Assessment of Spatial Heterogeneity of Ventricular Repolarization After Quinidine in Healthy Subjects

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Abstract

When spatial heterogeneity of ventricular repolarization (SHVR) increases, vulnerability to ventricular arrhythmias, including lethal ones, has also been observed to increase. Drug-induced multi-ion-channel blocks may increase SHVR. Aim of this study is to non-invasively assess whether quinidine, a strong hERG potassium channel blocker with weaker effects on calcium and late sodium currents, increases SHVR. We analyzed data from 21 healthy subjects that received both the drug and a placebo and underwent to 12 leads Holter monitoring. From the recording, three 10-s ECGs were extracted at each of 16 predefined time-points. SHVR was assessed by the $\mathcal{V}$–index, which evaluates the standard deviation of the repolarization times from multi-lead ECG recordings. At any time point, a value of $\mathcal{V}$–index was computed for each of the three 10s ECGs and averaged if the difference in the mean RR of the 10s ECGs was lower than 50 ms. The $\mathcal{V}$–index did not change after the placebo ($\mathcal{V}$–index pre-dose = 29.2 $\pm$ 9.9 ms vs. $\mathcal{V}$–index post-dose1h = 26.7 $\pm$ 10.3, ns), whereas, after quinidine, it significantly increased one hour post-dose ($\mathcal{V}$–index pre-dose = 29.5 $\pm$ 10.2 ms vs. $\mathcal{V}$–index post-dose1h = 46.5 $\pm$ 33.8 ms, p = 0.01). Quinidine had its maximum effect on the $\mathcal{V}$–index 2.5 h after dose ($\mathcal{V}$–index post-dose2.5h = 53.6 $\pm$ 39.6 ms).

1. Introduction

When spatial heterogeneity of ventricular repolarization (SHVR) increases, vulnerability to ventricular arrhythmias, including lethal ones, has also been observed to increase [1]. At the cell level, it is well known that the ion channel abnormalities are associated with the genesis of lethal arrhytmias as torsade de pointes or ventricular fibrillation. It is important to identify drugs that block relevant ion channels. The most significant block occurs to the human *ether-á-go-go*-related gene (hERG) potassium channel (an outward current) and prolongs the QT interval on the electrocardiogram (ECG) [2, 3]. However, a drug blocking the hERG potassium channel may not be associated to a high torsade risk because it may also block other channels (calcium and/or sodium, inward currents).

To estimate heterogeneity of ventricular repolarization or spatial dispersion of ventricular repolarization, the $\mathcal{V}$–index has been recently introduced [4]: the $\mathcal{V}$–index is a measure that provides an estimate of the standard deviation of the repolarization times of the myocytes across the entire myocardium from the surface ECG. The $\mathcal{V}$–index has been previously used to assess ventricular repolarization during moxifloxacin and solatol [5], and also in patients with Chagas disease, showing an increased dispersion of repolarization times correlated with the risk of death in a univariate survival analysis [6].

Aim of this study is to non-invasively assess whether quinidine, a strong hERG potassium channel blocker with weaker effects on calcium and late sodium currents, increases SHVR, as estimated by the $\mathcal{V}$–index.

2. Material and methods

2.1. Protocol

The design of this clinical study has been previously described [7]. Briefly, 22 healthy young subjects (27 $\pm$ 6 years, range 18-35, 11 males) without a family history of cardiovascular disease were included in the study. The subjects received a single dose of 400 mg quinidine sulfate (Watson Pharma, Corona, CA) or placebo under fasting conditions. Quinidine, not only blocks the hERG potassium channel, but also calcium and sodium channels at high concentrations [8].

During each period, standard 12-lead continuous ECGs were recorded at 500 Hz and then upsampled at 1 kHz. From the continuous recording, three 10-second ECGs were extracted at predose and 15 predefined time points post-dose (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 14, and 24 h) during which the subjects were resting in a supine position for 10 minutes and made available for further analysis. Data are available on physionet.org [9].

