Effect of the Restitution Properties of Cardiac Tissue on the Repeatability of Entrainment Mapping Response

Running title: Derejko et al.; Entrainment Mapping Response Repeatability

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Abstract:

**Background** - The difference between the postpacing interval (PPI) and the tachycardia cycle length (TCL) (PPI-TCL) is a useful tool in mapping macro-reentrant tachycardias. However, entrainment pacing causes some perturbation of the conduction velocity within the tachycardia circuit, which may affect the repeatability and consequently the accuracy of the measurement of PPI-TCL. The aim of this study was to assess PPI-TCL repeatability both *in vivo* and *in silico*.

**Methods and Results** - In the experimental part, entrainment pacing was performed twice at each of the 124 tested sites for 30 patients undergoing radiofrequency ablation of atrial and ventricular re-entrant arrhythmias. A similar protocol was used in a simplified computer model of the cardiac tachycardia circuit in a two-dimensional tissue strip using a Fenton-Karma model of cardiac tissue. *In vivo*, in the case of fast tachycardias (<350ms) PPI-TCL variability observed was doubled when compared to slow tachycardias (>350ms) (95% Limits of Agreement (LoA) ranged from –21.4ms to 21.6ms for TCL<350ms and from –10.8ms to 11.5ms for TCL>350ms). Simulations show that this increase of variability may be due to the oscillations of the conduction velocity inside the tachycardia circuits. The effect of the restitution properties of cardiac tissue on the outcome of entrainment pacing is discussed.

**Conclusions** - PPI-TCL is characterized by a high repeatability with the differences between the results for individual stimulations of up to 20ms. The variability of this parameter is significantly lower in the case of slow tachycardias.

**Key words:** electrophysiology mapping, arrhythmia, reentry, electrophysiology, entrainment mapping
Background

Entrainment pacing not only allows the mechanism of an arrhythmia to be established but also facilitates recognition of the components of the reentrant circuit\textsuperscript{1-8}. The difference between the postpacing interval (PPI) and tachycardia cycle length (TCL) (PPI-TCL) is an important entrainment response used to localize the mapping catheter in relation to the tachycardia circuit\textsuperscript{5,6,8}. Sites at which concealed entrainment together with a small difference between PPI and TCL (<30 ms) are observed are considered to be the isthmus of a tachycardia circuit\textsuperscript{5,6,8}. Due to the nonlinear restitution properties of myocardium, stimulation performed during ongoing tachycardia may induce changes in the effective refractory period (ERP), action potential duration (APD) and in the conduction velocity (CV)\textsuperscript{9-14}, which in turn may evoke temporary oscillations (alternans) in the TCL, resulting in variability of PPI-TCL. Based on experimental studies by Franz et al.\textsuperscript{9} and Cao et al.\textsuperscript{13}, we hypothesized that for shorter TCL it is more probable to have CL close to the ERP, so for shorter TCL we expect larger variations in the PPI.

As targets for radiofrequency ablation (RFA) are often identified on the basis of the PPI-TCL\textsuperscript{5,6}, the information as to whether this parameter is variable and to what extent may be useful from a clinical point of view. The aim of this study was to assess the entrainment mapping response repeatability evaluated during consecutive stimulations from the same site in reentrant circuits and to determine whether TCL influences the repeatability of PPI-TCL. To our knowledge, this has not yet been determined. To test this hypothesis, we studied two systems of macro-reentrant tachycardias: (1) clinical study of 30 patients undergoing radiofrequency ablation of atrial and ventricular re-entrant arrhythmias and (2) computer simulations in a two-dimensional model of a re-entrant circuit. The simulation was performed to obtain an insight into the processes leading to variations of PPI-TCL. The re-entrant circuit was formed around a
single anatomic obstacle, since the more detailed model of defined re-entry circuit channel was not necessary for variations of PPI-TCL to occur.

**Methods**

**Clinical study**

**Study population**

This prospective study comprised 30 patients (26 males, mean age 55±16 years) referred for ablation of either atrial or ventricular macro-reentrant tachyarrhythmias. The clinical characteristics of all the patients, including antiarrhythmic therapy, are presented in Table 1 in Supplemental Material. Each patient provided written informed consent to the study protocol, which had been approved by the Institutional Ethics Committee.

**Electrophysiology Study**

Diagnostic and ablation catheters were inserted via femoral vessels. Intracardiac bipolar electrograms together with 12-lead ECG were digitally recorded at 1000 Hz on the electrophysiology workstation (EPMed Systems, New Jersey, USA). Intracardiac signals were filtered at a bandpass of 30 to 500 Hz. Tachycardias were considered to be reentrant on the basis of activation mapping covering >75% of TCL and the demonstration of one of the criteria for transient entrainment. Criterion 1 and 4 for transient entrainment were most commonly observed1-6. Only regular tachycardias, with the CL interval variability ≤5ms, were included into the analysis. Bipolar stimulations were performed with a programmable stimulator (EPMed Systems, Model EP-3/EP-4) at a 2ms pulse width and at twice the diastolic threshold. Cases with the very high output (>12mA/2ms) were not included in the analysis to avoid the effect of large virtual electrode.

