

Quantification of the Ionic Current Contributions to Alterations in the Action Potential Repolarization by means of Piecewise-linear Approximation

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Abstract

At cellular level, changes in the cardiac action potential (AP) duration (APD) are relevant proarrhythmic markers. The assessment of single current contributions to APD changes allows the investigation of the complex interplay of ionic mechanisms underlying such repolarization changes.

In this paper, we present a new method to quantify the contributions of each membrane current to APD changes due to a perturbation from the basal to a different condition. To achieve our goal, we used a piecewise-linear approximation of the AP.

We tested our method on the O'Hara-Rudy model in case of rate adaptation: from the basal condition (pacing at 60 bpm), two different pacing rates are used as perturbations: 30 bpm, which prolongs APD by 21 ms, and 120 bpm, which shortens APD by -37 ms. At steady state, the most significant current contributions (30 bpm/120 bpm) are: I_{NaK} (68/-73 ms), I_{CaL} (-58/51 ms), I_{NaCa} (-10/25 ms), I_{Ks} (13/-7 ms) and I_{NaL} (7/-23 ms). Our method allows also quantifying the dynamic adaptation to rate changes from the perturbation until the steady state.

In conclusion, our method enables the quantification of the adaptive and compensatory mechanisms implemented by the (in silico model of) cell in response to a perturbation, such as the pacing rate change.

1. Introduction

Prolongation and shortening of the action potential (AP) are important proarrhythmic markers at the cardiac cellular level. To investigate the ionic mechanisms underlying such phenomena it is useful to quantify the contribution of each membrane current to the changes in AP duration (APD).

When considering a cardiac AP obtained in basal conditions (AP_b), its duration is conventionally measured at 90% of repolarization (APD₉₀). If the cell (or the computational model of the cell) undergoes any kind of perturbation affecting its AP, the duration will change to

APD_p. In other words, the perturbation leads to a quantitative change of APD equal to:

$$\Delta APD = APD_p - APD_b \quad (1)$$

Such variation is due to changes in the ionic currents flowing through the cell membrane and underlying any change in the membrane potential, as mathematically described by the fundamental equation of the Hodgkin-Huxley modeling paradigm:

$$\frac{dV}{dt} = -\frac{1}{C} I_{tot} = -\frac{1}{C} \sum_i I_i(t) \quad (2)$$

However, given the complex interplay between ionic currents and concentrations and the membrane potential, it is not possible to assess the quantitative contribution of each current to the AP modification. Namely, it is not possible to ascribe specific portions of ΔAPD to specific ionic currents.

To overcome this limitation, we propose a novel method to quantify the contribution of each current to the repolarization of *in silico* APs by sharing among the currents the APD prolongation/shortening due to a perturbation from a basal to another condition.

2. Methods

2.1. AP piecewise-linear approximation

The single current contributions are computed by means of a piecewise-linear approximation of the AP (Fig. 1). Starting from its peak value, and assuming a monotone decreasing time course, the AP is dissected in small pieces, each one corresponding to a “discrete decrease” of the membrane potential (e.g. $\Delta V = -1$ mV). In this way, the AP time course is divided into unevenly long time intervals, since they will be longer when the AP decrease is slower (e.g. during the plateau phase 2) with respect when the AP decrease is faster (e.g. during the repolarization phase 3). Indeed, the time needed to membrane potential for a single ΔV decrease varies along

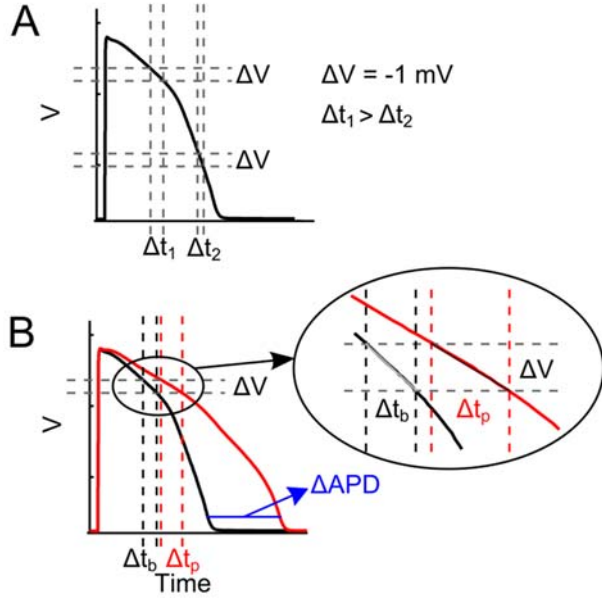


Figure 1. (A) Slicing the AP in discrete decreases ΔV ; (B) AP piecewise-linear approximation.

