

Document Version

Final published version

Licence

CC BY

Citation (APA)

de Groot, N. M. S., van Staveren, L. N., Lanters, E. A. H., Yildirim, V., Hendriks, R., de Boer, R. A., Rammanah, H., & van Schie, M. S. (2026). The irregularity factor: Mechanistic insights into beat-to-beat irregularities in atrial fibrillation cycle length. *Heart Rhythm*, 23(10), 2195-2204. <https://doi.org/10.1016/j.hrthm.2026.04.059>

Important note

To cite this publication, please use the final published version (if applicable).
Please check the document version above.

Copyright

In case the licence states "Dutch Copyright Act (Article 25fa)", this publication was made available Green Open Access via the TU Delft Institutional Repository pursuant to Dutch Copyright Act (Article 25fa, the Taverne amendment). This provision does not affect copyright ownership.
Unless copyright is transferred by contract or statute, it remains with the copyright holder.

Sharing and reuse

Other than for strictly personal use, it is not permitted to download, forward or distribute the text or part of it, without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license such as Creative Commons.

Takedown policy

Please contact us and provide details if you believe this document breaches copyrights.
We will remove access to the work immediately and investigate your claim.

The irregularity factor: Mechanistic insights into beat-to-beat irregularities in atrial fibrillation cycle length

Natasja M.S. de Groot, MD, PhD,^{1,2} Lianne N. van Staveren, MD,¹ Eva A.H. Lanthers, MD, PhD,¹ Vehpi Yildirim, PhD,¹ Richard Hendriks, PhD,² Rudolf A. de Boer, MD, PhD,¹ Hemanth Rammanah, MD, PhD,³ Mathijs S. van Schie, PhD¹

ABSTRACT

BACKGROUND Measures derived from the atrial fibrillation (AF) cycle length (AFCL) are used to identify regions crucial for AF maintenance or predict (ablation) treatment outcomes. However, mechanisms underlying *beat-to-beat* irregularities in AFCL are unknown.

OBJECTIVE We aimed to (1) investigate *beat-to-beat* changes in AFCL (Δ -AFCL) by relating temporal variation in AFCL with quantified beat-to-beat changes in activation patterns and conduction times (Δ -CTs) and (2) test whether the irregularity factor (IF) (standard deviation of the Δ -AFCL histogram) is indicative of the complexity of activation patterns.

METHODS Mapping was performed in 24 patients with long-standing persistent AF (LSPAF) and a reference group ($n = 25$, patients with induced [acute] AF). At the mapping area center, Δ -AFCL was calculated by subtracting each AFCL from the preceding AFCL and related to causes of Δ -CT ($CT_{(N)} - CT_{(N-1)}$) of fibrillation waves from the electrode array border toward the mapping area center.

RESULTS The IF was larger during LSPAF (52 ± 17 vs 25 ± 10 ; $P < .001$) than during acute AF. Δ -CTs were also larger (25 ± 8 ms vs 19 ± 7 ms; $P = .005$) and caused by beat-to-beat changes in conduction velocity (36 ± 6 cm/s vs 29 ± 6 cm/s; $P = .001$) and beat-to-beat changes in direction ($94^\circ \pm 13^\circ$ vs $64^\circ \pm 22^\circ$; $P < .001$); beat-to-beat changes in path length (13 ± 4 mm vs 14 ± 3 mm; $P = .333$) were comparable. The IF correlated with conduction block [probability (p) = 0.887], lines of conduction block lengths ($p = 0.900$), number of fibrillation waves ($p = 0.889$), and prevalence of focal waves ($p = 0.609$) ($P < .001$ for all).

CONCLUSION The IF indicates the underlying complexity of activation patterns, is higher during LSPAF than during acute AF, and is comparable throughout the atria during LSPAF. It is a novel, easy-to-calculate, objective electrical biomarker, which can be used for, for example, guiding patient-tailored treatment independently of the AF mechanisms.

KEYWORDS atrial fibrillation; biomarker; cardiac surgery; diagnostic tool; mapping; mechanisms

(Heart Rhythm 2026;23:2195–2204) © 2026 Heart Rhythm Society. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

The hallmark of the most common arrhythmia atrial fibrillation (AF) is the spatiotemporal irregularity in the AF cycle length (AFCL).¹ AFCL, defined as the interval between successive fibrillation waves, is determined by the action potential duration (refractory period) and an excitable period. Variation in excitable periods, in turn, gives rise to interval-dependent changes in action potential duration and conduction velocity (CV).²

The AFCL assessed during catheter ablation procedures has been proposed as a measure to, for example, identify regions crucial for AF maintenance or predict treatment outcomes.^{3,4} If AF depends on a single discharging source, irregularities in AFCL may occur as a result of variation in the excitation frequency of the source itself.⁵ In case of fibrillatory conduction in the presence of source(s) or multiple wavelets, irregularities in AFCL can also be explained by

From the ¹Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands, ²Department of Microelectronics, Signal Processing Systems, Faculty of Electrical, Engineering, Mathematics and Computer Sciences, Delft University of Technology, Delft, The Netherlands, and ³Department of Cardiology, Haga Hospital, The Hague, The Netherlands.

<https://doi.org/10.1016/j.hrthm.2026.04.059>

1547-5271/© 2026 Heart Rhythm Society. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

beat-to-beat changes in conduction of fibrillation waves.⁶ Beat-to-beat changes in conduction of fibrillation waves result in variable excitable periods because of different “waiting times” for the next fibrillation wave to arrive.