Pacing to evaluate entrainment response was performed with drive trains of 15-20 beats
at a cycle length 20ms to 40ms (28±7) ms shorter than TCL. At all sites, entrainment pacing was performed twice, separated by a 30-second intertrain pause. TCL was calculated as the mean of 10 consecutive cycles immediately before the onset of pacing. The analysis included only those episodes where no change in TCL and/or morphology occurred during both repeated stimulations from a given site.

PPI was only measured if more than 5 of the last arrhythmia cycles during pacing train were captured and accelerated to the PCL. The first PPI was considered to be the interval between the last stimulus artifact of the pacing train and the peak of the first rapid deflection of the first non-stimulated beat. All intervals were measured by the same observer. To avoid bias, for a given patient, initially all first PPI-TCL differences were assessed at each of the sites tested, followed by all second PPI-TCL evaluations at the same sites. For the current analysis, sites were considered to be “in circuit” if PPI-TCL≤30ms. All the episodes in which we could suspect, that recorded signal is not a local potential, were not taken into analysis.

**Simulation**

We performed an ensemble of simulations of macroreentrant tachycardia entrainment. We used a two-dimensional model of a myocyte sheet composed of 100x100 computational cells coupled diffusively at the interfaces. The Fenton-Karma 3V model was used to simulate cardiac action potential kinetics and will be referred to as the FK model. Tachycardia was formed by reentrant activation around a central obstacle, the geometry of which was kept constant throughout all simulations (Fig.1a). Recording and pacing electrodes were positioned as in Fig.1a.

We chose five parameter sets of Fenton-Karma cell action potential kinetics model to cover the range of action potential duration (APD), which occur in normal individuals as well as in patients with chronic arrhythmia. The restitution curves are presented in Fig.1b. The
parameters and implementation of the model are discussed in Supplemental Material.

Overall, repeated assessments of PPI-TCL were performed 447 times for 40 different parameter sets. In each simulation, pacing to evaluate entrainment response using drive trains of 15 to 20 beats at a cycle length 20ms shorter than TCL was performed. For each consecutive pair of PPI-TCL measurements their difference and absolute difference were calculated. To include errors of time interval estimation that occur in the clinic, a randomized uniformly distributed error from the range (-2.5ms, 2.5ms) was added to each TCL value.

**Statistical analysis**

The results of the clinical study and simulation are presented in Fig. 2 and 3. The agreement between consecutive assessments of the PPI-TCL at a given site in clinical trial was assessed by means of the kappa coefficient (κ), and the Bland-Altman test, which estimates the mean difference and 95% Limits of Agreement (LoA) (mean ±1.96SD) of repeated measurements. The correlation between the results obtained during repeated measurements was evaluated by Pearson’s correlation coefficient (r). A p value of <0.05 was considered significant. Statistical analyses were performed using Statistica 5.0 (StatSoft Inc., Tulsa, USA) and OriginPro 8 (OriginLab Ltd. Northampton, USA).

**Results**

**Clinical study results**

The results of the clinical study are presented in Fig. 2. Overall, repeated assessments of PPI-TCL were performed at 124 sites in 38 different reentrant circuits (25 sites in 7 VT circuits, 51 sites in 12 macroreentrant atrial tachycardia (MRAT) circuits and 46 sites in 19 AFL circuits). The TCL range in the group studied was 210-519ms. Based on the first assessment of PPI-TCL,
62 of 124 sites (51%) were classified to be “in circuit” using the gold standard PPI-TCL≤30ms; 11 in VT, 18 in MRAT and 33 in AFL circuits.

In the case of tachycardias with a cycle length below 350ms, the mean absolute difference between repeated measurements of PPI-TCL was 7.47ms with SD=6.01ms.

In the case of tachycardias with a cycle length above 350 ms, the mean absolute difference between repeated measurements of PPI-TCL was 4.44ms with SD=4.04ms.

When all evaluated pacing sites were included into the analysis, the agreement between repeated measurements was high, with the mean difference of 0.2±9.8ms for non-absolute values; r=0.98. When the results obtained were classified as categorical variables (first category: PPI-TCL≤30ms; second category: PPI-TCL>30ms), in only four out of 124 (3.4%) cases was there a discrepancy between repeated measurements regarding the position of the site in relation to the tachycardia circuit (in or out of circuit), and the kappa coefficient was 0.93. There was no clinically significant difference in the extent of repeatability of PPI-TCL irrespective of the type of analyzed arrhythmia (VT vs. MRAT vs. AFL). The mean value of the absolute difference of \(|(PPI-TCL)_n-(PPI-TCL)_{n+1}|\), for VT was lower than for other arrhythmias, since the mean value of TCL for the VT patients was higher. There was no difference either when sites “in circuit” and “out of circuit” were compared or whether antiarrhythmic drugs were used or not. Detailed study results are presented in Tables 1-2 and in Fig.2.

**Simulation results**

The results of the simulation study are presented in Fig.3. There was no difference when sites “in circuit” and “out of circuit” were compared. In the case of fast tachycardias (TCL<350ms), the observed PPI-TCL variability was higher when compared to slow tachycardias (TCL≥350ms).

In the case of tachycardias with a cycle length below 350ms, the observed variability of PPI-TCL
was nearly twice as high (mean value below 350ms: 4.59ms) as compared to tachycardias with a cycle length of ≥350ms (mean value above 350ms: 2.61ms). See also Table 2.

