Machine Learning of Drug Influence Based on iPSC Cardiomyocyte Calcium Transient Signals

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Abstract

Machine learning was applied to classify potential influence of two drugs on induced pluripotent stem cell-derived cardiomyocytes (iPSC-CM) on the basis of peak data detected from calcium transient signals of iPSC-CMs. The study shows that machine learning is capable to analyze such influence.

1. Introduction

Machine learning jointly with calcium transient signals of iPSC-CMs is so far studied infrequently. Machine learning was applied to the analysis of mechanistic action of drugs in cardiology [1] and electrophysiological influence of chronotropic drugs [2]. Recently, we began to study this approach by using machine learning to calcium transient signals of iPSC-CMs carrying mutations for a genetic cardiac disease, catecholaminergic polymorphic ventricular tachycardia (CPVT) [3]. In that study, the data consisted of calcium transient signals first with adrenaline to generate arrhythmias and second drug called dantrolene to potentially affect arrhythmias. Dantrolene was applied to cells and the response was classified into three classes, responders, semi-responders, and non-responders (3). In the current research, we reduced the number of classes to two to simplify classification and applied new data associated with two other antiarrhythmic drugs.

2. Material

The data of calcium transient signal of iPSC-CM used in the current research originated from an individual having a severe genetic arrhythmia, CPVT. iPSC-CMs were used to study the influence of two drugs from the signal data. Arrhythmias are induced in the patients with increasing of beating rate either with exercise or emotion. With cells, *adrenaline* was first used to increase beating and arrhythmias. Second, antiarrhythmic drugs either *flecainide* or *carvedilol* were given to iPSC-CMs and their influence was detected and analyzed. The response was analyzed with Ca^{2+}-imaging technique. Generation of the data of the iPSC-CMs was approved by the Ethics Committee of Pirkanmaa Hospital District as to culturing and differentiating of human iPSCs (R08070).

3. Methods

Peak detection was first executed for beats of calcium transient signals of cells given by the imaging technique when cells were exposed first to adrenaline and then to one of the drugs. Next, 14 peak attributes based on, e.g., peak duration and amplitude were computed from all valid peaks of every signal. The peak attribute data of 120 signals were applied to classify calcium transient signals into two classes depending on whether drug had an antiarrhythmic effect. Good antiarrhythmic response was obtained, if the drug had modified *abnormal* peaks (irregular, asymmetric peak shapes or peaks of varying amplitudes) to *normal* peaks (regular and symmetric shapes and similar amplitudes). At the beginning, all signals had been annotated by an experienced researcher to two classes along with antiarrhythmic effect (normal) or no influence (abnormal) of the drugs.

Classification was made with different machine learning methods containing *k*-nearest neighbor searching algorithm (*k*NN) with Mahalonobis measure and equal weights, random forests, and linear, quadratic, cubic and radial base function (RBF) support vector machines (SVM) generating results for a cell line representing the data origin from a patient.

4. Results

The contents of Tables 1 and 2 indicate that both drugs were quite effective since the maximum classification accuracies were high in the columns of normal versus abnormal and adrenaline versus normal being the most interesting classification alternatives showing that these signal classes were separable. However, both drugs produced approximately equal numbers of signals of the types normal and abnormal suggesting mainly a partial effect.

The columns of abnormal adrenaline versus abnormal with flecainide or carvedilol in Tables 1 and 2 are less important than those of two others, because all signals of class abnormal adrenaline were also irregular representing in a way class abnormal as well. In Table 1, the true positive values are high for both classes which means that these classes differ from each other, but their irregularities are not similar. Instead, in Table 2 class abnormal adrenaline was well classified shown by the high true positive values, but class abnormal with carvedilol poorly indicated by the low true positive values. In some respects, the signals of class abnormal with carvedilol resembled those of the majority class abnormal adrenaline.

5. Conclusion

The present results support our aim that machine learning could be used for the evaluation of cardiac drug effects. However, larger data sets than used could produce better or at least more confidential outcomes.

References

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Table 1. Flecainide results [%] for cell line 05605CPVT, classifications of calcium transient signals when cells exposed with adrenaline and then drug given: (1) flecainide changed 15 to normal versus 16 that stayed abnormal, (2) 31 abnormal adrenaline signals versus 16 that stayed abnormal, and (3) 31 abnormal adrenaline signals versus 15 that were converted to normal signals (total 31+16+15 signals). Abbreviation *k*NN is for *k*-nearest neighbor searching algorithm, here with Mahalanobis measure and equal weights, and SVM RBF for support vector machine method with radial base function. The highest accuracies given in Bold.

	Normal versus abnormal with flecainide			Abnormal adrenaline versus abnormal with flecainide			Abnormal adrenaline versus normal with flecainide		
Machine learning method	Accur-acy	True positive of normal	True positive of abnormal	Accur-acy	True positive of adrenaline	True positive of abnormal	Accur-acy	True positive of adrenaline	True positive of normal
*k*NN	67.7	53.3	81.3	68.1	77.4	50	84.8	96.8	60
Random forest	67.7	60.0	75	76.6	83.9	62.5	82.6	100	46.7
SVM linear kernel	71	85.7	56.3	**80.9**	74.2	93.9	80.4	77.4	86.7
SVM quadratic kernel	61.3	46.7	75	78.7	87.1	62.5	**89.1**	96.8	73.3
SVM qubic kernel	58.1	60	56.3	78.7	80.6	75	**89.1**	96.8	73.3
SVM RBF kernel	**74.2**	66.7	81.3	78.7	77.4	81.3	**89.1**	93.5	80

Table 2. Carvedilol results [%] for cell line 05605CPVT, classifications of calcium transient signals when cells exposed with adrenaline and then drug given: (1) 16 normal versus 13 abnormal calcium transient signals after carvedilol treatment, (2) 29 abnormal adrenaline signals versus 13 that stayed abnormal and (3) 29 abnormal adrenaline induced signals versus 16 that were converted to normal signals with carvedilol (total 29+13+16 signals).

	Normal versus abnormal with flecainide			Abnormal adrenaline versus abnormal with flecainide			Abnormal adrenaline versus normal with flecainide		
Machine learning method	Accur-acy	True positive of normal	True positive of abnormal	Accur-acy	True positive of adrenaline	True positive of abnormal	Accur-acy	True positive of adrenaline	True positive of normal
*k*NN	**79.3**	75	84.6	66.7	93.1	7.7	73.3	89.7	43.8
Random forest	**79.3**	81.3	76.9	64.3	89.7	7.7	73.3	86.2	50
SVM linear kernel	72.4	75	69.2	69	93.1	15.4	77.8	86.2	62.5
SVM quadratic kernel	75.9	81.3	69.2	**71.4**	82.8	46.2	75.6	82.8	62.5
SVM qubic kernel	62.1	75	46.2	69	86.2	30.8	71.1	82.8	50
SVM RBF kernel	**79.3**	87.5	69.2	69	100	0	**80**	89.7	62.5