Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 9, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.11.023

Misleading Long Post-Pacing Interval After Entrainment of Typical Atrial Flutter From the Cavotricuspid Isthmus

Dirk Vollmann, MD,*† William G. Stevenson, MD,† Lars Lüthje, MD,* Christian Sohns, MD,* Roy M. John, MD, PhD,† Markus Zabel, MD,* Gregory F. Michaud, MD†

Göttingen, Germany; and Boston, Massachusetts

Objectives The purpose of this study was to evaluate the prevalence and mechanism of a misleading long post-pacing interval (PPI) upon entrainment of typical atrial flutter (AFL) from the cavotricuspid isthmus (CTI).

Background In typical AFL, the PPI from entrainment at the CTI is expected to closely match the tachycardia cycle-length (TCL).

Methods Sixty patients with confirmed CTI-dependent AFL were retrospectively analyzed and grouped into short (≤30 ms) or long (>30 ms) PPI-TCL. Thereafter, we prospectively studied 16 patients to acquire the PPI-TCL at 4 CTI sites with entrainment at pacing cycle-lengths (PCLs) 10 to 40 ms shorter than the TCL. Conduction times during AFL and entrainment were compared in 5 segments of the AFL circuit.

Results Eleven patients (18%) in the retrospective analysis had a long PPI-TCL after entrainment from the CTI. Subjects with long PPI-TCL had similar baseline characteristics but greater beat-to-beat TCL variability. In the prospective cohort, PPI-TCL was influenced by the difference between PCL and TCL and site of entrainment. Conduction delays associated with a long PPI-TCL were located predominantly in the segment activated first by the paced orthodromic wave front, and were mainly due to local pacing latency, as confirmed by the use of monophasic action potential catheters.

Conclusions A long PPI upon entrainment of typical AFL from the CTI is common and due to delayed conduction with entrainment. Whether these findings apply to other macro–re-entrant tachycardias warrants further investigation.
(J Am Coll Cardiol 2012;59:819–24) © 2012 by the American College of Cardiology Foundation

A pacing site is considered to be part of the macro–re-entrant circuit if the first post-pacing interval (PPI) after entrainment is ≤30 ms of the tachycardia cycle-length (TCL) (1–3). It has been noted earlier, however, that the PPI-TCL may be misleadingly long if the pacing cycle-length (PCL) is ≥40 ms below the TCL (2–4).

Typical atrial flutter (AFL) is due to right atrial macro–re-entry, and the cavotricuspid isthmus (CTI) is a critical component of the circuit and the primary target for ablation (1). We aimed to evaluate the prevalence and mechanism of a misleading long PPI-TCL in patients presenting with typical AFL for CTI ablation.

Methods

This study was conducted in patients presenting with typical AFL for ablation therapy. A retrospective analysis addressed the prevalence of a misleading long PPI-TCL (>30 ms) upon entrainment from the CTI. Thereafter, we conducted a prospective study to systematically evaluate the PPI at different PCLs from pre-specified CTI sites.

Study population. Institutional ethics committees approved the study protocol, and subjects gave written informed consent. For the retrospective analysis, we reviewed data from 243 consecutive subjects referred for AFL ablation to the Brigham and Women's Hospital. A total of 60 patients met the following pre-defined criteria: 1) sustained AFL during the electrophysiological (EP) procedure; 2) atrial activation from the proximal to the distal coronary sinus; 3) documented entrainment with concealed fusion from the CTI; and 4) AFL termination during CTI ablation.

The prospective study was conducted at the University Medical Center in Göttingen. Patients with persistent AFL were eligible if the 12-lead electrocardiogram was suggestive of typical AFL. Prior atrial ablation or surgery were exclusion criteria.

EP study and catheter ablation. All catheters were introduced through femoral veins. Bipolar intracardiac electrograms were filtered between 30 and 500 Hz and recorded at a sampling rate of 1,000 Hz (Prucka CardioLab EP system, GE Healthcare, Waukesha, Wisconsin).

From the *Department of Cardiology and Pneumology, University Medical Center Göttingen, Germany; and the †Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Dr. John has received modest speaker honoraria from St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 16, 2011; revised manuscript received November 9, 2011, accepted November 17, 2011.

