Reliability of APD-Restitution Slope Measurements: Quantification and Methodological Comparison

M Orini[1], N Srinivasan[1] , P Taggart[1], P Lambiase[1]

[1] Insitute of Cardiovascular Science, University College London, London, United Kingdom

Abstract

The restitution of the action potential duration (APDR) is an important physiological property of the cardiac tissue and it is related to the development of fatal arrhythmia. Accurate measures of the slope of the APDR curve are crucial for a correct interpretation of the restitution properties. The two most commonly used methodologies for the estimation of the APDR slope are based on linear and exponential fitting. In this study, an accurate assessment and comparison of these methodologies is performed for the first time. Realistic APDR curves were simulated based on an analytical model of the APDR slope that was informed with data derived from unipolar electrograms recorded in structurally normal human ventricles. The impact of noise level was evaluated. When the activation and repolarization times for both the basic cycle length beat and the premature beat were measured with an error < 5 *ms, the linear method provided more accurate estimates, being its mean absolute estimation error significantly lower (*$11.3\% - 25.3\%$ *vs* $37.0\% - 38.2\%$*) and its linear correlation with reference values significantly higher (*$0.97 - 0.98$ *vs* $0.65 - 0.70$*) than for the exponential method. These relatively high estimation errors and high correlations suggest that restitution properties should be considered in relative terms, and discourage the use of fixed threshold values, such as 1.00, for the interpretation of the slope estimates. In conclusion, this study suggests to use a piece-wise linear fitting scheme for the estimation of the APDR curve, provided that all measured with an error lower than 5 ms.*

1. Introduction

The restitution of the action potential duration is a mechanism whereby cardiac excitation and recovery adapt to heart rate changes. The action potential duration (APD) restitution (APDR) curve is drawn by plotting the APD as a function of the diastolic interval (DI), i.e. $APD = f(DI)$, measured during specific cardiac pacing protocols [1]. The APD and DI are measures of the duration of electrical cellular excitation and recovery, measured as the amount of time during which the transmembrane potential is higher and lower than the threshold potential, respectively (see Fig. 1). Combined in-vivo and in-vitro work has demonstrated that APDR properties are associated with increased vulnerability to fatal arrhythmias [2]. These studies show that a steep APDR curve can contribute to create unstable wavefronts propagation [3], induce repolarization alternans [4], establishing the conditions for functional block and reentrant wavefronts independently of preexisting electrophysiologic heterogeneities in the tissue. Therefore, the APDR curve is of great interest to understand cardiac electrophysiological mechanisms, and accurate estimates of its slope are required in order to assess cardiac risk and to elucidate the mechanisms underlying arrhythmogenesis. However, this is challenging for several reasons. In particular, electrophysiological recordings are often noisy and present artifacts that can affect the estimation of the APDR slope.

In this study, we assess the accuracy of the two most commonly used techniques to quantify the APDR slope, namely the linear-piecewise and exponential methods [1, 5]. To this end, we derive an analytical expression for the APDR slope to identify its main determinants and to investigate how these affect the slope estimates. We then generate reference APDR curves by fitting data recorded in patients with structurally normal heart to the model, and we assess the accuracy of the two methodologies as a function of noise level.

2. Methods

2.1. Analytical expression of the APD restitution curve

The analytical expression used in this study to simulate the APDR curve was first derived in [6], with the aim of separately assessing the contribution that depolarization and repolarization dynamics have to the steepness of the slope. Briefly, as shown in Fig. 1, for each heart beat n, the APD and DI can be written as:

$$APD(n) = RT(n) - AT(n) \tag{1}$$
$$DI(n) = \underbrace{PI(n) + AT(n+1) - AT(n)}_{CL(n)} - APD(n)$$

where AT and RT are the activation (AT) and repolarization times (RT), while the expression in bracket represents the local cycle length (CL), and PI is the pacing interval (Fig. 1). During a standard S1S2 restitution protocol, a train of L electrical stimuli is delivered to pace the heart, such as the first $L-2$ beats has a constant pacing interval S_1, while the last paced beat has a different PI, i.e. $PI(kL-1) = S_2$. Usually, k trains of stimuli are delivered where S_2 is incrementally reduced until the effective refractory period is reached and cardiac capture is lost [1].
Using the operator $\Delta_\mathrm{L}(\cdot)$, such as $\Delta_\mathrm{L}(x) = x(n) - x(n-L)$, the local slope of the APDR evaluated for k S_2 pacing intervals is defined as:

$$\alpha(k) = \frac{\Delta_\mathrm{L}(APD(kL))}{\Delta_\mathrm{L}(DI(kL-1))} \tag{2}$$

