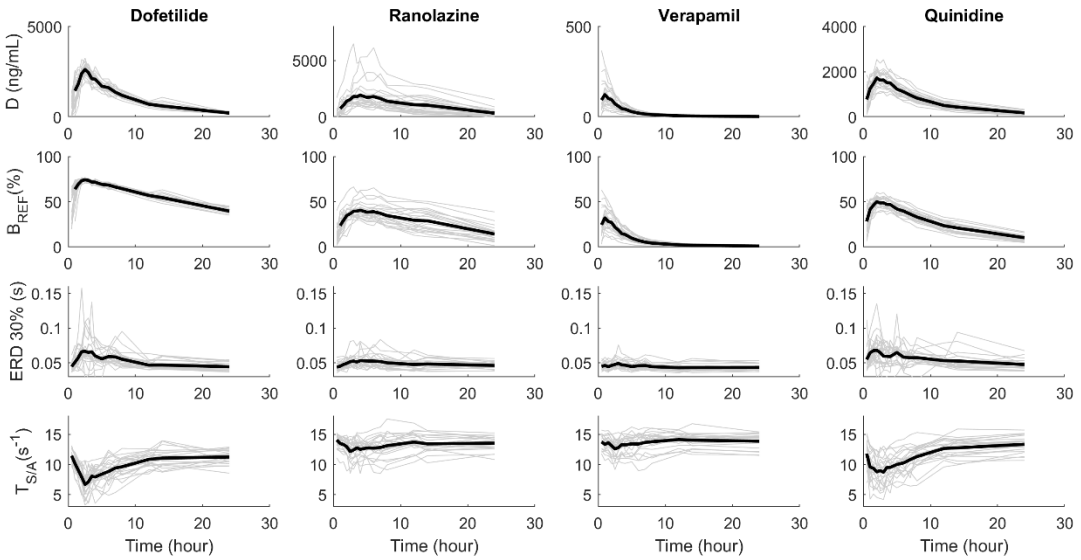

Dofetilide
Ranolazine
Verapamil
Quinidine
D (ng/mL)
B_{REF}(%)
ERD 30% (s)
$T_{S/A}$(s^{-1})
Time (hour)

Figure 2

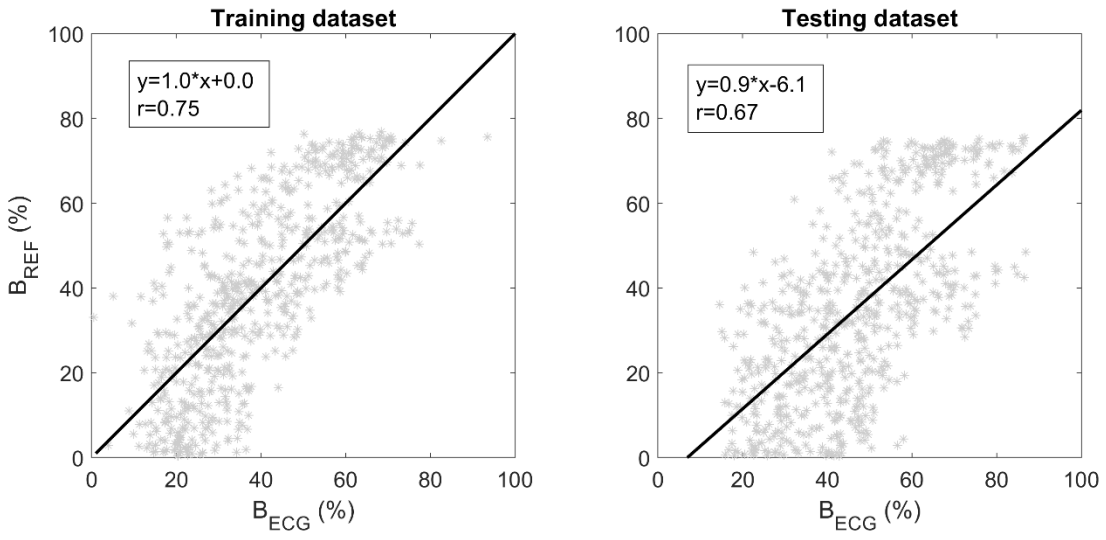

Training dataset
y=1.0*x+0.0
r=0.75
B_REF (%)
B_ECG (%)
Testing dataset
y=0.9*x-6.1
r=0.67
B_ECG (%)

