Distribution of Mean Cycle Length in Cavo-Tricuspid Isthmus Dependent Atrial Flutter

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Summary

Although cycle length (CL) constitutes a fundamental descriptor of any arrhythmia, there is not larger study describing mean CL in electrophysiologically confirmed cavo-tricuspid isthmus (CTI)-dependent atrial flutter (AFL). We analyzed retrospectively digital recordings of 121 patients (98 men; age 64±11 years) referred for radiofrequency ablation of persistent CTI-dependent AFL. Median of mean AFL CL was 240 ms (interquartile range (IQR) of 222-258 ms, overall range of 178-399 ms). The distribution of CL was not normal (Shapiro Wilk test, $p<0.001$). Both counterclockwise and clockwise (14.9 % of all cases) AFLs were comparable in their CL; 240 (IQR 222-258) ms vs. 234 (217-253) ms, respectively. AFL CL<200 ms and AFL CL<190 ms was noticed in 5 (4.1 %) and 3 cases (2.5 %), respectively. In multivariate regression analysis, age (increase by 6±3 ms per decade of age, $p=0.036$), treatment with specific antiarrhythmic drugs (increase by 11±6 ms, $p=0.052$) and the history of cardiac surgery (increase by 26±9 ms, $p=0.004$) were independently associated with AFL CL. In conclusions, the distribution of AFL CL is not normal. The prevalence of AFL with short CL is low. Short CL<200 ms does not rule out the CTI-dependent AFL, especially in young and otherwise healthy patients.

Key words

Arrhythmia cycle length • Cavo-tricuspid isthmus-dependent atrial flutter • Catheter ablation

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Introduction

Cavo-tricuspid isthmus (CTI)-dependent atrial flutter (AFL) is a right-atrial macro-reentrant tachycardia with the circuit bounded anteriorly by the tricuspid annulus and, posteriorly, by the venae cavae orifices, Eustachian ridge, and by the functional barrier of the crista terminalis (Feld *et al.* 1992, Olgin *et al.* 1995, Shah *et al.* 1997, Fukuzawa *et al.* 2008, Santucci *et al.* 2009, Gami *et al.* 2010). Radiofrequency catheter ablation of CTI is curative approach for both counterclockwise (CCW) and clockwise (CW) variants of CTI-dependent AFL (Feld *et al.* 1992, Waldo 2000, Cosio *et al.* 1993).

In clinical practice, the diagnosis of CTI-dependent AFL is based on the presence of characteristic sawtooth AFL waves in inferior ECG leads, low amplitude biphasic AFL waves in leads I and aVL, and upright AFL waves in V1 with transition to negative F waves in V6. However, atypical ECG pattern does not rule out CTI-dependent AFL (Barbato *et al.* 2009). This is particularly evident in case of CW CTI-dependent AFL, which displays more variable ECG patterns than more frequent CCW variant (Cosio *et al.* 1993, Waldo *et al.* 1997, Waldo 2000). Similarly, when atria are significantly affected by spontaneous or post-ablation scarring the morphology of F-waves may become "atypical" even in the case of CTI-dependent CCW AFL. On the other hand, atrial fibrillation with significant left-to-right gradient of dominant frequency may falsely suggest the CTI-dependent AFL. While an invasive electrophysiological study is necessary to make the final diagnosis, any effort should be made to come close to the

correct diagnosis non-invasively, because the management of CTI-dependent, non-CTI-dependent AFL and atrial fibrillation by catheter ablation differ substantially.

Although cycle length (CL) of CTI-dependent AFL constitutes a fundamental descriptor, there is not detailed study describing mean CL distribution in CTI-dependent AFL. To our knowledge, many previous studies concerning CTI-dependent AFL either did not report data on CL or included relatively small number of patients (Lewis *et al.* 1920, Olshansky *et al.* 1990, Feld *et al.* 1992, Kirkorian *et al.* 1994, Calkins *et al.* 1994, Olgin *et al.* 1995, Poty *et al.* 1995, Kalman *et al.* 1996, Cheng *et al.* 1999, Narayan *et al.* 2005, Santucci *et al.* 2009). Moreover, some of them lacked the electrophysiological confirmation of the diagnosis of CTI-dependent AFL (Lewis 1920, Wells 1979).

Therefore, our study was aimed at investigating the distribution of CTI-dependent AFL CL in a larger group of patients referred to the electrophysiological laboratory for catheter ablation of sustained CTI-dependent AFL and identifying the shortest AFL CL that can be successfully treated by CTI ablation.