the AP. Within each small time interval the AP time course can be satisfactorily approximated by a linear decreasing trend (Fig. 1, inset). In these conditions, Eq. 2 can be rewritten as:

$$\frac{\Delta V}{\Delta t_b} \cong -\frac{1}{C} \overline{I_{tot,b}} = -\frac{1}{C} \sum_i \overline{I_{i,b}} \quad (3)$$

for the basal condition, and

$$\frac{\Delta V}{\Delta t_p} \cong -\frac{1}{C} \overline{I_{tot,p}} = -\frac{1}{C} \sum_i \overline{I_{i,p}} = -\frac{1}{C} (\sum_i \overline{I_{i,b}} + \sum_i \overline{\Delta I_i}) \quad (4)$$

for the perturbed condition, where $\overline{I_{tot,b}}$, $\overline{I_{tot,p}}$, $\overline{I_{i,b}}$ and $\overline{I_{i,p}}$ are the average values of the corresponding currents over the time interval Δt_b and Δt_p , respectively; $\overline{\Delta I_i}$ represents the change of each specific average current.

By combining the two equations and setting $\Delta V = -1$ mV, the change in the duration of the time interval due to the perturbation, $\Delta \Delta t$, can be computed as:

$$\Delta \Delta t = \Delta t_p - \Delta t_b \cong C \left(\frac{1}{\overline{I_{tot,p}}} - \frac{1}{\overline{I_{tot,b}}} \right) = -C \left(\frac{\sum_i \overline{\Delta I_i}}{\overline{I_{tot,p}} \cdot \overline{I_{tot,b}}} \right) = \sum_i \Delta \Delta t_{I_i} \quad (5)$$

where

$$\Delta \Delta t_{I_i} = -C \frac{\overline{\Delta I_i}}{\overline{I_{tot,p}} \cdot \overline{I_{tot,b}}} \quad (6)$$

is the quantitative contribution of the i -th ionic current to

the local APD change $\Delta \Delta t$. The overall APD can be computed as:

$$APD = \sum_t \Delta t \cong C \sum_t \frac{1}{\overline{I_{tot}}} \quad (7)$$

and the total APD perturbation can be expressed as the sum of the contributions due to each single ionic current ($\Delta \Delta PD_i$):

$$\Delta APD = \sum_i \Delta \Delta PD_i = \sum_i \sum_t \Delta \Delta t_{I_i} \quad (8)$$

3. Results

In this paper we applied the AP piecewise-linear approximation to investigate the single current contributions to APD rate adaptation in human ventricular AP. From the basal pacing rate of 60 bpm, the state-of-art O'Hara-Rudy model (ORd) [1] was perturbed (i) slowing the pacing to 30 bpm or (ii) accelerating it to 120 bpm (Fig. 2).

3.1. Accuracy of the AP piecewise-linear approximation

Before assessing the current contributions to repolarization, we quantified the accuracy of the AP piecewise-linear approximation to estimate the APD. We reported in Table 1 the APD for the 3 different pacing rates and the APD prolongation/shortening after rate changes, computed on the original AP and reconstructed through the piecewise-linear approximation (eq. 7). The accuracy of the approximation was very high, the error being less than 1 ms.

Table 1. Comparison of the real and approximated (through the AP piecewise-linear approximation, Approx) measurements of APD.

Pacing rate (bpm)	APD (ms)		Δ APD (ms)	
	Real	Approx	Real	Approx
60	262.7	263.2	--	--
30	284.2	284.8	21.48	21.54
120	226.1	226.5	-36.65	-36.71

3.2. Quantification of ionic current contributions to rate adaptation

The first test aimed to quantify the contribution of the single ionic currents to the overall APD rate adaptation in steady state conditions (SS, 1000 beats after perturbation), as shown in Fig. 2. we show the AP prolongation and shortening consequent to the pacing rate

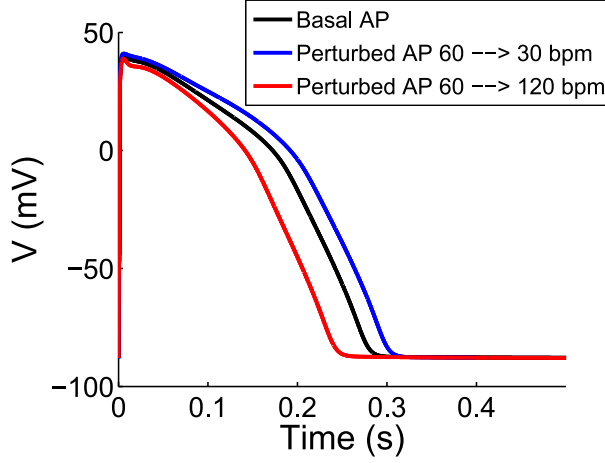


Figure 2. APs at different pacing rates: basal 60 bpm (black), perturbed 30 bpm (blue) and perturbed 120 bpm (red).