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2.2. $\mathcal{V}$–index

Myocytes' transmembrane potential (TMP) morphology and, particularly, durations differ when traversing the heart from apex to base and across the muscular tissue from the endo- to the epicardium. However, in first approximation, the slope of the TMP during phase 3 does not differ significantly across myocytes. Let's divide the myocardium in M nodes and let's suppose that each node m shares the same TMP during repolarization, which we represent here with a common function $D(t-\rho_m(k))$, where $\rho_m(k)$ marks the repolarization time of the k^{th} beat, as the point where the down-slope is maximal. $\rho_m(k)$ may be expressed as

$$\rho_m(k) = \bar{\rho}(k) + \Delta\rho_m(k), \tag{1}$$

where the repolarization delay $\Delta\rho_m(k)$ is the deviation from the average repolarization time $\bar{\rho}(k) = \frac{1}{M}\sum_{m=1}^{M}\rho_m(k)$ in the given heartbeat k.

Sassi and Mainardi [4] introduced a simple model to describe the distribution of these delays:

$$\Delta\rho_m(k) = \vartheta_m + \varphi_m(k), \tag{2}$$

where ϑ_m models the *spatial variability* of the repolarization times for a given subject at a given heart rate, and $\varphi_m(k)$ describes *temporal differences* in repolarization times which are observable among successive beats.

Under a few (common) hypotheses, usually enforced in forward and inverse electrocardiographical solversthe link between $\Delta\rho_m(k)$ and the T-wave $\mathbf{\Psi}(t)$ on the ECG (being $\mathbf{\Psi}(t)$ a $L\times 1$ vector containing the T-wave values for each lead) can be derived by analytically simplifying a biophysical model [10]. Specifically,

$$\begin{aligned}\mathbf{\Psi}(t) &\approx -\mathbf{A}\Delta\rho\, T_d(t) + 12\mathbf{A}\Delta\rho^2\, \dot{T}_d(t)\\ &= \mathbf{w_1}\,\mathbf{T_d(t)} + \mathbf{w_2}\,\dot{\mathbf{T}}_\mathbf{d}(\mathbf{t}),\end{aligned} \tag{3}$$

where the function $T_d(t)$ is the first derivative of $D(t)$ (which, with a sign reversal, is often termed "dominant T-wave" [10]) and $\Delta\rho = [\Delta\rho_1(k), \Delta\rho_2(k), \ldots, \Delta\rho_M(k)]^T$ is a vector of repolarization delays. $\mathbf{A}$ is a patient–dependent $[L\times M]$ transfer matrix accounting for the contribution of each node to the L-leads electrocardiographic recording in $\mathbf{\Psi}(t)$. The terms $\mathbf{w}_1$ and $\mathbf{w}_2$ are $[L\times 1]$ vector of scalars ("lead factors"), one for each beat.

An estimate of the SHVR, quantified as the sample standard deviation of the repolarization times across the myocardium, can be derived from the the lead factors through the $\mathcal{V}$–index, defined as:

$$\mathcal{V}_i = \frac{\mathrm{std}\,[\mathrm{w_2(i)}]}{\mathrm{std}\,[\mathrm{w_1(i)}]} \approx s_\vartheta = \left(\frac{1}{M}\sum_{m=1}^{M}\vartheta_m^2\right)^{1/2}, \tag{4}$$

where the standard deviations (std) are computed on the lead factors of lead i across a certain number of consecutive beats (not across different leads).

SHVR, as measured by the $\mathcal{V}$-index, has a straightforward physiological interpretation and does not suffer from an imperfect location of ECG fiducial points [4]. Moreover it was proved to be consistent by extensive numerical simulations [4, 5] and promising preliminary clinical validations [6, 11].

2.3. Preprocessing

Standard ECG preprocessing was performed in four steps. First, ECG signals were bandpass filtered (3rd order, Butterworth, 0.5 40Hz, zero-phase forward and reverse filtering) to reduce baseline wandering and high frequency noise. Second, for each lead independently, the isoelectric line was approximately set to 0 mV by subtracting a straight line estimated by linear regression of the points belonging to the TP segments (these points were identified through a binning of the ECGs amplitude distribution) [5]. Third, beats were detected by means of an ad-hoc implementation of the Pan-Tompkins detector on lead II and then, a QRS template was used to re-align the beats, using a cross-correlation-based algorithm, to obtain a common fiducial point. Fourth, lead quality was assessed by the average cross-correlation between the QRS template and the aligned QRS complexes. Leads with an average cross-correlation higher than 0.9 were considered of enough quality and then, further analyzed.