Both experimental and clinical mapping studies have demonstrated that AF persistence is associated with an increase in spatiotemporal irregularity in AFCL.^{7,8} However, the exact mechanism underlying beat-to-beat irregularities has never been investigated.

The goals of the present study were therefore to (1) investigate beat-to-beat irregularities in AFCL by relating temporal variation in fibrillation intervals with quantified beat-to-beat changes in patterns of activation and conduction times (Δ -CTs) and (2) test whether the irregularity factor (IF), a novel measure of beat-to-beat irregularities in AFCL, is indicative of the complexity of the underlying arrhythmogenic substrate.

Methods

Database of fibrillation maps

Mapping data were derived from a database containing a unique reference group, namely, 25 young patients with Wolff-Parkinson-White syndrome [16 (64%)] men; mean age 32 ± 11 years), sinus rhythm, and a normal left atrial (LA) size of 39 ± 6 mm, and 24 patients [14 (58%)] men; mean age 64 ± 9 years) with structural heart disease and long-standing persistent AF (LSPAF). In the first group, AF was induced by programmed electrical stimulation from the right atrial (RA) appendage. In the latter group, the LAs were dilated (anteroposterior dimension 58 ± 9 mm) and the left ventricular ejection fraction was $50\% \pm 12\%$. A detailed description of the study population and mapping technology has been published previously.^{8–11} This historical data set containing 6000 “beats” was also selected because of the large mapping array enabling detailed investigation of the activation patterns and the reference group consisting of healthy subjects, which, at present, no longer undergo open-chest surgery.

Sequential unipolar epicardial mapping of the RA and LA was performed after sternotomy and before cardiopulmonary bypass. The lateral walls of the RA and LA were mapped with a spoon-shaped electrode containing 244 unipolar electrodes (diameter 3.6 cm; inter-electrode distance 2.25 mm).

For the LA posterior wall, a smaller rectangular array of 8×8 electrodes was used (interelectrode distance 2.5 mm). Fibrillation electrograms were recorded with a custom-made 256-channel mapping system (bandwidth 0.5–500 Hz; sampling rate 1 kHz; resolution 12 bits). In patients with sinus rhythm at the onset of the mapping procedure, paroxysms of AF were induced by rapid atrial pacing.

In total, 313 seconds of acute AF and 598 seconds of LSPAF were analyzed, resulting in 6000 fibrillation maps, divided into 4 groups: RA free wall recorded during acute AF ($n = 2226$) and RA free wall [right atrial free wall (RAFW), $n = 1401$], LA lateral wall ($n = 1854$), and posterior atrium (PV, $n = 1148$) recorded during LSPAF.

Wave mapping using a custom-made software package was used to construct fibrillation maps. This mapping approach applies an algorithm that decomposes the complex spatiotemporal activation during AF into its individual elements (multiple fibrillation waves), as previously described in detail.^{9,10,12}

Assessment of AF regularity

At each electrode, fibrillation intervals were determined by measuring the time between activation by consecutive fibrillation waves. An AFCL histogram of all electrodes was constructed from these fibrillation intervals to determine the mean AFCL and spatiotemporal variation expressed as the difference between the 90th and the 10th percentile.

To examine whether there were episodes of regular cycles during AF, we calculated how often consecutive AF cycles differed ≤ 10 ms from each other. The incidence of each of these series of regular AF cycles was then determined for every mapping site.

Beat-to-beat irregularity (beat-to-beat changes in AFCL [Δ -AFCL]): The IF

Irregularities in AFCL were studied by computing beat-to-beat interval variation histograms by subtracting each fibrillation interval from the preceding interval (beat-to-beat changes in AFCL [Δ -AFCL] = Δ -AFCL_(N) – AFCL_(N-1)). The degree of irregularity in AFCL is expressed as the IF, which is the standard deviation (SD) of the Δ -AFCL histogram.

Variation in trajectories of fibrillation waves causing Δ -AFCL

Variation in trajectories of fibrillation waves causing Δ -CT (CT_(N) – CT_(N-1)) were quantified and related with Δ -AFCL. For this purpose, 9 electrodes located at the center of the circular mapping area were selected, as the distance from each entrance point of a fibrillation wave in the circular mapping area to the center electrode is approximately equivalent. For this analysis, we used only the large 3.8×3.8 cm fibrillation maps obtained from the RA free wall.

In each wave map, fibrillation waves activating the center electrode were identified. The moment of entrance of a fibrillation wave into the mapping area was defined as T = 0 ms. The CT from the entry site of the mapping area toward the center electrodes was measured. For each fibrillation wave, the length of its trajectory and CV was determined as previously described in detail.^{8,9}

Causes of Δ -CT of fibrillation waves from the border of the electrode array toward the center of the mapping area were analyzed in each fibrillation map. Fibrillation maps were used to assign a change in the relative activation time of the center

Abbreviations

AF: Atrial fibrillation

AFCL: Atrial fibrillation cycle length

CT: conduction time

CV: conduction velocity

IF: Irregularity Factor

LA: left atrium

LSPAF: long-standing persistent atrial fibrillation

PV: pulmonary vein area

PL: length of the pathway

RA: right atrium

area to one or more of the following phenomena: (1) alterations in CVs, (2) *direction of propagations* (defined as a difference of $>30^\circ$ between entrances of successive fibrillatory waves into the mapping area), and/or (3) changes in lengths of the pathways of fibrillation waves toward the center electrode (PL).

The IF as indicator of electropathology

In prior mapping studies, we determined in this same study population the prevalence of conduction block, the length of lines of conduction block, the number of fibrillation waves, and prevalences of focal ("epicardial breakthrough") waves. To test whether the IF can be used as an electrical biomarker of electropathology related to AF persistence, we correlated the IF with these parameters.