reduction (to 30 bpm, blue) and increment (to 120 bpm, red), respectively. O'Hara *et al* [1], when proposing the ORd model of human ventricular AP, indicated I_{Ks} , I_{NaL} , I_{CaL} , I_{NaCa} , I_{to} and I_{NaK} as the most influent currents during rate adaptation. With our algorithm, we quantified their contributions (Table 2 and Fig. 3). In particular, I_{NaK} is the main responsible for the physiological AP adaptation to the changed pacing rate. Notably, I_{CaL} changes would oppose such adaptation.

Table 2. Current contributions to the AP repolarization prolongation (60→30 bpm) and shortening (60→120 bpm) at steady state.

Current	ΔAPD_i (ms)	
	60 → 30 bpm	60 → 120 bpm
I_{Ks}	13.2	-7.4
I_{NaL}	6.9	-23.0
I_{CaL}	-58.1	50.7
I_{NaCa}	-9.8	24.8
I_{NaK}	67.8	-72.8
I_{to}	-1.5	-11.4
I_{Na}	-2.7	5.6
I_{Kr}	8.9	-5.8
I_{Kb}	-3.6	2.7
Total	21.1	-36.6
ΔAPD approx	21.54	-36.71

The second test aimed to quantify the ionic current contributions to dynamic adaptation to rate changes, that is to repolarization changes starting from the time of perturbation until the SS is reached. As shown in Fig. 4, the ionic current contributions to the AP prolongation and shortening were not constant from the perturbation to SS, but they changed sensibly during the simulation time course. As an example, in case of pacing at 120 bpm, after a single beat from perturbation the overall ΔAPD

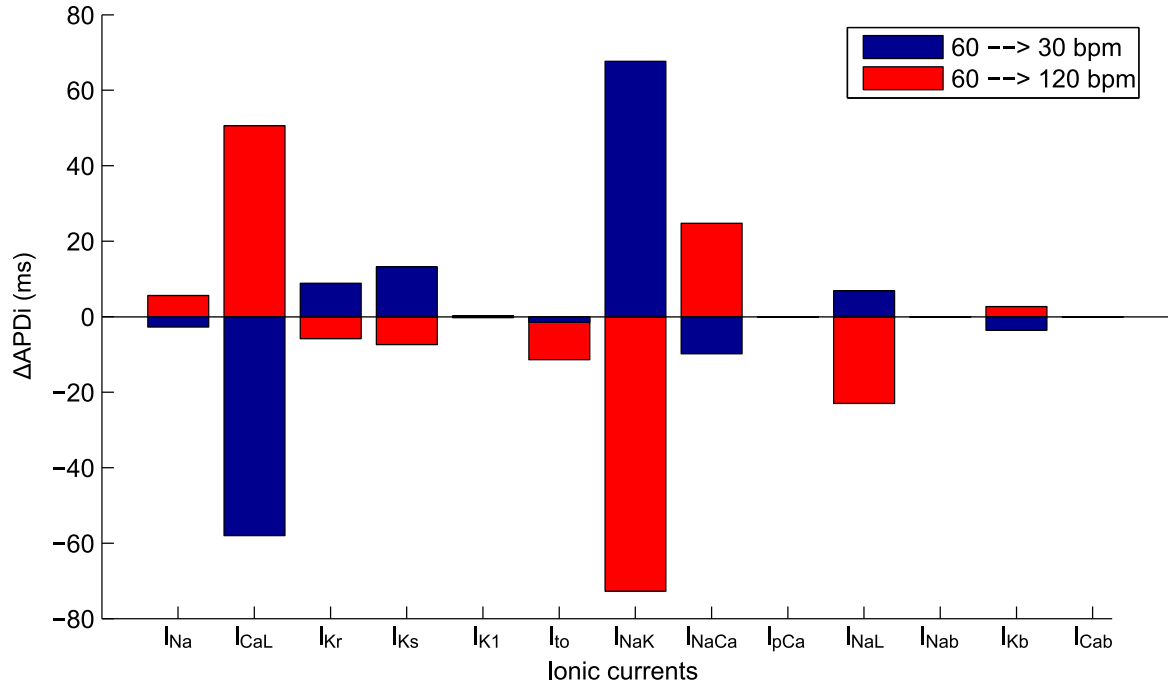


Figure 3. Contributions (ΔAPD_i) of each ionic current to AP shortening/prolongation due to rate adaptation, at steady state