To investigate the mechanisms underlying the oscillations of the PPI, we calculated the action potential duration restitution and conduction time properties of the used ensemble of FK models. An analysis of the influence of the restitution properties of the tissue on PPI measurements is provided in the Discussion section. To study the source of variability of the PPI obtained in the simulation we investigated membrane potential maps and the time intervals between activations at the recording sites remote from the pacing site during the simulated entrainment. One recording electrode was placed within the circuit, one out of the circuit, in anterogradely-activated area (Fig.1a). The simulation showed that PPI oscillations resulted from the intrinsic oscillations of the time of propagation in the entrained reentrant circuit, which in turn were determined by the oscillations of the effective refractory period and of the conduction velocity, as visible in (Fig.4). Two representative examples of PPI measurement are shown in (Fig.5). However, if the simulation was run with a fixed coupling interval and a constant number of stimuli, the result would not contain any PPI oscillations, regardless of the oscillations of the time of propagation in the circuit. This must be kept in mind, despite the fact that in clinical practice it is difficult to achieve a stable value of coupling intervals of first stimulus.

To assess the amplitude of ERP oscillations, we analysed the APD and conduction velocity (CV) as a function of the pacing cycle in the simulated myocardial tissue. We chose the APD as a good estimate of ERP, since the ratio between APD and ERP is independent of the TCL. The observed oscillations in the duration of the action potentials lead to an interval dependent changes in the conduction velocity CV (Fig.6). Our results, as well as those of previous studies, show that the faster the rate of overdrive pacing, the greater the likelihood of
the stimulation wavefront encroaching on the trailing edge of refractoriness. This may result in oscillations in the conduction velocity causing variability in the return cycle length after the termination of pacing (compare with Stevenson et al., Aizawa et al., Callans et al.)

Discussion

This study demonstrates a high repeatability of the PPI-TCL assessed during repeated overdrive stimulations, with the variability of this parameter of approximately 20ms. The variability was approximately twice lower in the case of slow (TCL ≥ 350 ms) tachycardias.

Ninety-five percent of the first and second assessments in the clinical measurements differed from one another by LoA = 19.6ms. Arenal et al. assessed the variability of the first PPI during RV pacing to differentiate between ventricular and supraventricular tachycardias in pts with ICDs. In their study they analyzed 23 relatively slow VTs (mean TCL 366±50ms) and demonstrated that the difference between two PPI measurements was below 10ms and 20ms in 90% and 100% of the measurements respectively, which is comparable to our results. Vollman et al. found, that repeated PPI measurements with a constant PCL from one single site in the mid cavotricuspid isthmus during CTI-dependent right atrial flutter demonstrated high reproducibility at single sites for 17 patients (STD=3±2ms). They also report a long PPI upon entrainment of typical AFL from the CTI is common and due to delayed conduction with entrainment.

It may seem that a difference of 20ms can be considered negligible, however the discrepancy of such magnitude may give results for first PPI-TCL assessment below and for the second above the cut-off value of 30ms. In our study, such a situation occurred in four out of 124 clinical cases, which gave the kappa coefficient of 0.93.

The mean value of variability of PPI-TCL in the simulations is smaller than in the results of the clinical study. This may be due to the simplicity of the generic model used to obtain the set
of simulation results. Still, in the case of tachycardias with a cycle length below 350ms, the observed variability of PPI-TCL was nearly twice as high as compared to tachycardias with a cycle length of ≥350ms.

The effect of PPI oscillations was obtained in the model without defining a fixed reentry circuit channel. The re-entrant circuit was formed around a single anatomic obstacle, as presented in Fig.1. The model of fixed, anatomically defined re-entry channel was not necessary for variations of PPI-TCL to occur in simulation.

Limitations of the study

Apart from the oscillations of the TCL, the difference between repeated measurements may result from an error made by the observer. This source of an error is at least partially explained by the inherent difficulty in establishing which features of the electrograms represent actual local activation. Resetting response curves were not systematically assessed in all the circuits studied. Since that would have required multiple stimulations from the same site, we did not test whether and to what extent the changes of the CL of the overdrive pacing shorter than the TCL by 20ms to 40ms affected the variability of PPI-TCL.

During every attempt at entrainment, we paid attention to factors such as concealed fusion on surface and intracardiac electrograms. However we kept in mind that concealed fusion might also be observed when pacing from the bystander attached to the common tachycardia pathway. That is why the PPI-TCL difference was the main criterion on which we focused our study.

Since the PPI measurements were done in the clinical setting before ablation, and most of the patients treated suffered from chronic or persistent arrhythmia, ERP assessment was not conducted systematically in the studied group prior to the PPI measurements.
In the assessment of the entrainment response it is assumed that overdrive pacing does not change either the conduction velocity or the reentrant pathway.

The bipolar pacing or the instability of the contact of the catheter can influence the PPI values, however we can assume, that such influence will be similar for all the patients and all TCL values.

Using more complete ion-channel models than the Fentron-Karma model would certainly be more exact. However, it would require exact anatomical information and knowledge of the exact values of the ion-channels parameters for each patient individually. Since neither information is available, a generic model was created. Such a choice also made the simulations less computationally demanding.

