Number Needed to Entrain
A New Criterion for Entrainment Mapping in Patients With Intra-Atrial Reentrant Tachycardia

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Background—Measuring postpacing intervals (PPIs) is the standard maneuver for localizing reentrant tachycardia circuits. However, changes or termination of the tachycardia during entrainment pacing, or difficulties in defining the correct local activity, limit the use of PPIs.

Methods and Results—We hypothesized that the number of pacing stimuli needed to entrain (NNE) was useful for mapping intra-atrial reentrant tachycardias. First, 10 patients with typical atrial flutter were studied to characterize the NNE. Next, 317 entrainment attempts in 30 patients with 76 intra-atrial reentrant tachycardias were analyzed to determine the efficacy of the NNE. The NNE was small at sites within the reentrant circuit (median 2) and large at remote sites during typical atrial flutter. The NNE depended on the pacing cycle length and coupling interval of the initial paced beat, where the NNE became smaller at shorter pacing cycle lengths and coupling intervals. The NNE highly correlated with the difference between the PPI and tachycardia cycle length ($r = 0.906; P<0.001)$. When the pacing cycle length and coupling interval were 16 to 30 ms below the tachycardia cycle length, a NNE ≤2 and >3 predicted a PPI–tachycardia cycle length ≤20 and >20 ms, respectively, with 100% accuracy. Thirty-six (11%) entrainment attempts changed or terminated intra-atrial reentrant tachycardia. Importantly, the NNE remained valid in those cases. Furthermore, the NNE provided additional information in cases with some difficulties with PPI measurements.

Conclusions—The NNE is a simple and reliable criterion, which facilitates mapping intra-atrial reentrant tachycardia.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT001747.

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Key Words: atrial flutter ■ catheter ablation ■ diagnostic techniques and procedures ■ electrophysiology

Intra-atrial reentrant tachycardia (IART) occurs with reentrant activations revolving around functional or anatomic barriers that form spontaneously or in association with prior cardiac surgery or radiofrequency catheter ablation (RFCA) for treating atrial fibrillation. IART has recently become more common due to a wide use of catheter ablation. Because rhythm and rate control of IART with antiarrhythmic drugs can be difficult to achieve, RFCA is the treatment of choice for IART. For successful RFCA of IART, it is key to pinpoint the critical isthmus of underlying reentrant circuits. Understanding the whole picture of reentrant circuits by constructing activation maps of IART using 3 dimensional (3D) electroanatomical mapping systems helps identify the critical isthmus, but it is time-consuming and not always possible when the targeted IART is not stable enough to create the entire activation map or multicomponent electrograms challenge correct annotation of the electrogram presenting the local electric activity.

Clinical Perspective on p 496

Entrainment mapping is an established electrophysiological technique and is used to delineate the localization of reentrant circuits. The postpacing interval (PPI) measured after entrainment overdrive pacing describes the distance from pacing catheter’s location to the reentrant circuit, and a difference between the PPI and the tachycardia cycle length (TCL) ≤20 ms indicates that the pacing site is part of the reentrant circuit. A major drawback of entrainment mapping is that overdrive stimuli for entrainment may terminate the tachycardia or cause degeneration into a different arrhythmia, which makes it impossible to evaluate the PPI. Moreover, PPI measurements can mislead us if conduction delays in slow conduction areas paradoxically...
### Table 1. Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Part I (n=10)</th>
<th>Part II (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±18</td>
<td>63±9</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>9/1</td>
<td>19/11</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>2 (20)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>4 (40)</td>
<td>13 (43)</td>
</tr>
<tr>
<td>History of atrial fibrillation, n (%)</td>
<td>1 (10)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Prior card surgery, n (%)</td>
<td>1 (10)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Prior RFCA, n (%)</td>
<td>0 (0)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Antiarrhythmic drugs, n (%)</td>
<td>5 (50)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>1 (10)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>44±10</td>
<td>45±6</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>65±9</td>
<td>61±11</td>
</tr>
<tr>
<td>Duration of tachycardia, mo</td>
<td>7±9</td>
<td>4±5</td>
</tr>
<tr>
<td>Tachycardia cycle length, ms</td>
<td>254±31</td>
<td>267±62</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; and RFCA, radiofrequency catheter ablation.

In this study, we devised a new technique for localizing the reentrant circuits of IART during entrainment pacing. The number of pacing stimuli needed to entrain (NNE) closely correlated with the PPI measurements, which would enhance the efficacy and accuracy of entrainment mapping.