Abbreviations and Acronyms

AFL = atrial flutter
CTI = cavotricuspid isthmus
EP = electrophysiological
MAP = monophasic action potential
PCL = pacing cycle-length
PPI = post-pacing interval
TCL = tachycardia cycle-length

Diagnostic catheters were positioned as shown in Figure 1. An open-irrigated 3.5-mm-tip catheter (Celsius Thermocool, Biosense Webster, Diamond Bar, California) was utilized for pacing and ablation. In the retrospective analysis, an 8-mm-tip catheter was also used.

Entrainment from the CTI was performed with ≥15 bipolar stimuli (pulse strength: 10 mA at 2 ms). In the retrospective analysis, stimuli were delivered with a PCL 10 to 40 (21 ± 9) ms below the TCL. In the prospective study, entrainment was performed from 4 pre-specified CTI locations (Fig. 1) with a PCL 10 ms, 20 ms, 30 ms, and 40 ms below the TCL. Reproducibility of repeated PPI measurements was evaluated by determining the standard deviation (SD) of 3 consecutive measurements from 1 pre-specified site at a constant PCL. In 2 patients, we utilized a monophasic action potential (MAP) recording and pacing catheter (EasyMap MAP, MedFact, Lörrach, Germany). Details on MAP catheter design and application have been described elsewhere (5). Conventional CTI ablation was performed as described earlier (6).

Definitions and data analysis. Local atrial activation was defined as the first sharp peak in the corresponding bipolar electrogram or as sharpest deflection of the local MAP upstroke. TCL was the mean value of 5 consecutive atrial cycles during AFL immediately before entrainment. TCL

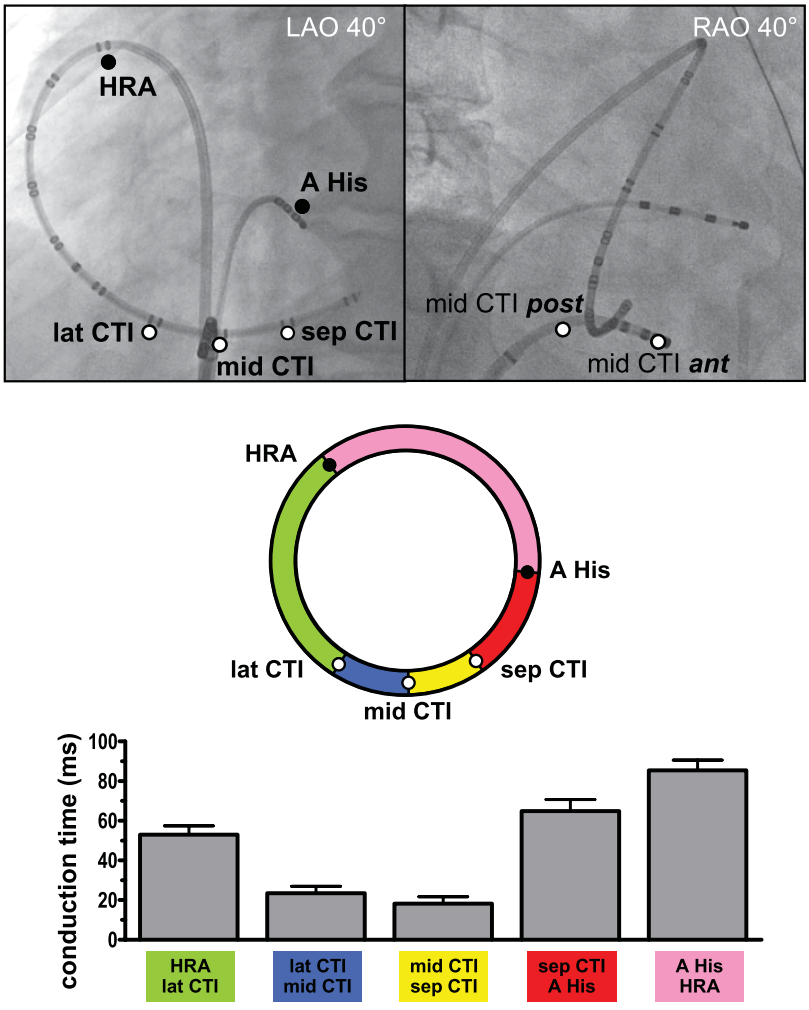

Figure 1 **Instrumentation for Entrainment and Measurement of Segmental Conduction Times**