Methods

We retrospectively analyzed digital recordings of intracardiac electrograms in series of 121 consecutive patients referred for first radiofrequency ablation of sustained CTI-dependent AFL from January 2003 to December 2008. Both demographic and clinical data were collected from standard medical records. Standard protocol was used for the electrophysiological study and for the catheter ablation. A 20-pole 7-Fr steerable catheter with 2-10-2 mm spacing (Duodeca, Daig Corporation, Minnetonka, MN, USA) was placed in the right atrium along the tricuspid annulus and anterior to the terminal crest with the catheter tip at the inferolateral CTI. A decapolar 6-Fr steerable catheter with 2-8-2 mm spacing (Livewire CSL, Diag Corporation) was placed into the coronary sinus. A 7-Fr ablation catheter with externally irrigated 3.5-mm tip (ThermoCool, Biosense-Webster Inc., Diamond Bar, CA, USA) was placed at CTI. Diagnosis of CTI-dependent AFL was made by observation of typical pattern on the surface 12-lead ECG together with concordant activation sequence recorded from intracardiac catheters and, in majority of patients, by the demonstration of concealed entrainment from CTI with postpacing interval < AFL CL + 20 ms. Diagnosis

was finally supported by the specific mode of AFL termination during CTI ablation.

Prucka Cardiolab 7000 (GE Healthcare, UK) served as recording system which stored intracardiac signals at sampling frequency of 977 Hz with voltage resolution of 0.001 mV. Being aware of cardiac cycle and respiratory variability of AFL CL, analysis was performed in continuous 18-second segments (one segment per case) of pre-ablation atrial electrograms which were exported and digitally analyzed. Single bipolar signal from lateral right atrium and from proximal coronary sinus with the most stable electrogram morphology were selected for the analysis by a purpose-made software package. Atrial electrograms were automatically detected using combination of threshold and derivative methods and their positions were adjusted by maximum correlation with signal-averaged electrogram template. All signals were carefully visually inspected and manually edited when needed. Such approach yielded ~ 180 CL readings from 2 sites which were finally averaged.

The mean AFL CL was calculated in subgroups according to underlying cardiac disease: hypertensives (with arterial hypertension, without structural heart disease); CAD patients (with coronary artery disease, including myocardial infarction, without history of cardiac surgery); surgery patients (after CABG and/or valve surgery) and compared with controls (without structural heart disease, without arterial hypertension). In addition, patients treated with specific antiarrhythmic drugs (AADs) (excluding beta-blockers), patients with hypertension and surgery patients were compared with the rest of the population. Mann-Whitney U-test for independent samples, Spearman's correlation analysis, Shapiro-Wilk W test, and multivariate regression analysis were used for statistical analysis as appropriate. P-value < 0.05 was considered significant.
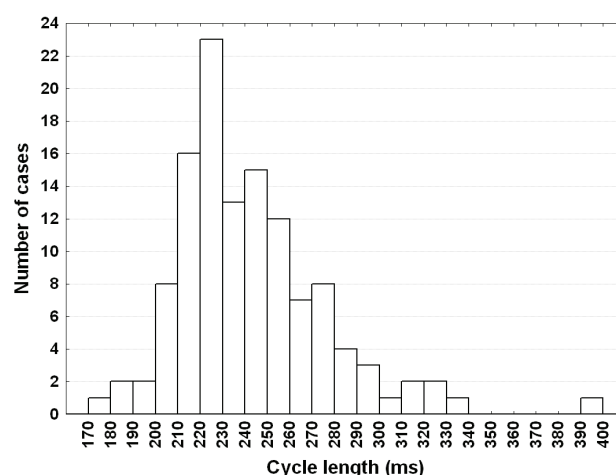
Results

Total 121 patients (98 men; age 64 ± 11 years) were included to the study. Clinical data are presented in Table 1. Mean CL of all AFLs was 243 ± 33 ms; range 178-399 ms; mode of 223 ms; median of 240 ms; interquartile range (IQR) of 222-258 ms. Distribution of CL was not normal (Shapiro Wilk test, W=0.922, p<0.001), was skewed to the right (skewness coefficient of 1.33 ± 0.22) and had positive kurtosis (3.6 ± 0.44). Figure 1 shows the distribution of AFL CL for total population.

Table 1: Demographics and clinical characteristics of studied population.