### Methods

#### Study Population

This study consisted of 2 parts. In the first part (part I), 10 patients with typical atrial flutter were enrolled. We took advantage of this population to characterize the electrophysiological properties of the NNE because typical atrial flutter’s reentrant circuit is anatomically defined. In the second part (part II), we studied 30 consecutive patients referred to Chiba-Hokusoh Hospital between April 2011 and July 2013 for RFCA of IART in which the location of the reentrant circuit was undetermined before the study. IART was confirmed by electroanatomical mapping and entrainment maneuvers in which activation mapping of the IART circuit accounted for ≥80% of the TCL, or a PPI ≤20 ms longer than the TCL was recorded from ≥2 atrial sites separated by ≥2 cm. We also included atria tachycardias of an undetermined origin as IARTs, if the PPI was reproducible at the same pacing cycle length (PCL) and the PPI became progressively longer in response to shorter PCLs. IART exhibiting spontaneous oscillations of >15 ms within 3 cycles before the onset of entrainment pacing were excluded from the study. The patient characteristics are summarized in Table 1. This study was approved by our institution’s ethics committee.

#### Electrophysiological Study and RFCA

After providing written informed consent, all patients underwent electrophysiological studies under deep sedation. To record intracardiac electrograms from the right and left atria including both their lateral ends, we positioned a 5F 10-pole electrode catheter (Japan Lifeline Co Ltd) within the coronary sinus (CS) and 7F 20-pole Halo catheter (Biosense Webster Inc) around the tricuspid annulus (Figure 1A), or a 6F 14-pole electrode catheter whose distal and proximal electrodes covered the CS and right atrium (RA), respectively (CS–RA catheter; Japan Lifeline). RFCA was performed at critical sites of the IART circuit using an open-irrigated catheter (NaviStar ThermoCool; Biosense Webster Inc or Saire BLU, St. Jude Medical) with the power and temperature limited to 20 to 35 W and 43°C.

#### Measurement of NNE

Entrainment is continuous resetting of reentrant tachycardias by overdrive pacing at a shorter cycle length than the TCL. If the pacing site is remote from the tachycardia circuit, entrainment requires that a paced wave front travels to and enters the circuit before resetting the tachycardia. In contrast, the tachycardia should be entrained immediately after initiation of pacing if the pacing site is inside the tachycardia circuit. Therefore, one would expect that the distance between the pacing site and the tachycardia circuit would correlate with how soon entrainment is achieved (ie, NNE). We hypothesized that when overdrive pacing is performed during IART at 1 atrial site, the contralateral end of the atrium could not be captured without entrainment of the IART, which would allow us to estimate the onset of entrainment using a limited number of intracardiac recordings. Intracardiac electrograms in the lateral RA (LRA) and lateral CS (LCS) were obtained as activations of the lateral end of the atrium (ie, LCS in this case) is captured first. Therefore, the pacing wave front resets the tachycardia and captures the contralateral end of the atrium (ie, LRA), Measurement of the NNE in this example is 4, see the text for details.

![Figure 1. Principle of the number of pacing stimuli needed to entrain (NNE).](image-url)
unlikely that the stimulus could capture an immediate electrogram arising within the marker period, especially at contralateral atrial sites (NNE is measured as 4 in this example). We paid attention to the occurrence of a capture loss during entrainment because the capture loss followed by re-entraining the tachycardia could cause false increases in the NNE.

In part I, typical atrial flutter was entrained from the cavotricuspid isthmus (CTI; ie, within the circuit) and distal CS (ie, remote site) at PCLs of 10, 20, 30, 40, and 50 ms below the TCL with coupling intervals (CIs) of the initial paced beat the same as the PCL, or fixed PCLs of 20 ms below the TCL with a CI the same as the PCL, 10, 20, 30, and 40 ms below the PCL. To study how the PCL and CI affected the NNE, we also calculated the entrainment index (EI) that was the total amount of prematurity during entrainment pacing at the pacing site, as described previously. Briefly, the EI was measured as the prematurity of the pacing stimulus at the time of the first atrial reset relative to the timing of the electrogram at the pacing site expected from an uninterrupted tachycardia. Because the EI depends on the PCL, the EI was corrected by subtracting the degree of advancement of the first reset beat from the measured EI.

In part II, overdrive stimuli during IART were delivered at PCLs of 5 to 50 (19±8) ms below the TCL with CIs identical to the PCL until the tachycardia was entrained with or without manifest fusion of the P- or F-wave morphology on the surface ECGs. In 3 patients, we created color-coded 3D NNE maps in combination with 3D PPI maps for the same IART using a NavX system (Endocardial Solutions/ST. Jude Medical).