The **white dots** indicate entrainment pacing sites at the cavotricuspid isthmus. **(Top)** Catheter position on fluoroscopy. **(Middle)** Schematic illustrating the 5 segments of the atrial flutter circuit (LAO view). **(Bottom)** Baseline segmental atrial conduction times during atrial flutter (mean values with standard error, data from the prospective study). A His = atrial signal at the His position; HRA = high right atrium; LAO = left anterior oblique; lat CTI = lateral cavotricuspid isthmus; mid CTI ant = anterior mid cavotricuspid isthmus (close to the tricuspid valve); mid CTI post = posterior mid cavotricuspid isthmus (close to the inferior vena cava); RAO = right anterior oblique view; sep CTI = septal cavotricuspid isthmus.

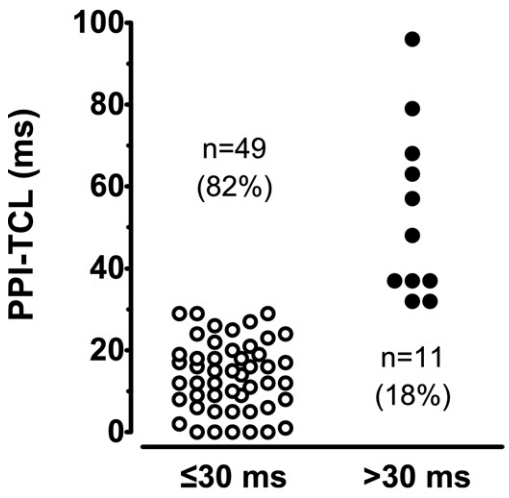

Figure 2 **Prevalence of Long PPIs at the CTI**

The dot plot illustrates the prevalence of short (≤30 ms) and long (>30 ms) PPI-TCL (post-pacing interval – tachycardia cycle-length) values in the retrospective analysis. CTI = cavotricuspid isthmus.

variability was quantified by TCL range (difference between maximum and minimum cycle length of 5 consecutive AFL cycles) and coefficient of variation (standard deviation of 5 consecutive AFL cycles divided by mean TCL × 100%).

PPI was defined as the interval from pacing impulse onset of the last captured beat during entrainment to subsequent local atrial activation at the pacing site. PPI was only measured if: 1) local electrograms from the pacing site indicated stable catheter position; 2) ≥5 of the last atrial cycles before cessation of pacing were captured and accelerated to the PCL; 3) surface electrocardiograms and intracardiac electrograms were suggestive of entrainment with concealed fusion (2); and if 4) AFL resumed after pacing without change in TCL or activation sequence.

Segmental conduction time was measured from local atrial activation (or stimulus artifact) at the beginning to local activation at the end of the 5 atrial segments, respectively (Fig. 1). Segmental conduction delay was the difference between segmental conduction time during AFL and during entrainment.

Statistical analysis. Continuous variables were tested for normal distribution, were compared using the independent Student *t* test, and are expressed as mean ± SD unless stated otherwise. Categorical values are stated as absolute and relative frequencies and were compared using Fisher exact test.