No. of patients	121
Age (mean ± SD)	64 ± 11 years
Male	98 (81 %)
LV EF (mean ± SD)	54 ± 12 %
CAD/MI	35 (30 %) / 17 (14 %)
Arterial hypertension	72 (59.5 %)
Diabetes mellitus	34 (28 %)
History of atrial fibrillation or atypical AFL	17 (14 %)
Previous cardiac surgery	21 (17 %)
CABG	12 (10 %)
Aortic valve replacement	4 (3 %)
Mitral valve repair or replacement	3 (2.5 %)
Other	2 (1.6 %)
MAZE procedure	0
Concomitant medication	
None	22 (18 %)
Amiodarone / sotalol	28 (23 %) / 3 (2.5 %)
Propafenone	16 (13 %)
beta-blockers / Ca-blockers (verapamil)	74 (61 %) / 7 (6 %)
Digoxin	11 (9 %)

AFL – atrial flutter, LV EF – left ventricle ejection fraction, CAD – coronary artery disease, MI – myocardial infarction, CABG – coronary artery bypass grafting.

CCW and CW direction of AFL wavefront was present in 103 (85.1 %) and 18 (14.9 %) subjects, respectively. In 5 cases both AFL circuit directions were observed during the procedure. Both CCW and CW AFLs had comparable CL (median 240, IQR 222-258 ms vs. median 234, IQR 217-253 ms, respectively). AFL CL was significantly longer in women than in men (median 250, IQR 227-283 ms vs. median 235, IQR 220-252 ms, p=0.043). However, women were significantly older than men (71.1±7.7 years vs. 62.8±11.5 years, p=0.001). There was weak correlation (r=0.27, p<0.01) between age and AFL CL. After exclusion of clear outliers (the youngest patient after surgery for congenital heart disease and the patient with the longest CL after complex mitral and tricuspid valve surgery), the correlation further improved (r=0.30, p<0.001). All patients with concomitant disease had significantly longer AFL CL than otherwise healthy persons: 34 (28 %) hypertensive patients (median 241, IQR 223-262 ms), 23 (19 %) CAD patients (median 239,

Fig. 1. Histogram of distribution of atrial flutter cycle length.

IQR 228-264 ms) and 21 (17 %) cardiac surgery patients (median 258, IQR 247-276 ms) vs. 28 (23 %) healthy controls (median 222, IQR 216-244 ms); p<0.05. Some patient subgroups had longer AFL CL when compared to the rest of population (Table 2). In multivariate regression analysis only age, treatment with AADs and the history of cardiac surgery were independently associated with AFL CL that increased by 6±3 ms per decade of age (p=0.036), by 11±6 ms in the presence of AADs (p=0.052), and by 26±9 ms in case of previous cardiac surgery (p=0.004), specifically by the regression equation of AFL CL [ms] = 191 + 0.6 . Age [yrs] + 11 . AADs [0=no;1=yes] + 26 . cardiac surgery [0=no;1=yes] (r=0.43, p=0.00002), while gender and the presence of structural heart disease were not independent covariates.

Short AFL CL (<200 ms) was observed in 5 (4.1 %) cases: in 2 CW AFLs (178 and 185 ms) and in 3 CCW AFLs (186, 196 and 198 ms). More detailed data are summarized in Table 3. In 4 cases of AFL with CL<200 ms arrhythmia terminated during CTI ablation. In one patient CCW AFL (CL 198 ms) converted into CW AFL during ablation with slightly longer CL (202 ms) and terminated during subsequent entrainment maneuvers. Termination of AFL with the shortest CL during CTI ablation is shown in Figure 2.

Only 1 of 78 AFLs (1.3 %) in patients with age >60 years had CL<200 ms compared to 4 of 43 AFLs (9.3 %) in patients with age ≤60 years (p<0.05).

Discussion

This is single-center, retrospective study which demonstrated that distribution of CL in CTI-dependent

Table 2. Differences in AFL CL for subgroups of patients versus the rest of population.

	Age > 60 yrs	Hypertension	Specific antiarrhythmic drugs	Structural heart disease	Cardiac surgery
Proportion of total population	78 (64 %)	72 (60 %)	54 (45 %)	56 (46 %)	21 (17 %)
AFL CL (ms) in subgroup					
Median	245	247	240	247	258
Interquartile range	228-270	224-264	223-266	227-268	247-276
AFL CL (ms) in the rest of population					
Median	223	229	232	230	230
Interquartile range	215-250	219-250	218-253	220-251	220-251
p	0.0006	0.027	0.17	0.044	0.0007

AFL – atrial flutter, CL – cycle length.