Statistical analysis

All data were tested for normality. Normally distributed data are expressed as mean $\pm$ SD, whereas skewed data are presented as median (interquartile range). For normally distributed data, an independent Student *t* test was used to determine differences in electrical properties between patients with acute AF and those with LSPAF, whereas nonparametric tests including Mann-Whitney *U* tests were used in case of skewed data. A χ^2 test was used to compare data in >2 categories. Correlations between electrical parameters were tested using the Pearson test or Spearman ρ test. A *P* value $<.05$ was considered statistically significant.

Results

The left panel of Figure 1 shows the mean AFCL for each patient individually in the 4 different patient groups. The AFCL at the RA wall in the patients with acute AF ranged from 124 to 205 ms; and in the patients with LSPAF, from 116 to 236 ms; fibrillation intervals during LSPAF were longer (178 ± 30 ms vs 159 ± 25 ms; $P = .019$). Neither minimum AFCL nor the 5th percentile (*P*) of the AFCL histogram differed between patients with acute AF and LSPAF (*P*0: 85 [68–99] ms vs 80 [69–99] ms, $P = .170$; *P*5: 121 [102–148] ms vs 109 [98–117] ms, $P = .193$). During LSPAF, fibrillation intervals recorded at the RA, LA, and pulmonary veins (PV) were comparable (AFCL: RA: 178 ± 30 ms; LA: 168 ± 27 ms; PV: 172 ± 31 ms; $P = .523$). There were no differences in mean AFCL between patients who did or did not use of antiarrhythmic drugs (174 ± 29 ms vs 180 ± 32 ms; $P = .719$). Spatiotemporal variation in AFCL during LSPAF was significantly higher than during acute AF (*P*90–*P*10: 100 ± 32 ms vs 56 ± 25 ms; $P < .0001$). In patients with LSPAF, there were no regional differences in spatiotemporal variation in AFCL (*P*90–*P*10: RA: 100 ± 32 ms; LA: 99 ± 50 ms; PV: 126 ± 39 ms; $P = .119$).

Temporal irregularity in fibrillation intervals

Prevalences of series of regular episodes during acute AF and LSPAF are demonstrated in the right panel of Figure 1. In all 4

groups, regular episodes consisting of >5 consecutive AF cycles differing <10 ms from preceding cycles were rare, though regular episodes occurred more frequently during acute AF at the RA (acute AF: 3.21%; LSPAF: RA: 0.88%, LA: 2.02%, PV: 1.36%; $P < .001$).

Beat-to-beat irregularity in fibrillation intervals

Beat-to-beat irregularity (Δ -AFCL) in all successive fibrillation intervals recorded at each mapping site in the 4 different groups is plotted in the left panel of Figure 2. The IF (SD of the histogram) during LSPAF at the RAFW was 48 ms, which was remarkably higher than the IF during acute AF (27 ms; $P < .001$). Within the LSPAF group, there were no significant differences between the IF at the RA (48 ms), LA (42 ms), or PV (53 ms) ($P = .430$). The IF for each individual patient is plotted in the right panel of Figure 2. Despite considerable interindividual variation in fibrillation intervals in both the acute AF and LSPAF groups, Δ -AFCL in patients with LSPAF was longer and more irregular.

Beat-to-beat variations in trajectories of fibrillation waves

Figure 3 shows typical RA successive wave maps of 3 consecutive fibrillation waves demonstrating the impact of Δ -CT caused by beat-to-beat changes in CV (Δ -CV) (upper panel) and propagation direction (Δ -direction) (lower panel) on AFCL. In the upper panel, time between the first-to-second and the second-to-third fibrillation wave entering the mapping area and activating the center is 214 and 208 ms, respectively ("source interval"; AFCL of the corresponding source interval [AFCL_s]). In every beat, the fibrillation wave enters the mapping array at nearly the same site ("linked fibrillation waves") propagating with only moderate alterations in CVs. This results in successive CTs to one of the center electrodes of 38, 25, and 32 ms, respectively. Consequently, AFCL at the center electrode (AFCL_c) (defined as $\text{AFCL}_s + [\Delta\text{-CT} = \text{CT}_{(N)} - \text{CT}_{(N-1)}]$) equals 201 and 215 ms, respectively.

In the lower panel of Figure 3, 3 consecutive fibrillation waves activating a part of the center area entering the mapping array from 3 different directions, particularly between the second and the third beat, arrive with source intervals of 173 and 157 ms. The subsequent changes in propagation direction of these fibrillation waves caused variations in CT of successively 36, 25, and 49 ms, giving rise to an AFCL_c of 162 and 181 ms. Hence, in these 2 examples, slowing of conduction of either linked fibrillation waves and/or alterations in propagation direction caused prolongation of AFCL_c.

Spatial variations in trajectories of fibrillation waves can also be the result of lengthening or shortening of the distance toward the center of the mapping area caused by lines of conduction block or focal waves, respectively. Typical fibrillation maps demonstrating the relation between these phenomena and variations in AFCL are shown in Figure 4.