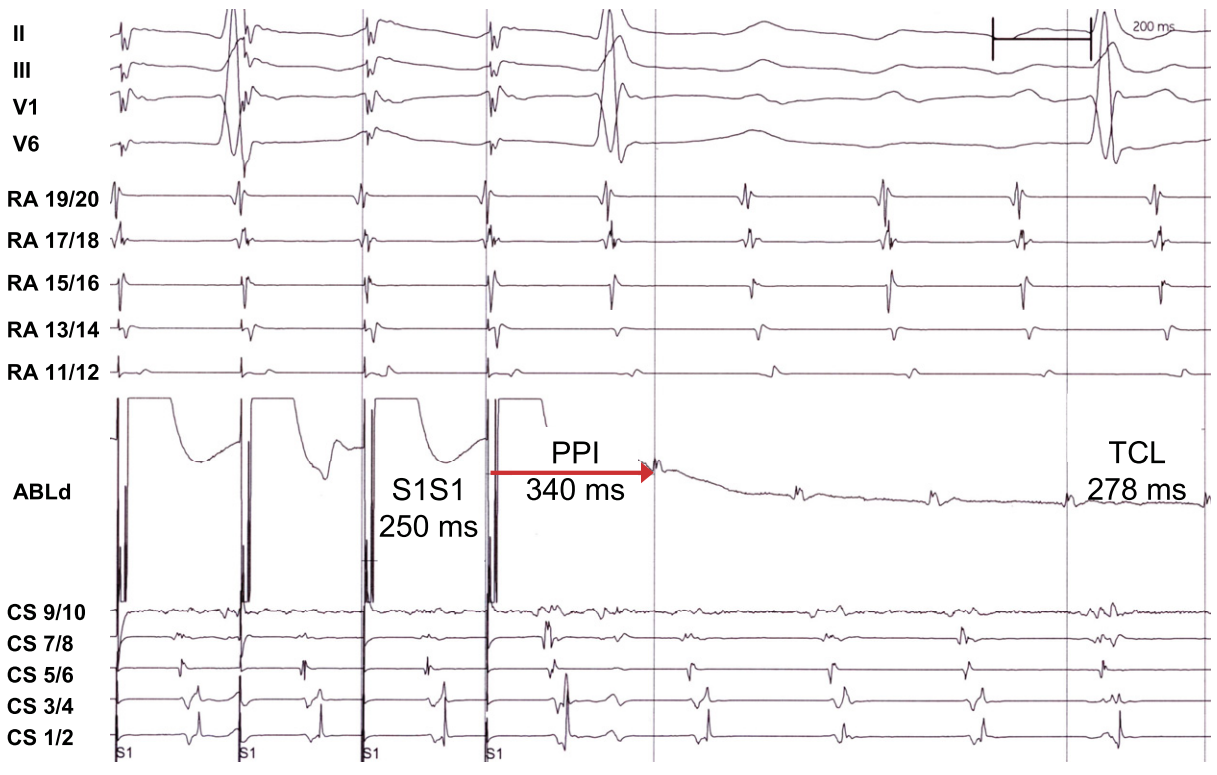

Figure 3 **Misleading Long PPI After Entrainment From the CTI**

Representative example (retrospective cohort). Entrainment with a pacing cycle-length (PCL) (250 ms) 28 ms below the tachycardia cycle-length (TCL) (278 ms) and with the stimulation electrode (ABLd) at the cavotricuspid isthmus produced a misleading long PPI (PPI-TCL = 62 ms). CS 1 to 10 indicates bipolar atrial recordings from distal (1 and 2) to proximal (9 and 10) coronary sinus (CS); RA 11 to 20 indicate bipolar atrial recordings from high (19 and 20) to low (11 and 12) right atrium. Abbreviations as in Figures 1 and 2.

JACC Vol. 59, No. 9, 2012
February 28, 2012:819–24

The effects of site of entrainment and PCL on PPI-TCL were assessed by 2-way repeated-measures analysis of variance followed by Tukey test, if applicable. Differences in conduction delay between atrial segments were compared using 1-way repeated-measures analysis of variance followed by Tukey test, if applicable. All tests were 2-tailed. Values of $p < 0.05$ was considered statistically significant.

Results

Retrospective analysis. A long PPI-TCL from the CTI was found in 18% of the 60 patients with typical AFL (Fig. 2). Figure 3 shows a representative example. Patient characteristics were similar between subjects with short or long PPI-TCL, but individual TCL variability was greater in patients with a long PPI-TCL (Table 1).

Prospective study. Twenty patients were eligible for enrollment and gave written informed consent. Four subjects were excluded because AFL was not present in the EP lab. Thus, data from 16 patients (age 69 ± 9 years, 94% male) were analyzed. Two patients were taking amiodarone, 1 dronedarone, and 1 flecainide. Mean TCL of AFL was 240 ± 28 ms. In 3 patients, the pacing protocol was not completed because AFL terminated with entrainment. In all remaining subjects, AFL terminated with CTI ablation.