The $\mathcal{V}$–index was computed on ECG signals having at least three high quality leads (out of 12) by means of an iterative numerical algorithm previously validated [6]. Briefly, the algorithm estimated alternatively the lead factors (i.e., $\mathbf{w_1}$ and $\mathbf{w_2}$) and on each T-wave, using a discretized version of the Eulero-Lagrange equations. In this way, we computed one $\mathcal{V}$–index value for each high quality lead. We considered their average as an overall estimate of the $\mathcal{V}$–index. Since each ECG recording lasted 10 s, the number of beats available for the $\mathcal{V}$–index computation was rather limited. To increase the robustness of the estimates in a specific time-point, we averaged the $\mathcal{V}$–index values obtained in the three ECG replica close to that time point. Given the fact that the $\mathcal{V}$–index might depends on the heart rate, the values were averaged only when the corresponding averaged RR did not differ more than 50 ms from each other (i.e., the heart rate was stable).

2.4. Statistical analysis

One-way repeated-measures Friedman test was performed to compare the parameters over time; if the p-value of the Friedman test was significant, a paired Wilcoxon test with Holms correction was applied. Paired t-test or

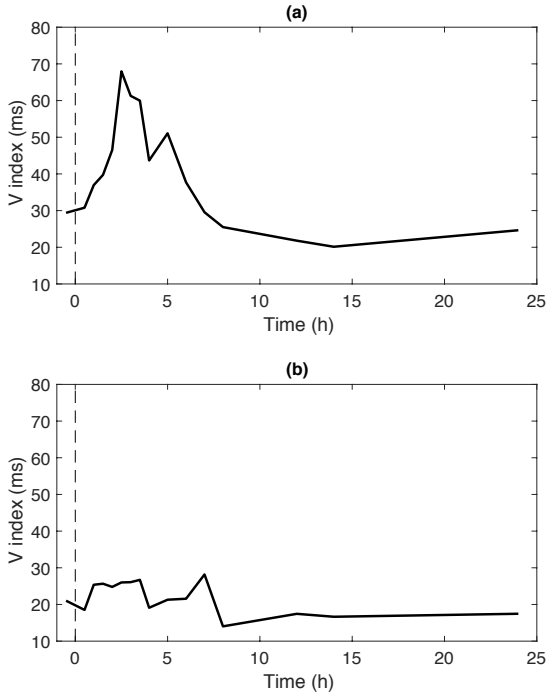

Figure 1. Example of $\mathcal{V}$–index for one subject over time during (a) quinidine and (b) placebo administration. The dash vertical line indicates the time of quinidine or placebo administration.

Wilcoxon test was also used to compare drugs and placebo parameters at the same time point. P values of < 0.05 were considered statistically significant. All analyses and statistical tests were performed using MATLAB R2016a (The MathWorks).

3. Results

The heart rate in each time point is quite stable for the three repetitions, with a range of the RR mean of 32 ± 18 ms for quinidine and 31 ± 18 ms for the placebo. Only 6% and 4% of the segments were excluded because of the lack of at least two repetitions with similar RR, for quinidine and the placebo, respectively.

Figure 1 shows the $\mathcal{V}$–index for one subject during (a) quinidine and (b) placebo administration. It can be observed that the placebo does not affect the $\mathcal{V}$–index. On the contrary, after the administration of the quinidine, an increase of $\mathcal{V}$–index is observed, going from 29 to 68 ms, from pre-dose time point to the peak. The peak of $\mathcal{V}$–index after quinidine administration is observed after 2.5 hours.

This result is confirmed on the whole population, as shown in Figure 2. It can be observed that quinidine leads to a significant $\mathcal{V}$–index increase, whereas there is no effect of the placebo. In particular, during quinidine, comparing the value of $\mathcal{V}$–index at each time point with the pre-dose one, a significant ($p < 0.05$) increase can be observed after one hour of quinidine. Moreover, in Figure 2 the average concentration of the drug is shown: it can be observed that the peak of $\mathcal{V}$–index is at the same time point as the peak of the drug concentration appears. No difference in the $\mathcal{V}$–index is observed after the placebo administration.

Table 1. Percentage of increase at the peak with respect to pre-dose values.