The successive wave maps in the upper panel of Figure 4 show that the center of the RA free wall is activated by a

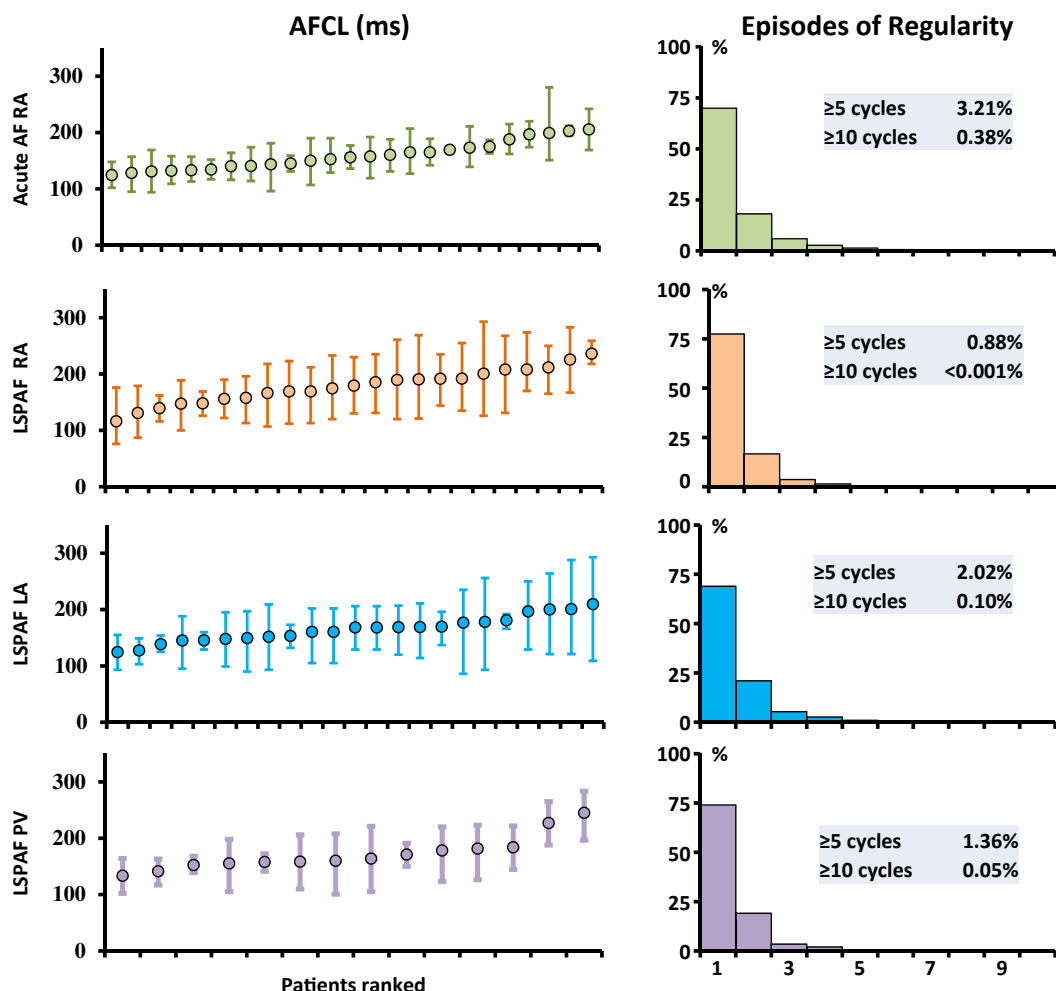


Figure 1

Left panel: The 10th percentile of atrial fibrillation cycle length (AFCL), mean AFCL, and the 90th percentile of AFCL plotted for every individual patient in each of the 4 patient groups. Right panel: Histograms demonstrating relative prevalences of regular atrial fibrillation (AF) episodes of variable length. See text for additional explanation. LA = left atrium; LSPAF = long-standing persistent atrial fibrillation; PV = pulmonary veins; RA = right atrium.

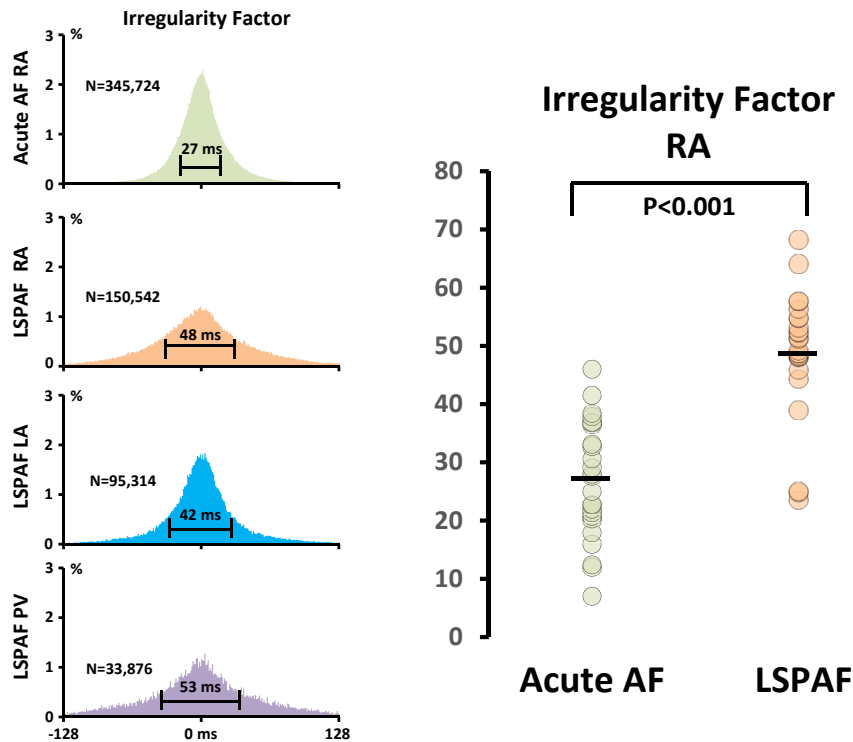
fibrillation wave entering the mapping area from the lower right corner in all 3 successive beats. In the first beat, the fibrillation wave propagates toward the center in 38 ms. Due to curving of its trajectory, the conduction time increases to 48 ms in the second beat. The long line of conduction block in the third beat causes further lengthening of the trajectory of the fibrillation wave activating the center area, thereby prolonging the conduction time up to 66 ms. As a result, $AFCL_c$ prolongs from 159 to 166 ms.