**Clinical implications**

PPI-TCL is characterized by a high repeatability with the differences between the results for individual patients up to 20ms. The variability of this parameter is significantly lower in the case of slow tachycardias. Our study results emphasize the need for using long CL (e.g., TCL~10ms) during entrainment pacing in fast tachycardias (TCL<350ms) to increase the accuracy of method. In doubtful situations, repeated assessment of PPI-TCL is suggested.

**Conclusions**

The difference between PPI and TCL is a highly repeatable result. The dispersion of PPI-TCL for individual result is around 20ms. The variability of PPI-TCL is significantly lower in the case of slow tachycardias. Our simulations demonstrated and explained an increased variability of PPI-TCL observed in the case of fast tachycardias, when pacing cycles may be close to the ERP of the myocardium during the entrainment manoeuvres.
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Conflict of Interest Disclosures: None.

References:


Table 1: Repeatability of PPI-TCL (Mean Difference, Standard Deviation and 95% Limits of agreement) during consecutive stimulations from the same site.

<table>
<thead>
<tr>
<th></th>
<th>(PPI-TCL1)-(PPI-TCL2)</th>
<th>ABSOLUTE VALUE OF (PPI-TCL1)-(PPI-TCL2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (ms)</td>
<td>SD (ms)</td>
</tr>
<tr>
<td>All sites</td>
<td>-0.2</td>
<td>9.1</td>
</tr>
<tr>
<td>’in circuit’ sites*</td>
<td>-2.1</td>
<td>8.3</td>
</tr>
<tr>
<td>’out of circuit’ sites†</td>
<td>1.1</td>
<td>9.2</td>
</tr>
<tr>
<td>VT sites‡</td>
<td>0.2</td>
<td>6.1</td>
</tr>
<tr>
<td>AFL sites§</td>
<td>-1.6</td>
<td>9.5</td>
</tr>
<tr>
<td>MRAT sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off AA therapy#</td>
<td>2.2</td>
<td>10.1</td>
</tr>
<tr>
<td>On AA therapy**</td>
<td>-1.2</td>
<td>8.2</td>
</tr>
<tr>
<td>TCL&lt;350ms††</td>
<td>0.1</td>
<td>10.7</td>
</tr>
<tr>
<td>TCL≥350ms‡‡</td>
<td>0.4</td>
<td>5.6</td>
</tr>
</tbody>
</table>

LoA=limits of agreement; SD=standard deviation; TC=tachycardia cycle length;
*‘in circuit’ sites:analysis for sites where PPI-TCL≤30ms; †‘out of circuit’ sites:analysis for sites where PPI-TCL>30ms; ‡VT sites:analysis performed in ventricular tachycardia cases; §AFL sites:analysis performed using data obtained from typical atrial flutter circuits; ||MRAT sites:analysis of data obtained from macro-reentrant atrial tachycardia circuits; #Off AA therapy:analysis of data obtained from patients not receiving antiarrhythmic therapy; **On AA therapy:analysis of data obtained from patients receiving antiarrhythmic therapy; ††TCL<350ms:analysis of data obtained from tachycardias with a cycle length below 350ms; ‡‡TCL≥350ms:analysis of data obtained from tachycardias with a cycle length equal to or above 350ms.
**Table 2:** Comparison of the results of the clinical and simulation study

| TCL range   | Mean value of absolute difference between two measurements of PPI-TCL \(|(PPI-TCL)_1-(PPI-TCL)_2|) | SD of absolute difference between two measurements of PPI-TCL \(|(PPI-TCL)_1-(PPI-TCL)_2|) |
|-------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
|             | CLINICAL STUDY | SIMULATION | CLINICAL STUDY | SIMULATION |
| 200ms to 250ms | 6.83ms | 5.33ms | 5.67ms | 3.94ms |
| 250ms to 300ms | 8.16ms | 5.62ms | 6.43ms | 4.49ms |
| 300ms to 350ms | 7.74ms | 3.43ms | 6.36ms | 2.89ms |
| 350ms to 400ms | 4.34ms | 3.18ms | 4.88ms | 2.36ms |
| 400ms to 450ms | 3.99ms | 2.53ms | 2.77ms | 1.41ms |
| 450ms to 500ms | 5.33ms | 2.47ms | 3.67ms | 1.48ms |
| 500ms to 550ms *4.67ms* | 2.47ms | 4.16ms* | 1.47ms |

*since only three measurements were made for this group the value may be biased.

**Figure Legends:**

**Figure 1:** Simulation preparation (A) A schematic presenting the geometry of the simulated myocardial sheet. Two different locations for the placement of pacing electrodes were used – one out of the circuit (1) and one within the circuit (2), yielding no difference in the result of the simulations. Two recording electrodes were added to provide insight into the time intervals between activation of different sites of the myocardial sheet. (B) Restitution curves for five sets of parameters for the FK cell model used in the simulation, drawn as Action Potential Duration
(APD) vs. Diastolic Interval (DI). Restitution curves were modified by varying the \( \tau_R \) parameter of the FK model\(^0\). The parameter sets were chosen so as to cover the range of restitution curves that can be obtained during measurements in patients with chronic and paroxysmal arrhythmias\(^17-19\).