Table 3. Baseline characteristics of patients with AFL CL<200 ms.

Patient #	**1**	**2**	**3**	**4**	**5**
Cycle length (ms)	178	185	186	198	196
Gender	Male	Male	Male	Female	Male
Age (years)	60	50	46	74	49
Direction of AFL	CW	CW	CCW	CCW	CCW
Termination of AFL	Catheter ablation	Catheter ablation	Catheter ablation	Catheter ablation	Conversion to CW AFL
Arterial hypertension	Yes	Yes	No	Yes	Yes
SHD	DCM	No	No	CAD / MI	CAD
LV EF	30 %	45 %	50 %	60 %	60 %
Previous cardiac surgery	No	No	No	No	CABG
Antiarrhythmic drugs	No	β-blockers	β-blockers	β-blockers	Propafenone
History of atrial fibrillation or atypical AFL	No	No	No	No	No

AFL – atrial flutter, CL – cycle length, CW – clockwise, CCW – counterclockwise, SHD – structural heart disease, LV EF – left ventricle ejection fraction, DCM – dilated cardiomyopathy, CAD – coronary artery disease, MI – myocardial infarction, CABG – coronary artery bypass grafting.

AFL is not normal, asymmetric with right-skewed pattern with an excess of values around the mean (excessive peakedness) and at the extremes (heavy tails). This is not surprising because AFL CL depends on conduction velocity and size of the reentry circuit. The shortest CL is constrained by the existence of anatomical or functional barriers bounding AFL circuit and limited by maximum velocity of wave front propagation in atria (Waxman *et al.* 1991). On the other hand, the longest CL is theoretically unlimited depending on the presence of significant zone of slow conduction. Interestingly, distribution of CTI-dependent AFL CL has not been previously studied in detail. Table 4 summarizes relatively small studies that reported the range of CTI-dependent AFL CL from 171 ms to 350 ms, i.e. 171-350 bpm. Extremely short CL has been documented only in two studies (Lewis *et al.* 1920, Wells *et al.* 1979). In both studies the diagnosis of CTI-dependent AFL was solely based on surface ECG so that it cannot be ruled out that these studies included non-CTI-dependent arrhythmia
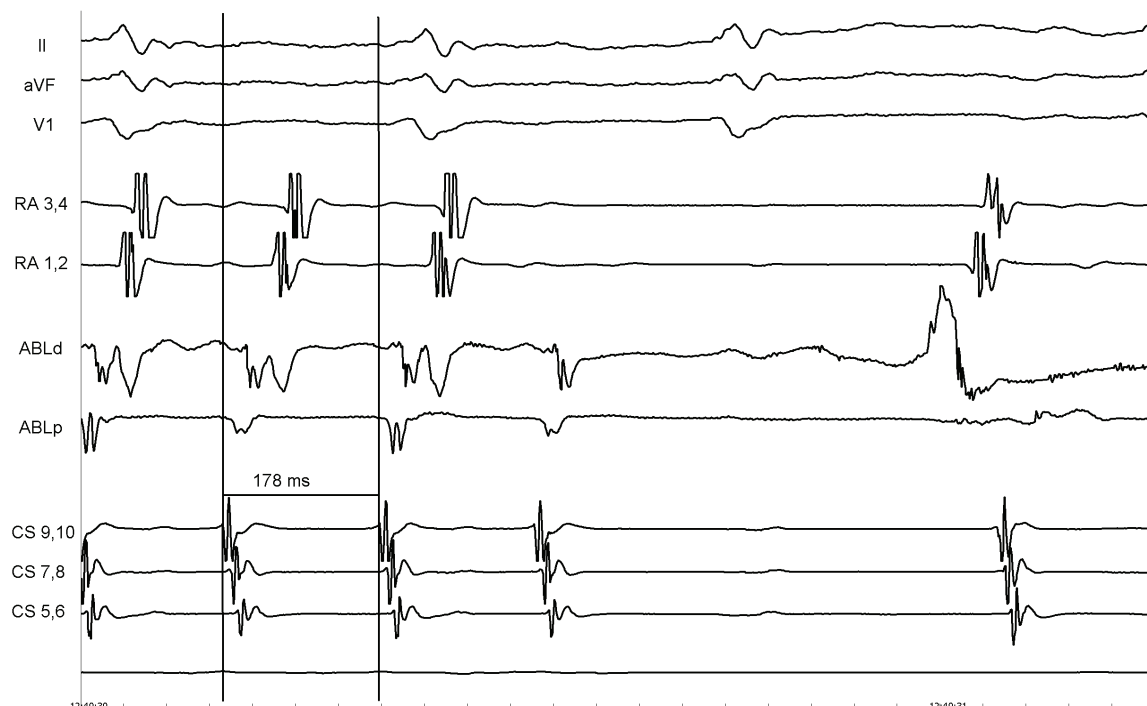
Fig. 2. Example of intracardiac signals during catheter ablation of CW AFL with the shortest CL (178 ms) at the moment of its termination. The AFL CL is marked with vertical lines. Note the missing second component of double potential in ABLd at the moment of flutter termination. II, aVF, V1 – surface ECG leads, RA – low lateral right atrium, ABLd a ABLp – ablation catheter distal and proximal pole, CS – coronary sinus.