In the lower panel of Figure 4, the first fibrillation wave enters the mapping area from the right and conducts in 46 ms toward the center area. An epicardial breakthrough then arises in the middle of the mapping area. As the distance from the breakthrough origin to the center area is smaller, the CT is shortened by 21 ms. The following fibrillation wave enters the mapping area again from its border, resulting in an increase in CT and hence prolongation of AFCL by 50 ms. However, as the focal wave does not emerge at the border of the mapping area, the true Δ -CT across a distance of 1.8 cm cannot be calculated.

The mean AFCL at the 9 center electrodes in acute AF and LSPAF was 152 ± 35 and 161 ± 50 ms, respectively ($P < .001$), and Δ -AFCL was 27 and 52 ms, respectively. The mean AFCL did not correlate with IF [acute AF: probability (ρ) = -0.310 , $P = .160$; LSPAF: $\rho = 0.459$, $P = .055$].

Histograms in the upper panel of Figure 5 show relative prevalences of all Δ -AFCLs and Δ -CTs measured at the 9 central electrodes in patients with acute AF or LSPAF. Compared to the acute AF group, beat-to-beat variations in trajectories of fibrillation waves during LSPAF caused significantly larger Δ -CTs (SD Δ -CT: 19 ± 7 ms vs 25 ± 8 ms; $P = .005$).

Histograms in the middle and lower panels of Figure 5 show relative prevalences of Δ -CVs and beat-to-beat changes in path length (Δ -PL), respectively; Δ -CVs of linked fibrillation waves were significantly larger in the LSPAF group (SD Δ -CVs: 36 ± 6 cm/s vs 29 ± 6 cm/s; $P = .001$). However, there was no significant difference in Δ -PL during acute AF and LSPAF (SD Δ -PL: 13 ± 4 mm vs 14 ± 3 mm; $P = .333$) but Δ -directions of consecutive fibrillation waves propagating toward the center were again larger in patients with LSPAF (SD Δ -direction: $94^\circ \pm 13^\circ$ vs $64^\circ \pm 22^\circ$; $P < .001$).

**Figure 2**

Left panel: Histograms demonstrating relative prevalences of beat-to-beat changes in atrial fibrillation cycle length (Δ -AFCL). The standard deviation of the Δ -AFCL histogram represents the irregularity factor (IF). Right panel: The right atrial (RA) IF for each individual patient in the acute atrial fibrillation (AF) and long-standing persistent atrial fibrillation (LSPAF) groups. LA = left atrium; PV = pulmonary veins.

Thus, both the phenomena of increased Δ -CVs and Δ -directions caused larger Δ -CTs during LSPAF.

Δ -AFCL correlated significantly with Δ -CT ($\rho = 0.906$; $P < .001$) in patients with acute AF. However, in patients with LSPAF, there was no correlation between Δ -AFCL and Δ -CT ($\rho = -0.092$; $P = .717$). The IF at the center area was comparable to that in the entire mapping area, significantly larger during LSPAF than during acute AF (IF: 52 ± 17 ms vs 25 ± 10 ms; $P < .001$).

The IF: Indicator of the arrhythmogenic substrate?

In order to determine whether the IF is a suitable electrical biomarker for identification of the arrhythmogenic substrate associated with LSPAF, we correlated the IF with the prevalence of conduction block, the length of lines of conduction block, the number of fibrillation waves, and the prevalence of focal waves as determined in prior mapping studies. As demonstrated in Figure 6, the IF correlated significantly with all parameters (prevalence of conduction block: $\rho = 0.887$, $P < .001$; length of lines of conduction block: $\rho = 0.900$, $P < .001$; number of fibrillation waves: $\rho = 0.889$, $P < .001$; prevalence of focal waves: $\rho = 0.609$, $P < .001$).

Discussion

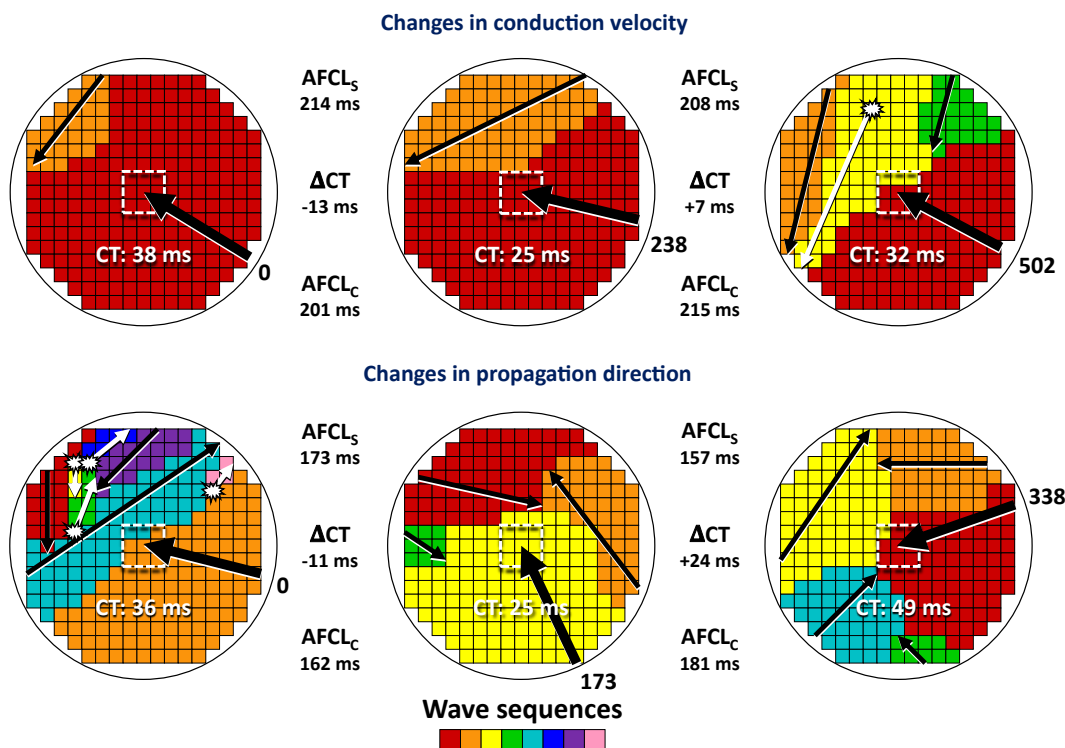
The key findings of this study are that (1) the IF, a novel, simple to determine measure of beat-to-beat irregularities in AFCL, assessed during LSPAF in patients with cardiovascular