Entrainment stimuli were applied at 2 ms and 10 mA. The PPI was also measured as the interval from the last stimulus to the initial sharp deflection of the first postspacing electrogram at the pacing site. By the definition of entrainment, the tachycardias must resume on cessation of overdrive pacing. However, even when the tachycardias terminated during pacing, we still used the term NNE for the sake of simplicity in this study.

**Statistical Analysis**

Continuous variables are expressed as the median (interquartile range [IQR]) or mean±SD. A Friedman test was used for analysis of the dependence of the NNE, PPI, and corrected EI on the PCL and CI. A Wilcoxon signed-rank test was conducted to compare the NNEs at the CTI and distal CS at various PCLs and CIs. To determine the diagnostic accuracy of the NNE according to the difference between the TCL and PCL (TCL−PCL), the area under the receiver operating characteristic curve was calculated. The relationship between the NNE and PPI was examined using a Spearman rank correlation test. The dependence of the difference between the PPI and TCL (PPI−TCL) on the NNE was studied by a linear regression analysis. A P≤0.05 was considered statistically significant.

**Part I: Characteristics of the NNE**

Typical atrial flutter was entrained with various PCLs and CIs from the CTI within the reentrant circuit (PPI−TCL: 8 [IQR: 0–10] ms) and distal CS remote from the reentrant circuit (PPI−TCL: 105 [IQR: 85–118] ms). The NNE measured at the CTI was 2 [IQR: 2–2], whereas that measured in the distal CS was larger (5 [IQR: 4–7]). The NNE was dependent on the PCL, where the NNE became smaller at shorter PCLs both at the CTI and distal CS (P<0.001). Similarly, the NNE also depended on the CI, and shorter CIs decreased the NNE both at the CTI and distal CS (P<0.001; Figure 2). These results were expected because shorter PCLs and CIs should make it possible for the paced wave front to reach the reentrant circuit earlier. The NNEs at the CTI were smaller than those in the distal CS at any PCL and CI (Figure 2). We calculated the corrected EIs to determine how the PCL and CI affected the NNE values. Shorter PCLs in the distal CS significantly increased the corrected EIs (P=0.002), suggesting that PCL-dependent conduction delays in the path between the pacing site and reentrant circuit increased the requisite prematurity at the pacing site when pacing from remote sites. Otherwise, the total amount of prematurity NNE seemed independent of the PCL and CI as long as the location of the pacing site and reentrant circuit was fixed (the corrected EIs did not alter with different PCLs and CIs at the CTI, and were also independent of CIs at the distal CS).

**Part II: Validation and Clinical Utility of the NNE in Patients With IART**

Five patients (17%) presented with a single IART, whereas 25 (83%) had multiple types of IART. In total, 76 IARTs were analyzed. The IART mechanisms were peri-mitral (n=18), through the LA roof (n=3), around the left atrial appendage (LAA; n=4), related to conduction gaps of prior pulmonary vein ablation lines (n=3), a ridge between the LAA and left pulmonary veins (n=3), CTI-dependent (n=13), within the RA free wall (n=17), within the interatrial septum (n=3), and not exactly determined (within RA [n=2], LA [n=10]).

Entrainment pacing was performed at 317 atrial sites (105 RA and 212 LA). Both the NNE and PPI were measured in 281 overdrive pacing trials successfully entraining IART without any changes in the IART. Typical examples of NNE measurements are shown in Figure 3. In this case, entrainment pacing was performed at a PCL of 20 ms below the TCL during an LA roof-dependent IART. When pacing was applied from the LA roof (in-the-circuit), the PPI equaled the TCL (Figure 3A). The cycle lengths measured both at the LRA and LCS accelerated to the PCL from the second pacing stimulus. Hence, the NNE at this site was 2. When entrainment pacing was performed at the RA free wall (remote site) where the PPI was 115 ms longer than the TCL, 8 pacing stimuli were needed for both cycle lengths at the LRA and LCS to accelerate to the PCL (NNE=8;
Figure 3B). Figure 4 shows the relationship between the NNE and PPI–TCL (n=281). The NNE positively correlated with the PPI–TCL indicating how distant the pacing site was from the reentrant circuit. Based on the results from the part I study, we assumed that the TCL–PCL should affect this relationship. Therefore, the entrainment data were classified into 3 groups according to the TCL–PCL: 5 to 15 ms (n=121); 16 to 30 ms (n=131); and 31 to 50 ms (n=29) below the TCL. The Spearman rank correlation coefficients were 0.906 for all data (P<0.001) and 0.943, 0.934, and 0.876 for TCL–PCLs of 5 to 15, 16 to 30, and 31 to 50 ms, respectively (all P<0.001). In agreement with the results of the part I study, the NNE tended to be smaller with larger TCL–PCLs. We constructed color-coded 3D NNE and PPI–TCL maps of the IART (2 peri-mitral and 1 RA free wall) by entrainment pacing at PCLs of 16 to 30 ms below the TCL (Figure 5). The NNE map was equivalent to the PPI–TCL map, confirming the spatial consistency of the NNE measurements. When the pacing site was defined as in-the-circuit by a PPI–TCL ≤20 ms, the pacing at a PCL of 16 to 30 ms below the TCL provided the highest accuracy for diagnosing whether the pacing site was within the circuit.