like atypical AFL or even organized atrial fibrillation. Total 233 patients with more clearly defined CTI-dependent AFL were investigated in remaining 11 studies (Table 4) with CL range 190-350 ms, i.e. 171-316 bpm. While only in 1 of 233 cases (Calkins 1994) the CL was <200 ms, we identified 4 % of all AFLs having CL<200 ms in our study. Two explanations for this discrepancy may be offered. First, selection of patients for some of former studies, which were not designed to investigate the distribution of AFL CL, were likely biased towards clear CTI-dependent AFLs with relatively long CL. Second, in our study, the CL assessment was performed with an accuracy of ~1 ms while in previous studies the mean CL was rounded to 10-ms multiples. That is why not 5 but only 3 AFL cases (all with age ≤60 years) can be considered as having the CL clearly <200 ms in our study. Although the number of patients is limited to assess exactly the lowest margin for AFL CL, the study documents existence of CTI-dependent AFL with rather short CL.

Nevertheless, there is considerable disagreement between finding of this study (and other mentioned studies) and the CTI-dependent AFL frequency of 240-350 bpm, i.e. CL of 171-250 ms, which is frequently

reverberated in cardiology/electrophysiology textbooks. It should be stressed, that CTI-dependent AFL frequency >300 bpm (CL<200 ms) is extremely rare, while significant proportion of AFLs (36 % in our series) has CL>250 ms. Seemingly, neither very short nor excessively long CL can serve as a reliable marker of non-CTI-dependent AFL or focal atrial tachycardia. Since CTI-dependent AFL may also have an atypical surface ECG pattern (Barbato *et al.* 2009) and eccentric coronary sinus activation (Oshikawa *et al.* 2002), it is believed that entrainment from the CTI should be performed prior to transseptal puncture in all patients with apparently left AFL.

Aging is a known factor influencing atrial electrophysiological properties, specifically, slowing of intra-atrial conduction, which can give rise to the initiation of reentry. Accordingly, we have found positive correlation between AFL CL and age. Further, it is known that AFL is more prevalent in men than in women (Granada *et al.* 2000) and women are usually older at the time of presentation (Humphries *et al.* 2004). Also these facts are well in line with our data. In the present study, women had longer AFL CL than men. This difference, however, resulted from excessively prolonged AFL CL in

Table 4. List of previously published reports on CTI-dependent AFL.

Mean AFL CL (ms)	CL range (ms)	Frequency range (bpm)	N pts	Author and date
−	171-250	240-350	−	Lewis et al. (1920)
205	177-250	240-338	18	Wells et al. (1979)
235±27	205-290	207-293	10	Olshansky et al. (1990)
253±39	200-350	171-200	12	Feld et al. (1992)
258±44	190-320	187-315	16	Calkins et al. (1994)
246±26	200-320	187-300	19	Kirkorian et al. (1994)
258±26	220-290	210-270	8	Olgin et al. (1995)
−	205-310	193-293	12	Poty et al. (1995)
258±24	216-292	205-278	13	Kalman et al. (1996)
270±40	−	−	28	Cheng et al. (1999)
247±31	>200	<300	39	Narayan et al. (2005)
250±29	210-325	185-286	50	Maury et al. (2008)
261±40	−	−	26	Santucci et al. (2009)

AFL – atrial flutter, CL – cycle length.