diseases is considerably higher than that assessed during acute AF in young patients with normal atria, (2) the IF is a good indicator of the complexity of the arrhythmogenic substrate underlying AF and correlates with electrical properties associated with AF persistence, and (3) the IF throughout the atria during LSPAF is comparable. In addition, we demonstrated the impact of the various beat-to-beat changes in patterns of activation on irregularities in fibrillation intervals.

AFCL

In both the acute AF and LSPAF groups, marked interindividual differences in mean AFCL were found. This finding is in line with prior studies that also reported on interindividual differences in mean AFCL, even in patients with similar clinical profiles.^{13,14} The mean AFCL during LSPAF in our population was longer than that during acute AF (178 ms vs 159 ms). This observation could not be explained by pharmacological therapy, as there was no difference in mean AFCL between patients who did or did not use antiarrhythmic drugs.

It is generally assumed that LSPAF induces shortening of the refractory period and reversal of rate adaptation, resulting in the well-known concept of "AF begets AF."^{6,15} Shortening of atrial refractoriness decreases atrial wavelength, and when the wavelength becomes shorter, the atria can contain more wavelets and AF becomes more persistent. Because of the increased number of circulating wavelets, intervals between activations by consecutive fibrillatory waves become

**Figure 3**

3 successive right atrial color-coded wave maps from the middle of the right atrium constructed during acute atrial fibrillation demonstrating the effect of changes in conduction velocity (upper panel) and propagation direction (lower panel) on the atrial fibrillation cycle length in the 9 center electrodes, encircled by the white dashed lines. Individual fibrillation waves are represented by different colors according to their sequence of appearance (color scale at the bottom), and arrows indicate their main trajectories. The thick-lined trajectories belong to fibrillation waves activating one or more of the center electrodes. Sites of focal waves are indicated by white asterisks and their trajectories by white arrows. $AFCL_s$ = atrial fibrillation cycle length at one of the center electrodes; $AFCL_c$ = atrial fibrillation cycle length of the corresponding source interval; CT = conduction time from the border of the mapping array to one of the center electrodes; Δ -CT = beat-to-beat changes in conduction time from the border of the mapping array to one of the center electrodes.

shorter, thereby decreasing the excitable period. Comparable to prior studies,¹⁶ we also used the 5th percentile or the minimum of AFCL as an estimation for the refractory period during AF but we did not find a difference in atrial refractoriness during acute AF and LSPAF. Absence of a difference in the “shortest” fibrillation interval between patients with acute AF and those with LSPAF could be explained by the fact that the 5th percentile or minimum AFCL does not equal the refractory period and that an excitable period to a variable degree is present. Prolongation of AFCL has been attributed to atrial dilatation and heart failure.^{14,17}

Long fibrillation intervals despite shortening of atrial refractoriness by electrical remodeling in patients with LSPAF can be explained by the higher prevalence of multiple areas of conduction block compared to patients with acute AF. Areas of conduction block either increase Δ -CT by curving of the fibrillation waves trajectories and subsequently slowing of conduction or by lengthening of their pathways, causing a longer waiting time for atrial myocytes to be activated by the next fibrillatory wave.