Figure 3. Measurement of the number of pacing stimuli needed to entrain (NNE). Examples of the NNE measured at sites within (A) and outside (B) the tachycardia circuit of intra-atrial reentrant tachycardia (IART) through the left atrium (LA) roof. The top panels show surface ECG lead V1, and the stimulus marker (Stim), and the bottom panels also exhibit intracardiac bipolar electrograms recorded from the LRA, LCS, and ablation catheter (Map) in an expanded timescale. Entrainment pacing was performed using the Map catheter at a cycle length 20 ms below the TCL (280 ms). A, During LA roof pacing, the cycle lengths at the lateral right atrium (LRA) and lateral coronary sinus (LCS) accelerated to the pacing cycle length (PCL; 260 ms) indicated by the asterisks, and the preceding pacing stimulus (arrowhead) was used to count the NNE (ie, NNE=2). B, When pacing from the right atrium free wall, the LRA electrogram was entrained immediately after initiating pacing, but required 8 beats for the cycle length at the LCS to accelerate to the PCL (asterisk). See the text for details.

Figure 4. Relationship between the number of pacing stimuli needed to entrain (NNE) and postpacing interval (PPI)–tachycardia cycle length (TCL). Superimposed scatterplots obtained from each group (5–15 ms [blue triangles], 16–30 ms [black circles], 31–50 ms [red squares]) are shown. See the text for details.

Figure 5. Concordant distribution of the postpacing interval (PPI)–tachycardia cycle length (TCL) and number of pacing stimuli needed to entrain (NNE). Three dimensional color-coded activation map (A), PPI–TCL map (B), and NNE map (C) of peri-mitral intra-atrial reentrant tachycardia (TCL: 240 ms). Activation and PPI–TCL maps reveal macroreentry around the mitral annulus (MA). Note that the NNE map is qualitatively the same as the PPI–TCL map. LAA indicates left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; and RSPV, right superior pulmonary vein.
the tachycardia circuit (Table 2). With TCL−PCLs of 16 to 30 ms, NNEs ≤ 2 were diagnostic for determining an in-the-circuit pacing site, whereas NNEs > 3 suggested that pacing sites are outside-the-circuit.

Thirty-six (11%) attempts of entrainment resulted in the IART changing into another type of IART or atrial fibrillation (n=30), or termination of the IART (n=6). The original IART was induced again after the tachycardia change or termination and was successfully entrained from the same site in 8 of 36 failed entrainment trials (5 tachycardia changes and 3 terminations). All NNE values obtained from subsequent entrainment of the reinduced IART were consistent with NNEs measured during the failed entrainment attempts (Figure 6).

Figure 7 shows a case of a difficult PPI measurement because of multicomponent electrograms. In this example, the NNE was useful in determining whether the pacing site was part of the IART circuit. Figure 8 shows an example of an erroneous PPI measurement. The NNE correctly predicted the location of the IART circuit even when a misleading PPI value was obtained. Thus, the NNE provides additional information when the PPI results disagree with other findings.

Table 2. Diagnostic Yield of Different TCL−PCLs and Selected Cut-Off Values for Localization of Reentrant Circuits

<table>
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<tr>
<th>TCL−PCL</th>
<th>n</th>
<th>AUC</th>
<th>NNE Cut-Off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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</thead>
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<tr>
<td>5−15 ms</td>
<td>121</td>
<td>0.920</td>
<td>≤2</td>
<td>47</td>
<td>98</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≤3</td>
<td>90</td>
<td>92</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≤4</td>
<td>100</td>
<td>81</td>
<td>64</td>
<td>100</td>
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<tr>
<td>16−30 ms</td>
<td>131</td>
<td>0.989</td>
<td>≤2</td>
<td>84</td>
<td>100</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≤3</td>
<td>100</td>
<td>86</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>31−50 ms</td>
<td>29</td>
<td>0.961</td>
<td>≤3</td>
<td>83</td>
<td>87</td>
<td>63</td>
<td>95</td>
</tr>
</tbody>
</table>

AUC indicates area under the receiver operating characteristic curve; NNE, number of pacing stimuli needed to entrain; NPV, negative predictive value; PCL, pacing cycle length; PPV, positive predictive value; and TCL, tachycardia cycle length.