Effect of PCL and site of entrainment on PPI-TCL. Entrainment site and stimulation rate both influenced the PPI-TCL ($p < 0.001$) (Fig. 4). Overall, a PPI-TCL >30 ms was found in 20%, 20%, 37%, and 45% of the cases for a TCL-PCL of 10 ms, 20 ms, 30 ms, and 40 ms, respectively. PPI values at constant PCL varied considerably among different CTI sites but were highly reproducible at single sites (3 ± 2 ms).

Table 1 Patient Characteristics and Procedural Data (Retrospective Analysis)

	Short PPI-TCL n = 49 (82%)	Long PPI-TCL n = 11 (18%)	p Value
Age, yrs	62 ± 12	65 ± 9	0.46
Male gender	41 (84%)	10 (91%)	1.00
Hypertension	27 (55%)	7 (64%)	0.74
Coronary artery disease	15 (31%)	4 (36%)	0.73
Other cardiovascular disease	26 (53%)	5 (45%)	0.74
No cardiovascular disease	6 (12%)	0 (0%)	0.58
Left ventricular ejection fraction, %	50 ± 13	56 ± 6	0.19
History of atrial fibrillation	26 (53%)	5 (45%)	0.74
Class I/III AA drug treatment	6 (12%)	1 (9%)	1.00
History of prior CTI ablation	2 (4%)	1 (9%)	0.46
Counterclockwise AFL	40 (82%)	10 (91%)	0.67
TCL, ms	263 ± 31	261 ± 38	0.82
TCL-PCL, ms	22 ± 9	19 ± 9	0.36
PPI-TCL, ms	14 ± 9	53 ± 21	<0.0001
Individual TCL range, ms	8 ± 5	13 ± 6	0.011
TCL coefficient of variation	1.3 ± 0.8	2.1 ± 1.0	0.0051
CTI ablation time, min	15.2 ± 12.8	14.8 ± 10.3	0.92
AFL termination with ablation	49 (100%)	11 (100%)	1.00

Values are mean ± SD or n (%).

AA = antiarrhythmic; AFL = atrial flutter; CTI = cavotricuspid isthmus; PCL = pacing cycle-length for entrainment; PPI = post-pacing interval; TCL = tachycardia cycle length.

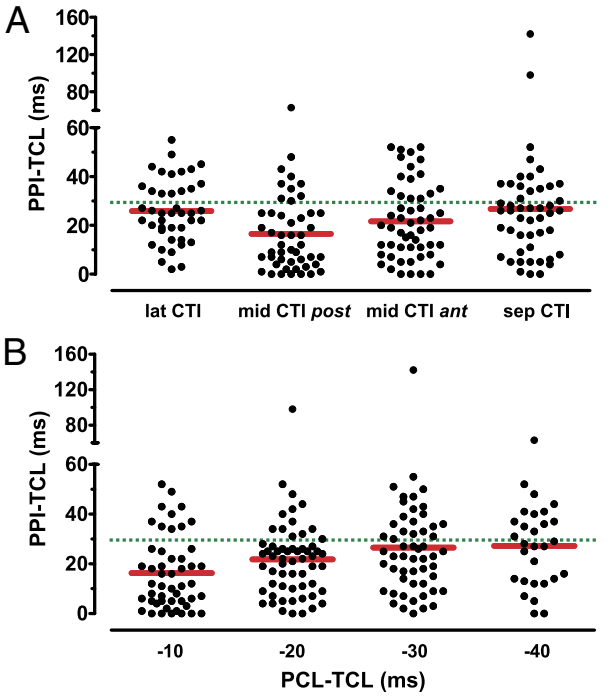

Figure 4 Effect of Entrainment Site and Pacing Rate on the PPI

Dot plots of individual PPI-TCL values grouped by entrainment site **(A)** or adjusted pacing cycle-length (PCL-TCL) **(B)**. **Red lines** indicate mean values, **green lines** mark the border between short and long PPI-TCL (30 ms). See legend of Figure 1 for explanation of entrainment sites. Both entrainment site and pacing rate had an independent effect on PPI-TCL values ($p < 0.001$, respectively). PPI-TCL values were shorter at the posterior mid CTI ($p < 0.005$) and increased with the difference between pacing cycle-length and tachycardia cycle-length (PCL-TCL). Abbreviations as in Figures 1 and 2.