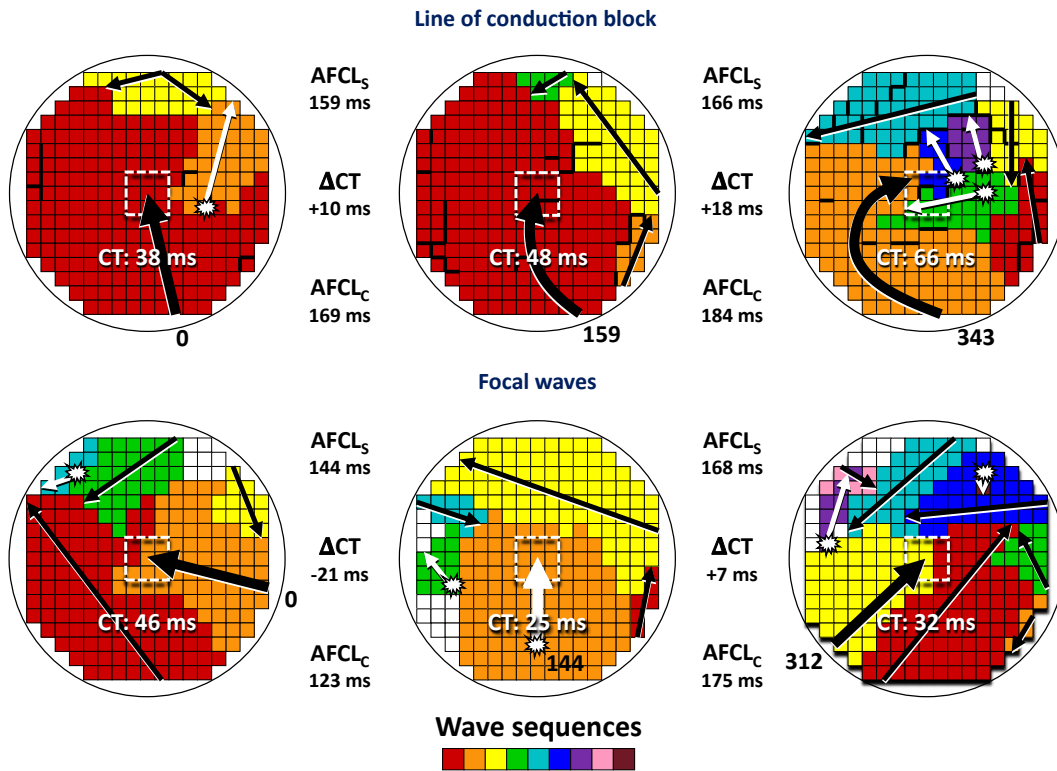
There were also no differences in AFCL between the RA and LA mapping sites during LSPAF. This finding is consistent with prior studies demonstrating the absence of a left-to-right gradient in patients with persistent AF and advanced structural remodeling.^{18–20}

Series of regular episodes

It is assumed that episodes of regular AFCL represent repetitive atrial activation patterns that may play a role in the initiation and perpetuation of AF and may therefore be suitable target sites for ablation.^{21–23} However, the occurrence of series of regular episodes was rare in all our patients despite the fact that our mapping arrays covered large parts of the RA and LA. If a stationary driver was present, it would have been disclosed as an area with a short AFCL driving the fibrillatory process or by continuous linking of fibrillation waves. Also, we most likely would have encountered it at least once. Yet, a nonstationary driver with fibrillatory conduction cannot be excluded.

Mechanisms underlying irregularities in AFCL

This study provides novel insight into the relation between Δ -CT and Δ -AFCL. Δ -CT indicates the degree to which Δ -AFCL are caused by changes in conduction of fibrillation waves within 1.8 cm of the mapping area propagating toward the center electrodes. We assumed that the electrophysiological properties of atrial tissue outside the mapping area are comparable with tissue beneath the mapping array. This assumption is supported by the observation that in all patients, source intervals did not differ from center fibrillation intervals.

**Figure 4**

3 consecutive color-coded right atrial wave maps constructed during long-standing persistent atrial fibrillation demonstrating the effect of a line of conduction block (upper panel) and focal waves (lower panel) on the atrial fibrillation cycle length in the 9 center electrodes, encircled by the white dashed lines. Individual fibrillation waves are represented by different colors according to their sequence of appearance (color scale at the bottom), and arrows indicate their main trajectories. The thick-lined trajectories belong to fibrillation waves activating one or more of the center electrodes. Sites of focal waves are indicated by white asterisks and their trajectories by white arrows. AFCL_c = atrial fibrillation cycle length at one of the center electrodes; AFCL_s = atrial fibrillation cycle length of the corresponding source interval; CT = conduction time from the border of the mapping array to one of the center electrodes; Δ-CT = beat-to-beat changes in conduction time from the border of the mapping array to one of the center electrodes.

In patients with LSPAF, slowing of conduction and Δ-direction caused larger Δ-CT than in patients with acute AF, which can be attributed to the higher degree of nonuniform anisotropic conduction caused by AF-induced structural remodeling.^{6,11}

In patients with acute AF, an increase in Δ-AFCL can be explained by an increase in Δ-CT caused by Δ-CV, Δ-direction, or increased pathway length toward the center electrodes caused by lines of conduction block. However, the effects of these different phenomena on beat-to-beat changes in AFCL_c (Δ-AFCL_c) may be counteracted by beat-to-beat changes in AFCL_s. For example, a fibrillation wave entering the mapping area with a short “source” interval may conduct considerably slower to the center electrodes, thereby “regularizing” AFCL_c and reducing Δ-AFCL_c.

In patients with LSPAF, we did not find a relation between Δ-AFCL_c and Δ-CT. The absence of this correlation could be attributed to the high prevalence of focal fibrillation waves during LSPAF. The contribution of focal waves to Δ-CT and Δ-AFCL could not be accurately calculated because the source is outside the view of the mapping array and thus the true CT and hence also the Δ-CT across a distance of 1.8 cm could not be calculated. A focal wave may preexcite the center electrodes, thereby shortening AFCL_c. However, when conduction of the focal wave toward the

center is slow or when the expanding wavefront encounters a long line of conduction block around which it must turn, shortening of AFCL is diminished or may even be prolonged. Focal waves therefore give rise to a variable degree of preexcitation and thus a large Δ-AFCL.

The IF: An easy-to-measure electrical biomarker?