**Figure 2:** Clinical study (A) Results of the clinical study. Data are presented as a box chart with bins of 50 ms cycle length. The following information is provided for each box: double standard deviation above and below the mean of the data (whiskers), the lower and upper quartile (box ranges), the median (middle box line) and the mean (black diamond). Because only three measurements were made for tachycardia cycle lengths longer than 500 ms, the last box is colored grey to indicate very low statistics. In the case of tachycardias with cycle length below 350 ms the observed variability of PPI-TCL was nearly twice as high (total mean value below 350 ms: 7.47 ms) as compared to tachycardias with cycle length \( \geq 350 \) ms (total mean value above 350 ms: 4.44 ms). (B, inset) Scatterplot of the differences between repeated assessments of PPI-TCL plotted against the average of these assessments for the Bland-Altman statistical test. The solid line indicates the mean difference between repeated assessments of PPI-TCL. The dashed lines indicate the 95% Limits of Agreement of the results.

**Figure 3:** Simulation results. Results of the *in silico* study. Data are presented as a box chart with bins of 50 ms length. In the case of tachycardias with a cycle length below 350 ms, the observed variability of PPI-TCL was nearly twice as high (total mean value of \(|[PPI-TCL]_1 - [PPI-TCL]_2|\) below 350 ms: 4.59 ms) as compared to tachycardias with a cycle length \( \geq 350 \) ms (total mean value above 350 ms: 2.61 ms).
**Figure 4:** Simulation example. Representative membrane potential map during entrainment simulation. The pacing site was in the left upper corner of myocardial sheet; the reentry cycle was induced counterclockwise around the central obstacle. The rows are labeled by the simulation time at the leftmost column while the columns are marked with the time shift (30ms) between them. The simulated TCL was 220ms and the PCL 200ms. At the beginning, the pacing electrode initiates tissue activation, which travels through the myocardial sheet and entrains the existing tachycardia reentry wave. Note the oscillations (alternans) in wavelength between two consecutive entrained evolutions (compare the first row (30ms) and the second row (240ms)).

**Figure 5:** Measurements of transient oscillations of cycle length recorded during entrainment in remote electrodes. (A) A tachycardia with a cycle length of around 322ms was initiated in the myocardial sheet presented in Fig.1. Activation times were measured at the pacing electrode (position 1 in Fig.1.) and at the two recording electrodes placed as in Fig.1. Small TCL oscillations of amplitude below 2ms were present before entrainment. Three entrainment pacing drive trains of 15 beats are visible on the graph. No oscillations of cycle length were recorded on the pacing electrode during entrainment, as the pacing cycle is fixed. After three to five paced beats, the reentrant wave becomes fully entrained. Oscillations of activation times measured on recording electrodes placed in circuit and out of circuit are visible. In each entrainment pulse train, the oscillations have a different morphology, and in none of them a steady state is reached before entrainment has ended. This leads to three different values of PPI for the same tachycardia circuit. (B) A tachycardia with a CL of around 240ms was initiated in the myocardial sheet presented in Fig.1. Activation times were recorded at the pacing electrode and at two recording.
electrodes placed as in Fig.1. One entrainment pacing train of 45 pulses is visible in the graphs. After six initial paced beats the reentrant wave becomes fully entrained. A steady state of oscillations is observed at both recording electrodes, however the oscillation amplitude at the electrodes is different and a different steady state is reached.

**Figure 6:** Conduction time oscillations during external pacing. The conduction velocity CV restitution curve was obtained from a simulation conducted in a tissue strip of 9.4 cm x 0.32 cm. This corresponds to a tachycardia reentry circuit of 3 cm in diameter. An external pacing with the cycle length CL was delivered to one end of the tissue strip. The time of propagation between both ends of the strip was measured. The differences between time of propagation for two consecutive activations for different CL are presented for three of the five FK model parameters sets. Only the stimulations, for which no conduction block occurred, were taken into account. The alternans of the conduction time appears for the shorter pacing cycle lengths. **Inset:** The time of propagation through the tissue strip was divided by the tissue strip length to obtain an estimation of the conduction velocity. The alternans of the conduction velocity appear for the shorter pacing cycle lengths.
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Supplemental Material

The difference between the postpacing interval (PPI) and the tachycardia cycle length (TCL) (PPI-TCL) is a useful tool in mapping macro-reentrant tachycardias. However, entrainment pacing causes some perturbation of the conduction velocity within the tachycardia circuit, which may affect the repeatability and consequently the accuracy of the measurement of (PPI-TCL). The aim of this study was to assess PPI-TCL repeatability both in vivo and in silico.

This is the supplemental material of the manuscript entitled Effect of the restitution properties of cardiac tissue on the repeatability of entrainment mapping response. The Supplemental material consist of non-critical, secondary conditions results and limitations of the study.

1. **COMMENT ON THE TITLE OF THE MANUSCRIPT**

The term repeatability (or test-retest reliability or test-retest variability) was introduced by Bland and Altman in Bland J.M., Altman D.G.: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: pp. 307-310., and this is why we are using this term. According to Bland and Altman, repeatability is the variation in measurements taken by a single instrument on the same item and under the same conditions. Term variability would be probably more intuitive to understand. However we have decided to keep the term repeatability, following Bland and Altman\(^{20,\text{i-ii}}\) (for the explanation of the Bland-Altman method see reference (20) in main manuscript and references (i-ii) of Supplemental Material).