Variables affecting PPI-TCL. Subjects of the prospective cohort with at least 1 long PPI-TCL upon entrainment from the CTI (n = 11) had a similar rate of antiarrhythmic drug use (25% vs. 25%, p = 1.0) and comparable TCL (238 ± 29 ms vs. 245 ± 31 ms, p = 0.68) but tended to have greater TCL variability as compared with patients with only short PPI-TCL (individual TCL range: 10 ± 3 ms vs. 7 ± 2 ms, p = 0.064; TCL coefficient of variation: 1.7 ± 0.5 ms vs. 1.2 ± 0.2 ms, p = 0.070).

Segmental atrial conduction. Segmental atrial conduction times during AFL are summarized in Figure 1. Segmental conduction delays with entrainment in cases of long PPI-TCL are shown in Figure 5. With different entrainment sites, the greatest delay was not bound to one specific segment but was always located in the segment activated first by the orthodromic paced wave front. Accordingly, MAP catheter utilization showed local stimulus response latency (Fig. 6).

Discussion

This study provides several important findings: In patients with typical AFL, long PPI-TCL values >30 ms after entrainment from the CTI were observed:

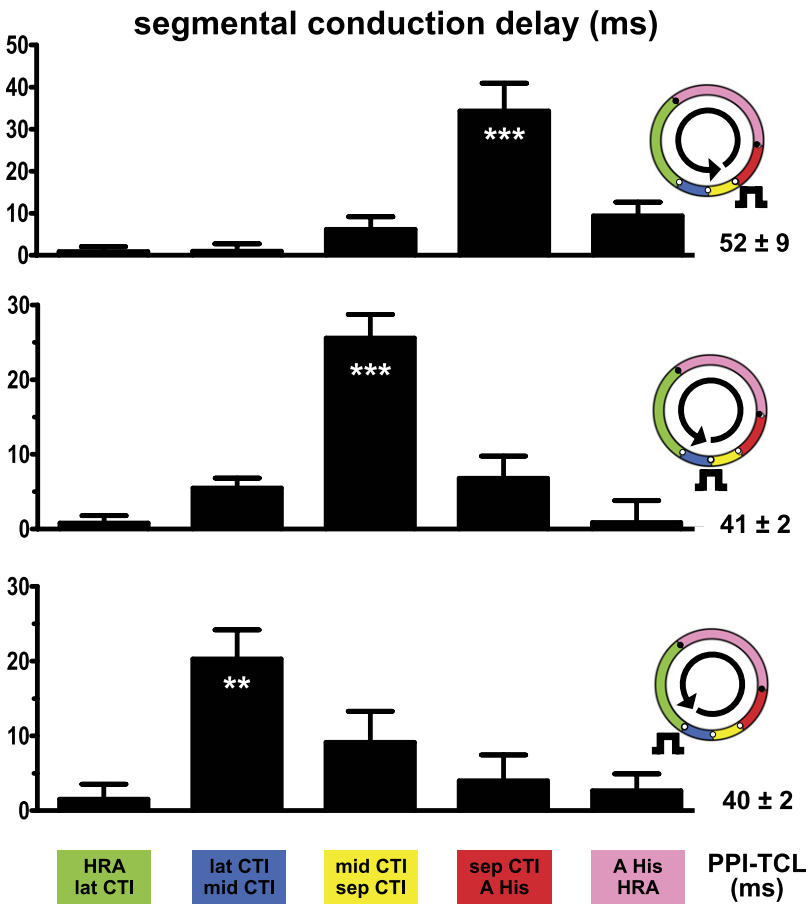

Figure 5 Segmental Conduction Delays During Entrainment With Long PPI-TCL

Segmental conduction delays during entrainment of typical counterclockwise atrial flutter from different sites at the cavotricuspid isthmus. Pacing location as indicated by the icon at the **right of each graph** (see Fig. 1 for details). Mean values with standard error from cases with long PPI-TCL. With changes in pacing site, the greatest conduction delay always occurs in the segment activated first by the paced orthodromic wave front. Note that for each entrainment site, the sum of conduction delays throughout the entire re-entry circuit explains the corresponding long PPI-TCL. **$p < 0.01$ and ***$p < 0.001$ as compared with the other respective segments. Abbreviations as in Figures 1 and 2.