Parameter	% increase
$\mathcal{V}$–index	143 ± 111
QTc	26 ± 6
Tpeak-Tend	83 ± 45
J-Tpeak	7 ± 6

Finally, Table 1 shows the percentage of increase of $\mathcal{V}$–index (measured at the peak) and three classical parameters (obtained together with the dataset) to assess ventricular repolarization heterogeneity, namely, the corrected QT interval (QTc), the interval between the peak and the end of T wave (Tpeak-Tend) and the interval between the J-point to the peak of T-wave (J-Tpeak). It can be observed that the increase of the $\mathcal{V}$–index is much larger than that of QTc, Tpeak-Tend, J-Tpeak.

4. Conclusions

These preliminary results show that the $\mathcal{V}$–index can recognize changes in SHVR due to quinidine. The percentage of increase of $\mathcal{V}$–index (measured at the peak) is much larger than that of three classical parametersto assess ventricular repolarization heterogeneity. The short duration of the analyzed recordings (a limitation of this study) may be the cause of the high standard deviation observed in the results, however, these may be reduced when analyzing longer recordings.

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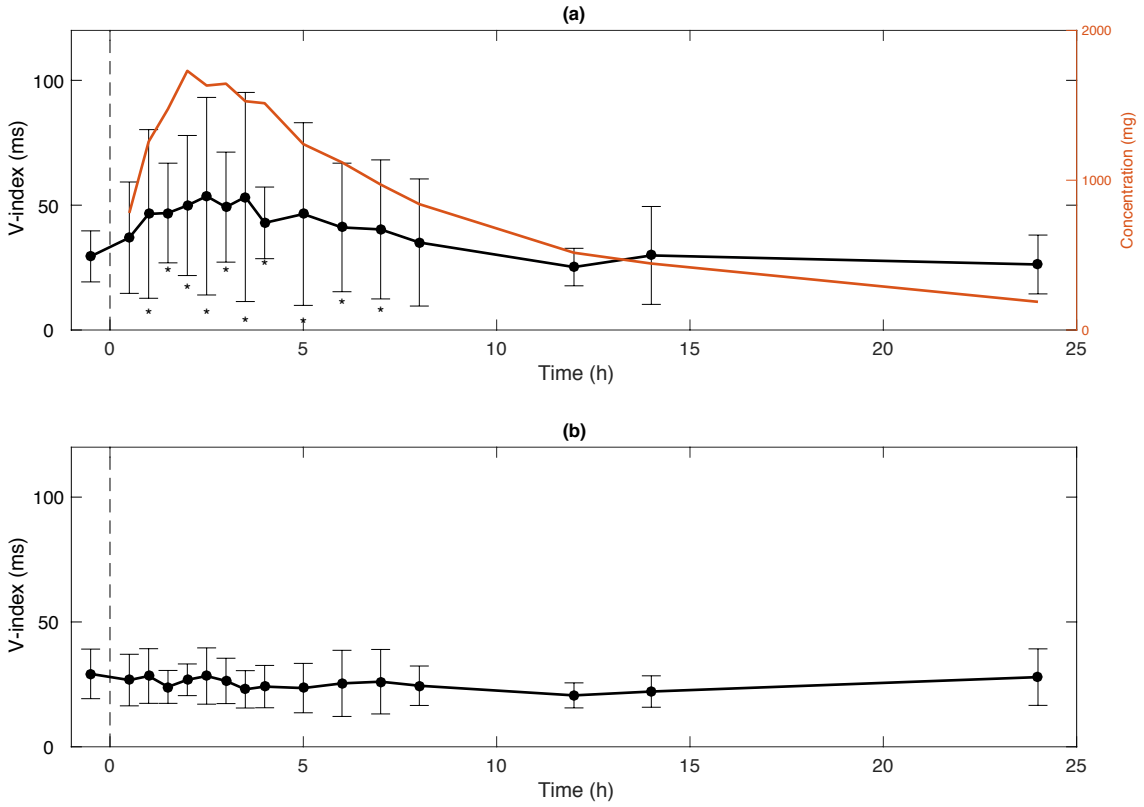

Figure 2. Average of $\mathcal{V}$–index for all the subjects over time during (a) quinidine and (b) placebo administration. The dash vertical line indicates the time of quinidine or placebo administration. * $p < 0.05$ when comparing the $\mathcal{V}$–index of a time point versus the pre-dose value. The average plasma concentration is superimposed (red line) in (a).

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