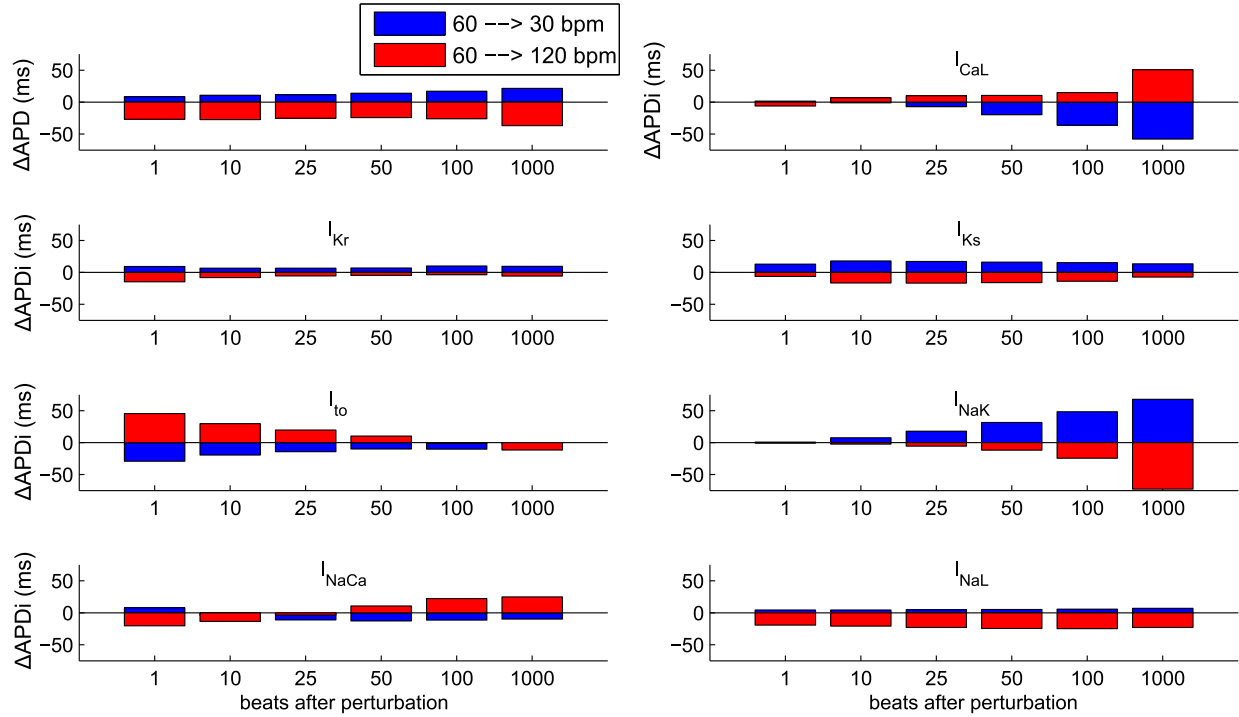


Figure 4. Contributions (ΔAPD_i) of the main currents from the onset of perturbation to steady state.

(Fig. 4, top left panel, red bars) was -27 ms. It was due to many currents, with the main contributions by I_{NaCa} (-20 ms), I_{NaL} (-19 ms) and I_{Kr} (-15 ms). But the AP shortening was also counteracted by a large prolonging contribution by I_{to} (+45 ms). At SS, the AP shortening was much larger ($\Delta APD = -37$ ms) mainly because of the contribution by I_{NaK} (-73 ms), while the contribution of I_{to} underwent an inversion, eliciting a shortening (-12 ms) instead of a prolongation of the AP.

4. Discussion and conclusions

In this paper, we show how a piecewise-linear approximation of the AP enables the quantification of the contributions of the single ionic currents to AP changes following a perturbation. Moreover, this analysis captures the dynamic adaptation to rate changes from the beat immediately after the perturbation to SS, allowing the assessment of the contribution changes over time, e.g. I_{NaCa} and I_{to} ones during rate adaptation. Our analysis provides a comprehensive picture of the complex and fine interplay of opposing currents that in the end results into the AP rate adaptation. Of note, the presented results are produced by the ORd model: a future work will consist in assessing the potential model-dependency of rate adaptation. Furthermore, here we focused on rate adaptation, but our algorithm can be used in all those situations where changes in the repolarization phase occur. As a future development we aim to extend the

piecewise-linear approximation of the AP also for more complex AP shapes, e.g. spike-and-dome.

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References

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