Figure 3

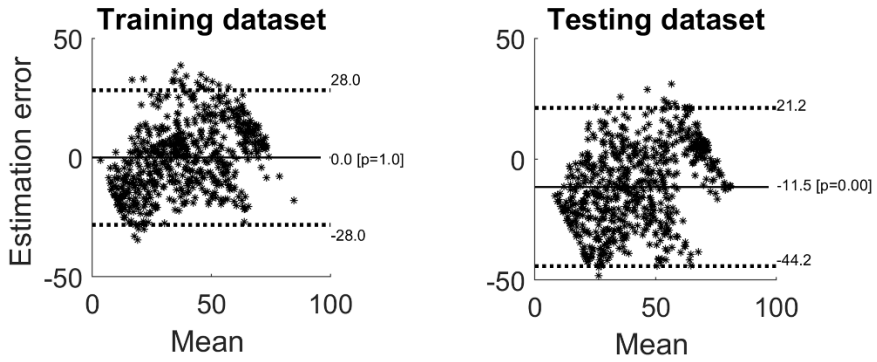
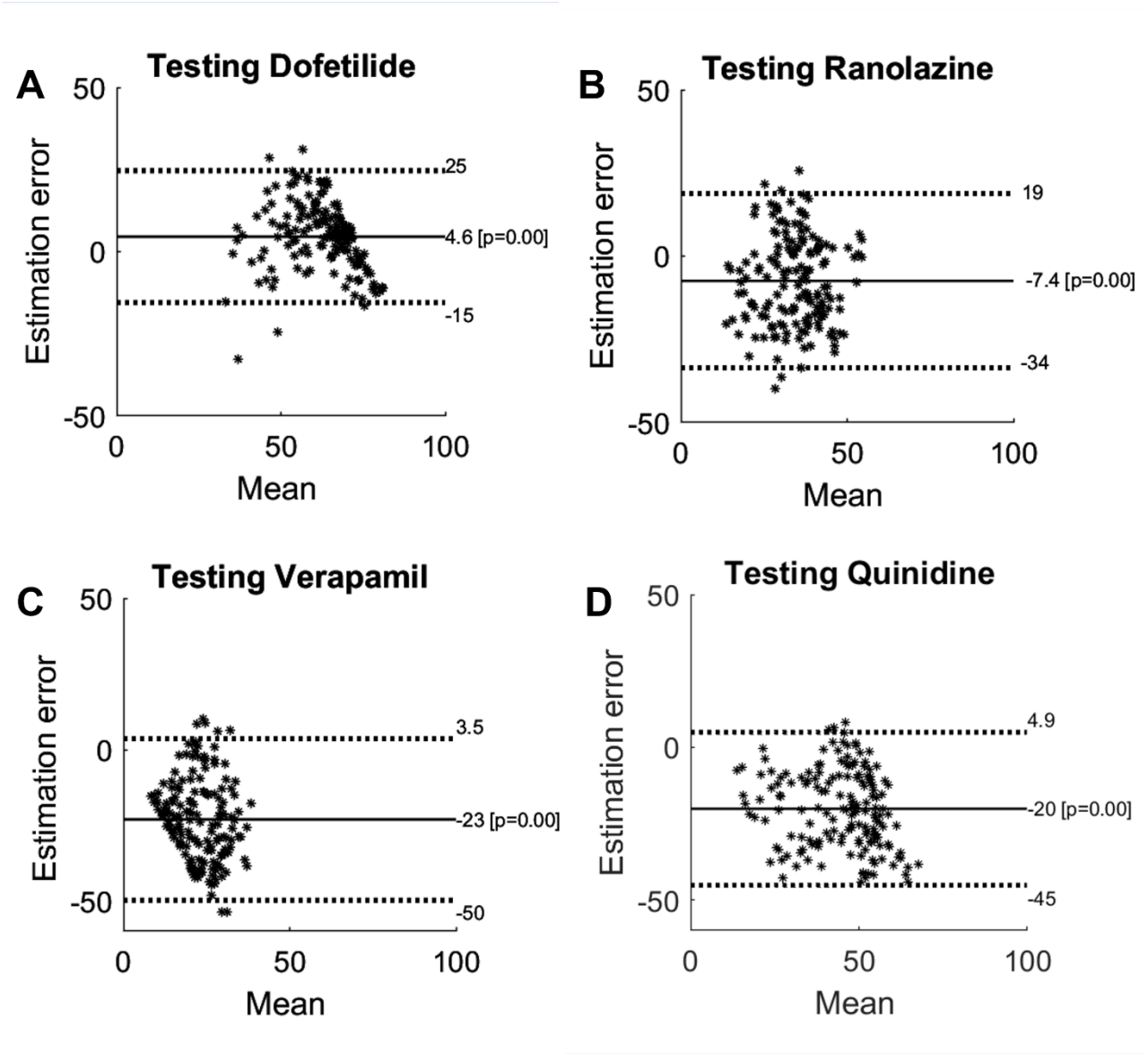

Training dataset
Testing dataset
Estimation error
Mean
50
0
-50
100
28.0
0.0 [p=1.0]
-28.0
21.2
-11.5 [p=0.00]
-44.2

Figure 4


A
Testing Dofetilide
Estimation error
Mean
25
-4.6 [p=0.00]
-15
B
Testing Ranolazine
19
-7.4 [p=0.00]
-34
C
Testing Verapamil
3.5
-23 [p=0.00]
-50
D
Testing Quinidine
4.9
-20 [p=0.00]
-45