1. In 18% of patients referred for catheter ablation
2. Despite a PCL within 20 ms of the TCL
3. More frequently when the PCL was ≥30 ms shorter than the TCL
4. Less frequently when pacing the posterior mid CTI and when AFL had low TCL variability
5. To be caused mainly by local pacing latency.

Misleading long PPI upon entrainment from the CTI. It was noted earlier that entrainment from a site within the re-entrant circuit may be misleading when the PCL is ≥40 ms below the TCL (2–4). Misleading long PPI values in our study were common even when the PCL was 10 to 20 ms below the TCL. Fatemi et al. (7) found PPI-TCL values >20 ms after entrainment of typical AFL from the CTI in 27% of the cases using a PCL 30 ms below the TCL. Long PPI-TCL values were more common in subjects on amiodarone. In our analysis, a long PPI-TCL was associated with greater TCL variability. Prior investigations have related increased TCL variability during typical AFL with the loss of a fully excitable gap (8).

Mechanism of misleading long PPI. It has been postulated that misleading long PPI-TCL values may be caused by rate-dependent slowing of conduction or alterations of the activation path (3,4). It is also known that conduction significantly prolongs in the human atrium with premature stimuli delivered during the relative refractory period (9). This conduction delay is caused by local pacing latency and results from incomplete recovery of excitability of the tissue that is immediately adjacent to the pacing electrodes (5,10).

Pacing latency explains why the greatest conduction delay in our study was not confined to one distinct anatomical site but was always located in the segment immediately downstream from pacing. Other segments were less delayed, probably because additional time was available for recovery

JACC Vol. 59, No. 9, 2012
February 28, 2012:819–24

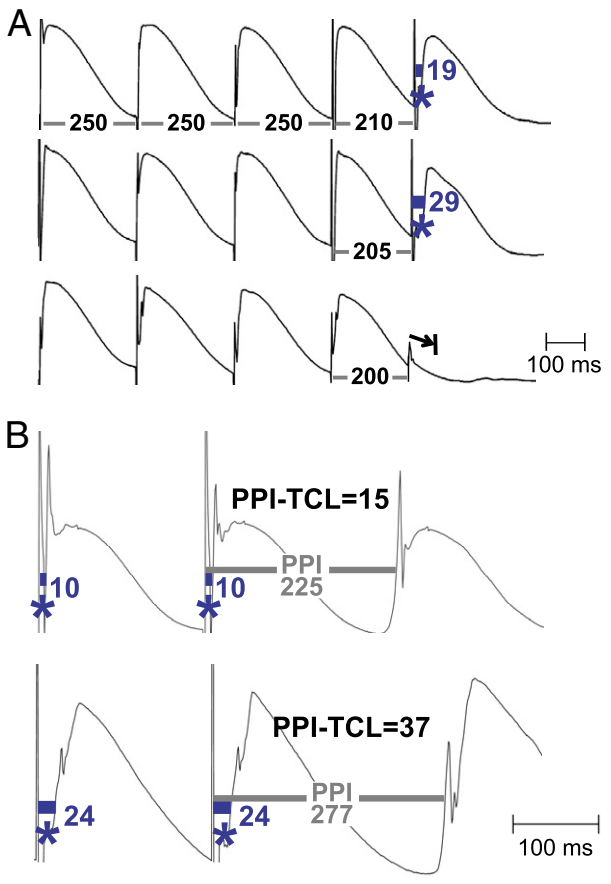

Figure 6 Local Pacing Latency at the CTI

Simultaneous pacing and signal acquisition with a monophasic action potential catheter to illustrate local pacing latency **(asterisk)**. **(A)** Programmed stimulation during sinus rhythm. Progressive latency is seen as the extrastimulus approaches the refractory period. **(B)** Entrainment of typical atrial flutter from the cavotricuspid isthmus. **(Upper tracing)** Little latency (10 ms) with entrainment, short PPI-TCL upon pacing cessation. **(Lower tracing)** Marked local pacing latency (24 ms) and long PPI-TCL (37 ms). Abbreviations as in Figures 1 and 2.

of repolarization. MAP recordings provided further support for this hypothesis. We cannot exclude, however, that other potential mechanisms, e.g., rate-dependent slowing of impulse propagation or altered pathways of conduction, may contribute in some patients.