2. **EXPANDED METHODS DESCRIPTION**

**EP STUDY AND CATHETER ABLATION**

- During every attempt of entrainment, we were paying attention to factors, such as concealed fusion on surface and intracardiac electrograms. However we kept in mind, that concealed fusion may also be observed, when pacing from the bystander attached to the common tachycardia pathway. That is why the PPI-TCL difference was the main criterion, on which we focused our study.
Bipolar stimulations were performed with a programmable stimulator (EPMed Systems, Model EP-3 or EP-4) at a 2-ms pulse width and at twice the diastolic threshold. Cases with the very high output (>12 mA/2 ms) were excluded from the study to avoid the effect of large virtual electrode. For high threshold, electrograms at the pacing site are frequently distorted, often due to the filtering and saturation of the preamplifiers from stimulation artifact, rendering it impossible to determine the PPI. Such situation did not occur in our study group.

Pacing to evaluate entrainment response was performed with drive trains of 15-20 beats at a cycle length 20 to 40 ms (28 ± 7) ms shorter than TCL. The influence of TCL-PCL on the repeatability of entrainment mapping response was checked and is presented in the extended results section. Moreover, the ratio between PCL and TCL was calculated for all measurement sites.

All intervals were measured on the screen using electronic calipers at a sweep speed of 100-200 mm/sec, at a gain setting of 0.1 to 0.2 mV/cm.

The clinical characteristics of all the patients, including antiarrhythmic therapy and range of TCL measured during the study are presented in Table 1 of Supplemental Material.

The coupling interval of the first pacing stimulus was not fixed both in the clinical study and simulation.

SIMULATION

To have the best agreement possible between clinical study and simulations, in the latter we reproduced the procedure used in the clinic. Since it is possible using the prepared simulation to run the simulation in real-time, again to match the clinical study conditions, all the pacing runs in the simulations were initiated manually for the given TCL.

a. Description of the Fenton–Karma 3V model for atrial tissue

The Fenton-Karma 3V cardiac action potential kinetics model, first reported in ref. 16 of the manuscript is a three variable ion-channel model of cardiac cell electrical activity. It was designed to reproduce the APD and CV restitution curves rather than the shape of action potential, for the restitution properties indicate the dynamics of the depolarization wavefront and conduction - fundamental quantities for the modeling of wave dynamics. The equations and different parameter sets, along with the APD and CV restitution curves corresponding to these parameters can be found in reference 16 of the manuscript and are presented in Supplemental Table 2. The parameters for the Fenton–Karma 3V model of atrial tissue are presented in Supplemental Table 3.
b. Description of the myocyte sheet simulation

We used a 2-dimensional model of myocyte sheet composed of 100x100 computational cells coupled diffusively at the interfaces (monodomain conduction model\textsuperscript{16}).

In this setting we:

- Changed the parameters responsible for the diffusive conduction to obtain different tachycardia cycle lengths (TCL) from 200 to 550 ms. This is equivalent to varying the diameter of the obstacle tissue from 4 to 10 cm with the conduction velocity fixed at 50 cm/s. The change of diffusion parameters may be also interpreted as the result of changing the tissue conduction velocity from 24 cm/s to 65 cm/s for a fixed size of a central obstacle tissue of length of 5 cm. In total, eight diffusion coefficients were randomly chosen together with a random choice of stimulation electrode (inside or outside the circuit).

- Changed the restitution properties of the tissue to obtain a diversity that can be met in clinical patients. Specifically that was done by setting the parameters of the FK model to obtain a fit to the restitution curve of the Beeler Reuter model and altering the time constant $\tau_R$ of the slow outward current.

- For each APD restitution curve, one of eight diffusion coefficients was randomly chosen together with a random choice of the stimulation electrode (inside or outside the circuit) to obtain different conduction velocities that may appear in the circuit of tachycardia.

- We chose five parameter sets of Fenton Karma cell action potential kinetics model to cover the range of action potential duration (APD), which occur in normal individuals as well as in patients with chronic arrhythmia. The restitution curves are presented in Fig. 1b in manuscript.

c. Model implementation

The model was implemented in C++. The Euler explicit integration scheme was used throughout this paper with a time step $\Delta t = 0.001$ s. The model runs as a standalone application and was provided with a graphical interface allowing to define the anatomical details of the simulation and its parameters.

3. EXPANDED RESULTS AND DISCUSSION

During every attempt of entrainment, we were paying attention to factors, such as concealed fusion on surface and intracardiac electrograms. However we kept in mind, that concealed fusion may also be observed, when pacing from the bystander attached to the common tachycardia pathway. That is why PPI-TCL difference was the main criterion, on which we focused our study\textsuperscript{iii}. 
THE INFLUENCE OF TCL-PCL ON THE REPEATABILITY OF ENTRAINMENT MAPPING RESPONSE

The faster the rate of overdrive pacing, the greater the likelihood of the stimulation wavefront to encroach on the trailing edge of refractoriness. For patients with shorter TCL (closer to ERP), stimulations with shorter CL can give larger PPI-TCL variability. This was confirmed in simulations (Fig. 6 of manuscript).

Note that entrainment pacing with the CL shortened by the same value during tachycardias with different cycle lengths means stimulating with a different percentage of TCL, which can affect the entrainment response. We checked the influence of TCL-PCL (shortness of CL) on the PPI-TCL for the whole range of TCL in our study group. The result is provided in Supplemental Material, Fig 1. There was no significant influence of shortness of CL on reproducibility of PPI-TCL. In our study group we observed, that sole value of TCL is more important for the variability of PPI-TCL.