Inserting (1) in (2) and considering infinitesimally small ΔS_2, with $k = [1 : \infty]$, the expression in (2) can be written as a function of the continuous variable s representing the pacing interval [6]:

$$\alpha(s) = \frac{y'_\mathrm{RT}(s) - y'_\mathrm{AT}(s)}{1 + y'_\mathrm{AT}(s) - w^\mathrm{S1}_\mathrm{APD} - w^\mathrm{S1}_\mathrm{AT}} \tag{3}$$

where $y_\mathrm{X}(s)$ represents the changes of the the quantity $X = \{AT, RT, APD, DI\}$ as a function of s, and $y'_\mathrm{x}(s) = \frac{1}{ds}x(s)$. The terms $w^\mathrm{S1}_\mathrm{APD}$ and $w^\mathrm{S1}_\mathrm{AT}$ represent the changes in APD and AT within the last S1 beat of two consecutive pacing trains, i.e. $[X(kL-1) - X((k-1)L-1]/[PI(kL-1) - PI((k-1)L-1)]$, with $X = \{AT, APD\}$. The expression in (3) shows that the steepness of the slope is determined by RT and AT after the short pacing intervals S_2 as well as by fluctuations in AT and APD within beats at the basic cycle length S_1. In this study, we used this expression to carry out a simulation study to assess how different levels of noise affect the restitution slope estimates provided by the two most commonly used methods.

2.2. Population study

Five patients with structurally normal hearts and preserved left ventricular ejection fraction were considered for an electrophysiological study. Decapolar catheters were placed in the right and left ventricular endocardium, and on the epicardium of the LV via the coronary sinus. Electrical stimulation was performed from the right ventricle at a pulse width of 2 ms. The restitution protocol was performed using drive trains of 9 beats at a basic cycle length

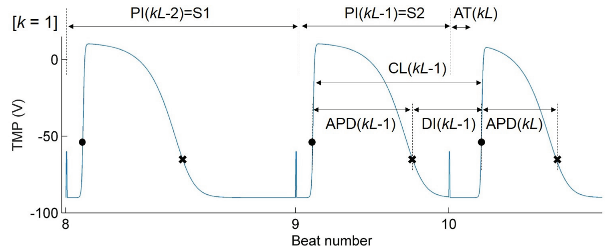

Figure 1. Diagrammatic illustration of the transmebrane potential during a restitution protocol. The last pacing interval, $PI(kL-1)$, is shorter than the previous ones. AT and RT: activation and repolarization time. APD: action potential duration. DI: diastolic interval. CL: local cycle length.

$S_1 = 600$ ms, followed by an extra stimulus at a pacing interval S_2 that was decremented in steps of $\Delta S_2 = 50$ ms between 1000 and 400 ms, by $\Delta S_2 = 20$ ms between 400 and 300 ms, and by $\Delta S_2 = 5$ ms from 300 ms until effective refractory period (ERP) of the tissue. Then, the PI was increased at $S_2 = ERP + 10$ ms and subsequently decremented in steps of $\Delta S_2 = 2$ ms.
The unipolar electrograms were analysed off line with bespoke algorithms as in previous studies [7–9]. Activation time was defined as the moment of minimum downslope within the QRS complex, and RT was defined as the moment of maximun upslope within the T-wave. The local activation recovery interval, defined as $ARI = RT - AT$, was used as measurement of local APD.

2.3. Simulation study

The effect that noise has on the accuracy of APDR slopes estimates was assessed as follows. AT and RT were measured from the unipolar electrograms. AT and RT series were fitted over the PI in the range $s = [180 - 1000]$ ms with polynomial functions of order from 4 to 9 (see Fig. 2). The least absolute residual scheme was used to reduce the impact of possible outliers and the functions that minimize the median absolute deviation was taken as $y_\mathrm{AT}(s)$ and $y_\mathrm{RT}(s)$. The curve that describes how the DI changes as a function of the PI was obtained as $y_\mathrm{DI}(s) = s + y_\mathrm{AT}(s) - \overline{AT_\mathrm{S1}} - \overline{APD_\mathrm{S1}}$, where the last terms represent the mean AT and APD within the last S1 beat (see (1)). Values for which $y'_\mathrm{DI}(s) \leq 0$ were discarded. The reference value for the APDR slope, α^0, was defined as maximum ration $\Delta y_\mathrm{APD}/\Delta y_\mathrm{DI}$ evaluated in moving widows 40 ms wide.White Laplacian noise with standard deviation equal to $\{1, 3, 5\}$ ms was added to the APD and AT of the last S1 beat as well as to the RT and AT of the last S2 beat, i.e. $y_\mathrm{RT}(s)$ and $y_\mathrm{AT}(s)$. After having added noise, AT, RT, APD and DI series were down-sampled, to