Considerable spatial differences exist in right atrial refractoriness, which may explain why PPI-TCL values from the CTI region showed significant dependence on pacing location in our study: At sites with a long PPI-TCL, the local refractory period may have been relatively longer, which produced more pacing latency. One may speculate that refractory periods are shorter at the mid CTI close to the inferior vena cava (where shorter PPI-TCL values were found in our study).

Study limitations. Antiarrhythmic medication was not discontinued, but use was low and not different between subjects with short or long PPI-TCL values. MAP recordings were acquired in subjects without anti-arrhythmic medication.

We did not map the re-entry pathway, but the inclusion criteria make arrhythmia mechanisms other than typical AFL unlikely. Intra-isthmus re-entry may have similar electrocardiographic appearance as typical AFL (11). However, intra-isthmus re-entry is a rare finding that is mostly linked to a history of prior CTI ablation, which was excluded in our prospective cohort.

Clinical implications. Entrainment from the CTI is commonly utilized to rapidly confirm or exclude CTI-dependent AFL. Our results demonstrate that a misleading long PPI-TCL is common, even if the PCL is within 20 ms of the TCL. Entrainment from near the inferior vena cava in the mid CTI may help to minimize the chances of a misleading PPI value. Although we identified limitations of entrainment during typical AFL, the findings may also apply to other macro–re-entrant tachycardias.

Reprint requests and correspondence: Priv. Doz. Dr. med. Dirk Vollmann, University Medical Centre Göttingen, Georg-August-University, Department of Cardiology and Pneumology, Division of Clinical Electrophysiology, Robert-Koch-Str. 40, 37075 Göttingen, Germany. E-mail: d.vollmann@med.uni-goettingen.de.

REFERENCES

1. Feld GK, Srivatsa U, Hoppe B. Ablation of isthmus-dependent atrial flutters. In: Huang SKS, Wood MA, editors. Catheter Ablation of Cardiac Arrhythmias. Philadelphia, PA: Saunders Elsevier, 2006:195–218.
2. Deo R, Berger R. The clinical utility of entrainment pacing. J Cardiovasc Electrophysiol 2009;20:466–70.
3. Stevenson WG, Sager PT, Friedman PL. Entrainment techniques for mapping atrial and ventricular tachycardias. J Cardiovasc Electrophysiol 1995;6:201–16.
4. Cosio FG, Lopez Gil M, Arribas F, Palacios J, Goicolea A, Nunez A. Mechanisms of entrainment of human common flutter studied with multiple endocardial recordings. Circulation 1994;89:2117–25.
5. Koller BS, Karasik PE, Solomon AJ, Franz MR. Prolongation of conduction time during premature stimulation in the human atrium is primarily caused by local stimulus response latency. Eur Heart J 1995;16:1920–4.
6. Vollmann D, Luthje L, Seegers J, Hasenfuss G, Zabel M. Remote magnetic catheter navigation for cavotricuspid isthmus ablation in patients with common-type atrial flutter. Circ Arrhythm Electrophysiol 2009;2:603–10.
7. Fatemi M, Mansourati J, Rosu R, Blanc JJ. Value of entrainment mapping in determining the isthmus-dependent nature of atrial flutter in the presence of amiodarone. J Cardiovasc Electrophysiol 2004;15:1409–15.
8. Cheng J, Glatter K, Yang Y, Zhang S, Lee R, Scheinman MM. Electrophysiological response of the right atrium to ibutilide during typical atrial flutter. Circulation 2002;106:814–9.
9. Cosio FG, Palacios J, Vidal JM, Cocina EG, Gomez-Sanchez MA, Tamargo L. Electrophysiologic studies in atrial fibrillation. Slow conduction of premature impulses: a possible manifestation of the background for reentry. Am J Cardiol 1983;51:122–30.
10. Fananapazir L, Packer D, Prystowsky EN. Differential effects of changes in local myocardial refractoriness on atrial and ventricular latency. Circulation 1996;94:1364–71.
11. Yang Y, Varma N, Badhwar N, et al. Prospective observations in the clinical and electrophysiological characteristics of intra-isthmus reentry. J Cardiovasc Electrophysiol 2010;21:1099–106.

Key Words: atrial flutter ■ conduction ■ entrainment ■ mapping ■ pacing latency.