The choice of PCL from 20 to 40 ms rule used in the electrophysiology lab reveals also that for shorter cycle lengths the ratio PCL/TCL is relatively smaller (Supplemental Material, Fig. 2). Further study is needed to evaluate if the choice of PCL depending on the magnitude of TCL will provide results with a smaller variability, thus enabling to use smaller criteria for in circuit and out of circuit discrepancy than the 30 ms used commonly in clinical practice.

THE INFLUENCE OF TRANSIENT STATES DURING ENTRAINMENT PACING ON THE REPEATABILITY OF
ENTRAINMENT MAPPING RESPONSE

Simulation showed that oscillations of the PPI resulted from the intrinsic oscillations of the time of propagation in the entrained reentrant circuit, which in turn were determined by the oscillations of the effective refractory period and of the conduction velocity, as visible in Fig. 4 of the manuscript.

To show the dependence of the action potential duration on the pacing cycle length, additional simulation were performed. One cell of the model was stimulated externally at a fixed cycle length (CL). All action potential duration (APD) values obtained for the corresponding cycle length (CL) were recorded during a steady state. The result, the APD vs CL restitution curves for four of five sets of FK cell model parameters used in the simulation are presented in Supplemental Material Fig. 3. For the longer stimulation cycle lengths, a flat, non-alternating APD response can be seen beginning at a CL, which depends on $\tau_R$. For the shorter stimulation cycle lengths, the APDs begin to alternate - a bifurcation occurs.

To check the influence of transient states during entrainment pacing on the repeatability of entrainment mapping response, a pair of APD and CL values was obtained by pacing a single model cell at a fixed cycle length. For each cycle length the first two APD values are recorded and compared with APD values from a steady state. The transient state lasted up to 10 paced beats. We can see that in a transient state the maximum cycle length for alternans to appear is longer than in the steady state and
the alternans amplitude may be larger. This indicates that the PPI value may depend on the length of the pacing train.

Oscillations in the refractoriness of the ventricular myocardium have been demonstrated after a sudden change in heart rate in animal and human studies\textsuperscript{9,11}. The magnitude of these oscillations is, in most cases, largest immediately after a change in the stimulation rate and they are most likely to occur when the stimulation cycles are close to the effective refractory period of the myocardium\textsuperscript{9,13}.

\textbf{INFLUENCE OF THE CHOICE OF THE MODEL OF TISSUE ELECTROPHYSIOLOGY ON THE RESULTS}

Using more complete ion-channel models than the FK model would certainly be more exact. However, attaining an exact tissue model would require exact anatomical information about the patient and the knowledge of the exact values of the parameters for the ion-channels for each patient individually. Since neither the exact anatomy nor the ion channel parameters are available, a generic model was created. This is the rationale behind the choice of the simple geometry with a single obstacle and the 3V Fenton-Karma model. Such a choice also made the simulations less computationally demanding.

\textbf{VARIABILITY OF PPI-TCL VS. LOCATION DISCREPANCY}

It may seem that a difference of 20 ms can be considered negligible, however a discrepancy of such magnitude may give results for first PPI-TCL assessment below and for the second one above the cut-off value of 30 ms. In our study, such a situation occurred in four out of 124 clinical cases, which gave the kappa coefficient of 0.93. Moreover, assuming safely that the conduction velocity in the cardiac tissue may vary from 25 to 100 cm/sec\textsuperscript{iv-vi}, the difference between results equaling 20 ms may correspond to a location discrepancy ranging from 0.5 to 2 cm. Since the diameter of a typical radiofrequency lesion is about 5 mm, the discrepancy observed can matter in some cases.

\textbf{TREATMENT WITH ANTI-ARRHYTHMIC DRUGS}

Treatment with anti-arrhythmic drugs may affect ERP and have potential effect on the PPI-TCL. However, we did not observe significant effect of anti-arrhythmic drugs on PPI-TCL variability in our group (see Table 1 in the manuscript and references vii-viii in Supplemental Material).

\textbf{SEGMENTAL CONDUCTION DELAYS DURING ENTRAINMENT WITH LONG PPI-TCL}

The fact reported by Vollman et al.\textsuperscript{25} that with changes in pacing site, the greatest conduction delay always occurs in the segment activated first by the paced orthodromic wave front, seems to be confirmed by our simulation study and is visible in the video from simulations provided in Supplemental Material.
4. **ADDITIONAL TABLES**

**Supplemental Table 1. Clinical characteristics of patients**

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AA therapy = antiarrhythmic therapy; AF = atrial fibrillation; AFL = atrial flutter; ARVC = arrhythmogenic right ventricular cardiomyopathy; ASD = atrial septal defect; AVR = aortic valve replacement; BB = betablocker; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DCM = dilated cardiomyopathy; F = female; HA = arterial hypertension; HCM = hypertrophic cardiomyopathy; LVH = left ventricle hypertrophy; M = male; MI = myocardial infarction; MRAT = macro-reentrant atrial tachycardia; MS = mitral stenosis; MV mitral valve; PBMV = percutaneous balloon mitral valvuloplasty; VT = ventricular tachycardia
Supplemental Table 2. Equations for the Fenton–Karma 3V model of atrial tissue.