8 women of advanced age, who had undergone cardiac surgery. This is in agreement with the results of multivariate analysis which showed that longer AFL CL in women was not gender-related. However, proportion of woman in study population was low to draw any general conclusions about gender difference in AFL CL.

Cardiac surgery was the strongest factor independently associated with longer AFL CL. Presence of advanced right atrium scarring as a result of right atrium cannulation or incision may be the explanation because majority of procedures were performed „on-pump". Nevertheless, AFL CL<200 ms was also present in one patient after cardiac surgery (CABG). Therefore, short AFL CL does not preclude the possibility of CTI-dependent AFL even in cases with a history of previous cardiac surgery.

Antiarrhythmic medication affects AFL CL. Acute administration of propafenone prolonged the AFL CL to a greater extent than did amiodarone or ibutilide (Tai et al. 1998). An impact of chronic AADs medication on AFL CL in our study seemed to be minor compared to the effects of aging and underlying heart disease.

Both CCW and CW CTI-dependent AFL had comparable CL. This finding is in agreement with previous studies (Friedman et al. 2000, Marine et al. 2001). However, we cannot rule out the possibility that our study also included the variant form of CTI dependent AFL, termed "lower loop reentry" (LLR). Compared to CTI-dependent AFL, LLR utilizes the conduction gap in terminal crest leading to short-cutting of the AFL circuit (Cheng et al. 1999, Zhang et al. 2004). Thus, not surprisingly, previous studies showed that CL in LLR was significantly shorter than that in CTI-dependent AFL (Cheng et al. 1999, Yang et al. 2001). Due to the retrospective nature of the present study, we were not able to differentiate between CTI-dependent AFL and LLR variant. Analogically, we did not study the active circuit course in the upper portion of right atrium, where substantial variability exists (Santucci et al. 2009) which can significantly affect the AFL CL. However, successful therapy of all forms of CTI-dependent AFL (including LLR) is based on achievement of conduction block across the CTI without need for detailed discrimination between these subtypes. We therefore believe that this limitation did not lead to any bias in the data analysis and practical implications.

Short-term variability of AFL CL can be influenced by various maneuvers that change right atrial volume and, thus, have a direct effect on AFL circuit size (Waxman et al. 1991, Ravelli et al. 2008, Mase et al. 2009). Unlike atrial fibrillation, where vagal excitation is associated with shortening of dominant fibrillatory CL (Takahashi et al. 2006), the CL of AFL, arrhythmia with fully excitable gap, is independent of autonomic modulation. At resting conditions, ventriculophasic and respiratory-synchronous variations in AFL CL prevail. Their impact on results of the present study was minimized by analysis of sufficiently long segment

covering several respiratory cycles.

      Co-incidence of AFL and atrial fibrillation is high. Previous studies have documented various degree of left-to-right atrium gradient of dominant frequency during sustained atrial fibrillation (Lazar *et al.* 2004). Presence of spatiotemporal organization of fibrillatory activity can mimic both CW and CCW AFL pattern on surface ECG. Similarly, extensive catheter ablation in left atrium alters ECG morphology of newly developed CTI-dependent AFL (Chyou *et al.* 2010, Shah 2011). Noninvasive differentiation of CTI-dependent AFL and atrial fibrillation is crucial for effective workflow in EP laboratory because of completely different management of both arrhythmias. New ECG-based methods were recently introduced to make correct AFL diagnosis prior to invasive electrophysiological study. Spectral ECG analysis and wavefront variability analysis were shown to be useful tools in identification differences in CTI-dependent and non-CTI-dependent AFL versus atrial fibrillation when visual separation is difficult (Hoppe *et al.* 2005). Although sophisticated methods might be helpful, simple manual measurement of AFL CL using surface ECG can be also useful. Measurement of AFL CL from standard ECG is possible with accuracy ±2 ms when assessed over 10 AFL waves which is critical for short AFL CL. According to the results of this study when AFL CL is found <200 ms, particularly in elderly patients, the diagnosis of CTI-dependent AFL is doubtful.

      In conclusion, the study described the distribution of AFL CL in larger cohort of patients with strict electrophysiological confirmation of CTI-dependent AFL. It confirmed that very short CL does not rule out the possibility of CTI-dependency. At the same time, such situation is quite rare, especially in elderly patients. This may have practical implications for the management of patients with suspected CTI-dependent AFL.

Conflict of Interest
There is no conflict of interest.

Acknowledgements

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