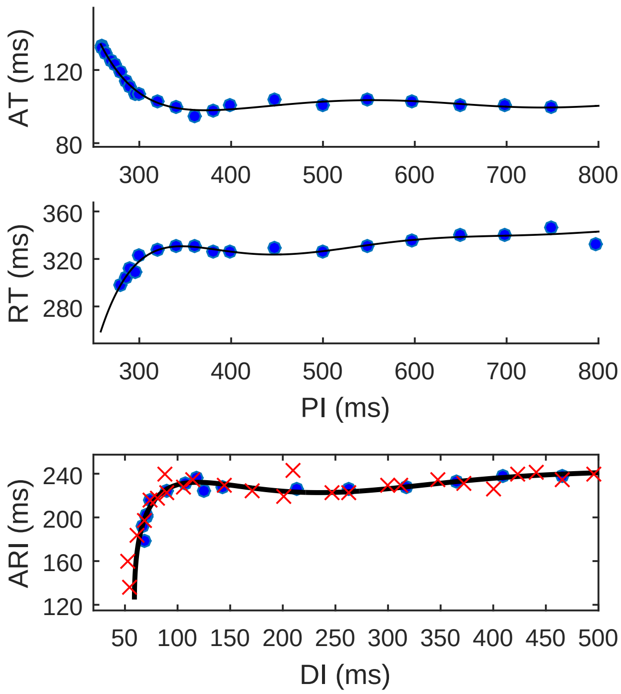

Figure 2. Example of a representative restitution curve before adding noise. Blue dots: interpolated curves before adding noise. Solid line: interpolated curves. Red crosses: APD restitution curve with noise with standard deviation equal to 3 ms added to AT, RT and last S1 APD and AT.

simulate the case in which the restitution protocols were performed by using pacing protocols with PI for the last premature beat decreasing in steps of $\Delta S_2 = 5$ ms for $S_2 \leq 350$ ms, and in steps of $\Delta S_2 = 25$ ms for $S_2 > 350$ ms.

The steepness of the APDR curve was then quantified by performing either piece-wise linear fitting or exponential fitting. In the former, linear fitting is performed in sliding windows 40 ms wide and the maximum slope is taken as estimate of α^0. In the latter, the curve is fitted using the exponential function $y_{\mathrm{APD}} = y_0 - a \cdot \exp(1/b \cdot y_{\mathrm{DI}})$, where y_0 is the mean y_{APD} for $y_{\mathrm{DI}} \geq 450$ ms. Estimates of α^0 were then taken as the mean value of the first derivative of the exponential curve in an interval starting at the lowest y_{DI} and lasting 40 ms, i.e. $-(\exp(-[x+40]/b) - \exp(-x/b)) \cdot a/40$, with $x = \min(y_{\mathrm{DI}})$.

Seventy APDR curves were considered. For each curve the following indices were calculated: the mean absolute error $\mathrm{mean}_j(|(\hat{\alpha}_{i,j} - \alpha_i^0)/\alpha_i^0|)$, and the correlation coefficient, $\mathrm{corr}(\alpha_i^0, \mathrm{mean}_j(\hat{\alpha}_{i,j}))$, where $i = \{1, \ldots, 70\}$ and $j = \{1, \ldots, 100\}$ represent i-th restitution curve and the j-th noise realization, respectively, and $\hat{\alpha}$ is an APDR slope estimate.

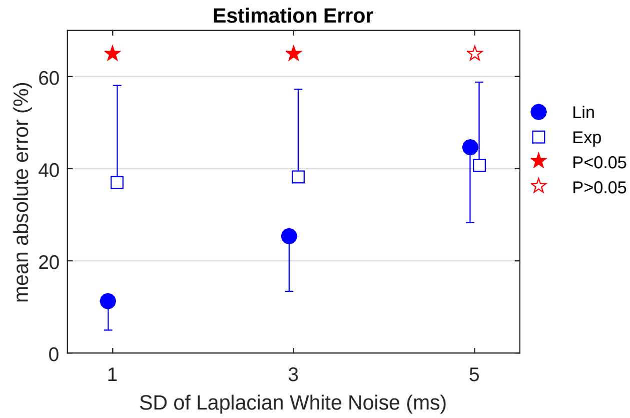

Figure 3. Mean absolute estimation error across 70 simulated APD restitution curves (mean $\pm$ sd). Noise was added with standard deviation equal to 1, 3 and 5 ms to the APD and AT of last S1 beat as well as to RT and AT of S2 beat. Red and white stars: statistically significant differences ($P < 0.05$, Wilcoxon rank sum test).