The time is in ms; $C_m = 51 \text{mF/cm}^2; \tau_d = C_m / g_{fi}$ with $g_{fi}$ in mmho/cm$^2$, and $k = 10$. The membrane potential $u$ was kept dimensionless as in ref. 16. $V$ – membrane potential in mV, $J_{so}, J_{si}$ are ionic currents that have units of inverse time. $\Theta(x)$ is the standard Heaviside step function defined by $\Theta(x)=1$ for $x>0$ and $\Theta(x)=0$ for $x<0$. $D$ represents the diffusion coefficients varied in the simulation (8 randomly chosen diffusion coefficients) Parameters are described in Supplemental Table 3.

$$
\partial_t u = \nabla \cdot (D \nabla u) - J_{fi}(u; v) - J_{so}(u) - J_{si}(u; w)
$$

$$
\partial_t v = \Theta \frac{(u_c - u)(1 - v)}{\tau_v^- (u)} - \Theta \frac{(u - u_c)v}{\tau_v^+ (u)}
$$

$$
\partial_t w = \Theta \frac{(u_c - u)(1 - w)}{\tau_w^-} - \Theta \frac{(u - u_c)w}{\tau_w^+}
$$

$$
J_{fi}(u; v) = -\frac{v}{\tau_d} \Theta(u_c - u)(1 - u)(u - u_c)
$$

$$
J_{so}(u) = \frac{u}{\tau_0} \Theta(u_c - u) + \frac{1}{\tau_v} \Theta(u - u_c)
$$

$$
J_{si}(u; w) = -\frac{w}{2\tau_{si}} (1 + \tanh[k(u - u_c^s)])
$$

$$
V = \frac{(V - V_c)}{(V_{fi} - V_c)}
$$

Supplemental Table 3. Parameters for the Fenton–Karma 3V model of atrial tissue.

The time is in ms; $C_m = 51 \text{mF/cm}^2; \tau_d = C_m / g_{fi}$ with $g_{fi}$ in mmho/cm$^2$, and $k = 10$. The membrane potential $v$ was kept dimensionless as in Fenton et al.\textsuperscript{16}

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5. **ADDITIONAL FIGURES**

**Supplemental Figure 1. Pacing Cycle Length vs Tachycardia Cycle Length Ratio obtained in the Clinical Study**

We checked the influence of TCL-PCL (shortness of CL) on the PPI-TCL for the whole range of TCL in our study group. There was no significant influence of shortness of CL on reproducibility of PPI-TCL, however the mean value of \(|[\text{PPI-TCL}]_1 - [\text{PPI-TCL}]_2|\) was higher for the range of TCL-PCL between 30 and 40 ms compared to the range 20-30ms - (8 ± 6) ms vs. (6 ± 6) ms. In our study group we observed, that value of TCL is more important for the variability of PPI-TCL.
Supplemental Figure 2: Pacing Cycle Length to Tachycardia Cycle Length Ratio in obtained in the Clinical Study.

Supplemental Figure 2: Pacing Cycle Length to Tachycardia Cycle Length Ratio in obtained in the Clinical Study. Pacing to evaluate the entrainment response in all clinical measurements was performed with pacing cycle length (PCL) of 20 to 40 ms shorter than TCL. The ratio between PCL and TCL was calculated for all measurement sites. The choice of PCL from the 20 to 40ms rule used in practice reveals that for shorter cycle lengths PCL/TCL ratio is relatively smaller. Different symbols were used for points in different bins of 50 ms cycle length. Comparing to the clinical results presented in Fig. 2 in the main article, it is visible that increased variability of PPI-TCL between 300 ms and 350 ms is not correlated to the decrease of the PCL to TCL ratio.
Fig. 3: For shorter cycle length, an oscillation of APD occur. (A) Action potential duration (APD) versus cycle length (CL). One cell of the model was stimulated externally at a fixed cycle length (CL) until a steady state was reached. All action potential duration (APD) values obtained for the corresponding cycle length (CL) were recorded. For clarity, APD vs CL restitution curves for only four of five sets of FK cell model parameters used in the simulation are presented. For the longer stimulation cycle lengths, a flat, non-alternating APD response can be seen beginning at a CL, which depends on $\tau_R$. For the shorter stimulation cycle lengths, the APDs begins to alternate — a bifurcation occurs. The pacing cycle length required for alternans to occur is shorter for a shorter basic APD (i.e., the APD obtained for long, natural cycle length). (B) APD vs CL using the dynamical protocol (see ref. ix) – comparison of the transient and the steady state. A pair of APD and CL values is obtained by pacing at a fixed cycle length. For each cycle length the first two APD values are recorded and compared with APD values from a steady state. The transient state lasted up to 10 paced beats. We can see that in a transient state the maximum cycle length for alternans to appear is longer than in the steady state and the alternans amplitude may be larger. This indicates that the PPI value may depend on the length of the pacing train.
Representative membrane potential map during simulated entrainment. The pacing site was in the left upper corner of myocardial sheet, reentry cycle was induced counterclockwise around the central obstacle. The simulated TCL was 220 ms and the PCL 200 ms. At the beginning, the pacing electrode initiates tissue activation, which travels through the myocardial sheet and entrains the existing tachycardia reentry wave. Note the oscillations (alternans) in wavelength between two consecutive entrained evolutions.

**VIDEO FILE**

**Expanded References**