Discussion

NNE as a New Index of Entrainment Mapping

The PPI consists of the time for the wave front to travel from the pacing site to the reentrant circuit, revolve around the circuit, and return from the circuit to the pacing site. If the pacing site is exactly in-the-circuit, the PPI only takes 1 revolution through the circuit and the PPI−TCL becomes 0. However, PPIs can be longer at shorter PCLs because PPIs include the time through slow conduction pathways of reentrant circuit that generally have decremental conduction properties. In contrast, the NNE is associated with the time for the wave front to reach the circuit. The NNE becomes smaller at shorter PCLs because greater TCL−PCLs accelerate the arrival of wave fronts to reentrant circuits. The corrected EI significantly increased when pacing at shorter PCLs was applied from remote sites, which indicates that conduction in the path to the circuit may somewhat slow with short PCLs. However, the NNE never increased at shorter PCLs because greater TCL−PCLs accelerate the arrival of wave fronts to reentrant circuits. Therefore, the NNE is predictable in proportion to the distance between the pacing site and reentrant circuit when the TCL−PCL and CI are taken into account. To identify whether pacing sites are part of the circuit, the NNE measured with a TCL−PCL of 16 to 30 ms is most accurate, where a NNE ≤ 2 and >3 definitely predicted in-the-circuit and outside-the-circuit, respectively. Nevertheless, the NNE still has diagnostic value even if the TCL−PCL does not fall within this range. A NNE ≤ 2 is highly specific for in-the-circuit and a TCL−PCL of 5 to 15 ms, whereas a NNE >4 with a TCL−PCL of 5 to 15 ms and NNE >3 with a TCL−PCL of 31 to 50 ms can rule out in-the-circuit (Table 2).
Advantages of the NNE Over the PPI

Changes or termination of IARTs during entrainment pacing is not uncommon (7%–19%, 1,12 11% in this study), which precludes PPI measurements. The NNE can solve this limitation of PPI mapping. Fatemi et al14 reported that amiodarone significantly altered entrainment responses by enhancing slow conduction, and a PPI−TCL >20 ms did not exclude the possibility that the pacing site was in-the-circuit. The NNE may provide more accurate results in this setting because it is independent of the time through slow conduction areas within the circuit. Moreover, the NNE is useful if difficulties occur when measuring PPIs (Figures 7 and 8).

The NNE is determined from intracardiac electrograms on each side of the atrium. Because sites with distinct local electrograms can be chosen in the LRA and LCS, automated measurement of cycle lengths would be possible. This might allow us to automatically construct color-coded 3D NNE maps,
while creating 3D PPI maps can only be achieved manually and are somewhat time-consuming.

Study Limitations
RFCA was not performed on the basis of the NNE mapping in the majority of IARTs except for some particular cases (Figure 7). Prospective comparative studies will be needed to evaluate the net clinical benefits of adding NNE mapping to the conventional techniques (eg, success rate of RFCA, procedure and fluoroscopic times, etc.).

In this study, we excluded IART with a large spontaneous variation in the TCL. Practically, the NNE is countable if the TCL-PCL is larger than the magnitude of the TCL oscillation; however, the usefulness of the NNE remains unclear in those cases.

Finally, this study did not include nonreentrant automatic atrial tachycardias. Theoretically, the NNE would also predict distances from the automatic atrial tachycardias focus. Further studies are needed to determine the value of the NNE in automatic atrial tachycardias.

Conclusions
The NNE is a new criterion for entrainment mapping to localize reentrant circuits of IART. This simple and reliable procedure covers conventional entrainment mapping limitations using PPI measurements. If entrainment pacing is performed at the isthmus that is already defined by anatomy or substrate mapping (ie, a conduction channel between dense scars),3 the NNE can determine whether the isthmus is critical or not even when the IART alters or terminates during entrainment pacing. Consequently, the NNE greatly facilitates the mapping and RFCA of IART when combined with PPI mapping.

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Disclosures
None.

References
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