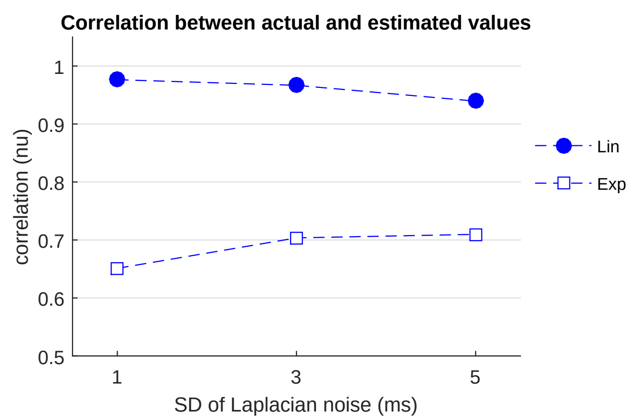

Figure 4. Linear correlation between APD restitution curve from the model and slopes estimated after adding noise. See caption of Fig. 3 for details.

3. Results

The slope of the 70 simulated APDR curves was in the range $0.26 - 4.0$, and mean and standard deviations were 1.11 ± 0.65. The results of the study are shown in Figs. 3 and 4. The linear method had significantly lower mean absolute estimation error than the exponential method except when the standard deviation of Laplacian noise was equal to 5 ms ($P < 0.05$ Wilcoxon rank sum test). On average, the estimation error of the exponential method did not substantially increase with noise, going from 37.0% to 38.1% to 40.7% for noise levels equal to 1, 3 and 5 ms, respectively. This is because using this method the APDR curve is fitted with an exponential function over the entire range of DI, thus reducing the impact of noise. The exponential method provided biased estimates due to the fact that the restitution curve is not a monotonic function, but it exhibits humps that reduce the match with an exponential curve [1]. On the other hand, the estimation error of the linear method was strongly affected by the noise level. This is because of the reduced range of DI over which the linear fitting is performed (40 ms in this study). However, on average the estimation error was significantly lower as compared to the exponential method for noise level equal to 1 ms (11.3%) and 3 ms (25.3%), while it was equal to 44.7% for noise levels equal to 5 ms.

By definition, the estimation error depends on the specific definition of the reference value α^0. To provide an assessment that is less dependent on α^0, correlation analysis was performed. Considering all noise levels, the Pearson's correlation coefficient between reference values and slope estimates was higher for the linear method than for the exponential method (0.96 ± 0.02 vs 0.69 ± 0.03, $P \approx 0$). Similar results were obtained when considering the Spearman's correlation coefficient.

4. Discussion and conclusion

In this study, we used unipolar electrograms recorded in 5 patients with structurally normal ventricles to simulate 70 APDR curves with realistic shapes in order to assess the accuracy of the linear and exponential methods. We derived an analytical expression of the APDR slope [6] to determine the intervals that primarily contribute to the APDR slope estimates. This expression shows that the APD and AT after the short pacing interval S_2 as well as the RT and AT at basic cycle length S_1 contribute to the slope. We added white Laplacian noise with different standard deviations to all the aforementioned intervals simultaneously.

The results of the study show that the linear method is more sensitive to noise than the exponential method. This is mainly due to the fact that the exponential fitting uses the entire range of DI, while the linear fitting is performed in short sliding window. However, the estimation error was significantly lower and the linear correlation was significantly higher for the linear method, that overall provided better slope estimates. This study shows that both estimators may be characterized by a high estimation error, in the range of $11.3 - 44.7\%$ for the linear method and $37.0 - 40.7\%$ for the exponential method, while correlation between reference and estimated values were always higher, being in the range $0.94 - 0.98$ for the linear and $0.65 - 0.71$ for the exponential methods. These results should discourage the use of fixed threshold values, such as 1.00, for the interpretation of APDR properties, and suggest to consider APDR properties in relative terms, comparing slopes from different tissues or hearts. In conclusion, this study suggests to use a piece-wise linear fitting scheme for the estimation of the APDR curve, provided that all measured with an error lower than 5 ms.

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