We previously demonstrated that by comparing fibrillation maps obtained from patients with acute AF and LSPAF, AF persistence was characterized by a high prevalence of conduction, block, long lines of conduction block, increased tissue anisotropy, and a high number of fibrillation waves, particularly of focal fibrillation waves.^{9–11} The IF correlated significantly with all these parameters suggesting that the IF is a suitable indicator of the complexity of the arrhythmogenic substrate underlying AF. Hence, the IF could serve as an objective electrical biomarker to “stage” AF according to the complexity of the activation patterns. The IF can be easily determined without the necessity of high-resolution activation maps and in contrast to AFCL directly reflects the complexity of patterns of activation. Also, the IF in the RA and LA were comparable. We also demonstrated by performing simultaneously mapping of the RA endo- and epicardium that there is no difference in

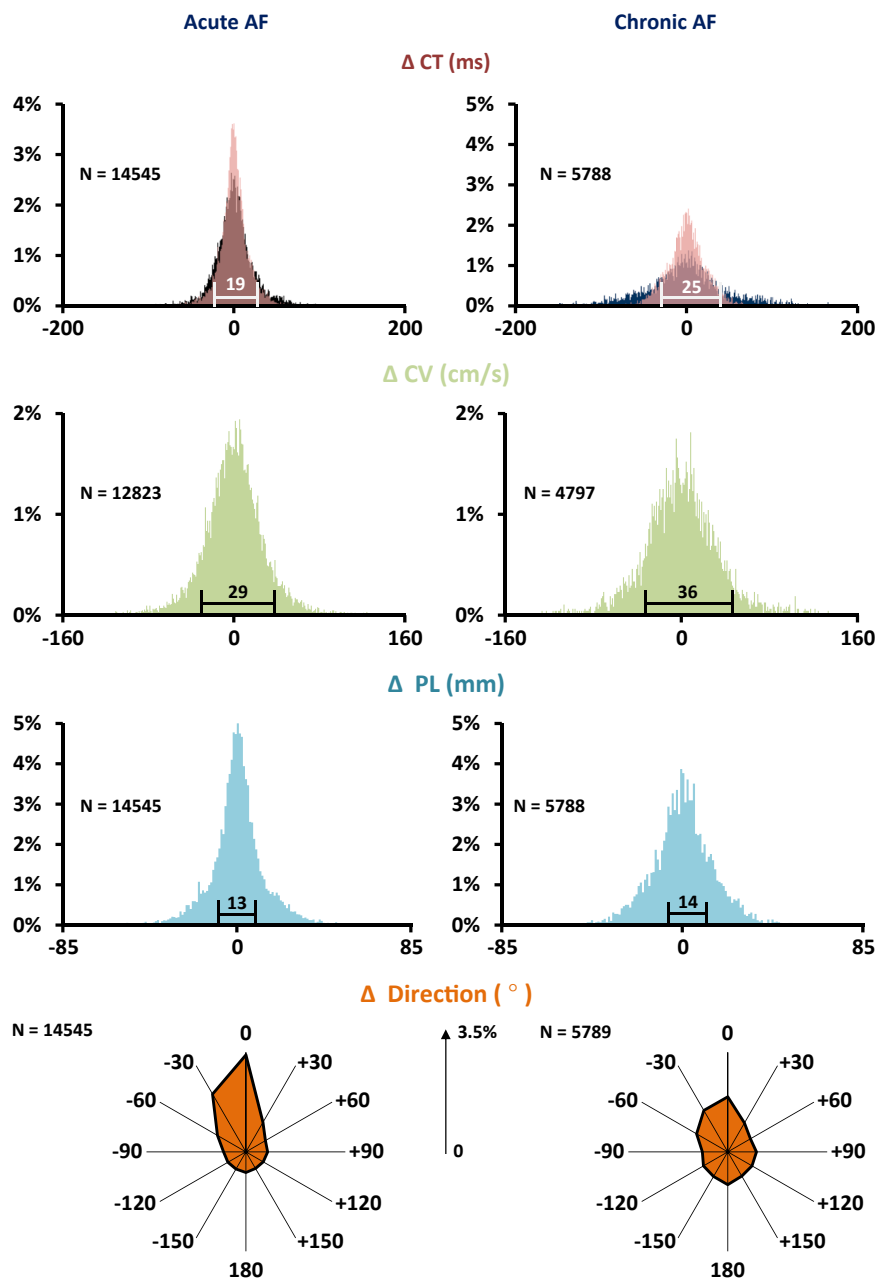


Figure 5

Histograms demonstrating relative incidences of all beat-to-beat changes in conduction time (Δ CT) during acute atrial fibrillation (AF) (left panel) and long-standing persistent AF (right panel) plotted on the top of histograms demonstrating relative prevalences of beat-to-beat changes in AF cycle length (upper panel), relative prevalences of beat-to-beat changes in conduction velocity (Δ CV) and beat-to-beat changes in path length (Δ PL) (middle panels), and changes in propagation direction (Δ -direction) (lower panel).

AFCL between both sites. We also demonstrated that the electrical properties (eg, number of fibrillation waves, prevalence of focal waves, conduction abnormalities, degree of anisotropy, and potential morphology such as degree of fractionation and unipolar voltages) of the endo- and epicardium are comparable between both layers. Hence, the epicardial IF will not differ from the endocardial IF. However, because of areas of electrical endo-epicardial asynchrony in patients with persistent types of AF, localized endo-epicardial differences in the IF may occur. Although the outcomes of this study are promising, additional studies are required to

demonstrate the clinical relevance of the IF. In a following study, the predictive value of the IF for AF recurrences after pulmonary vein isolation will be determined. If the IF is indeed a suitable electrical biomarker, it can be used to guide patient-tailored (ablation) therapy by, for example, stratifying patients to pulmonary vein isolation only or additional ablation approaches in case of a high IF.

Study limitations

We used a historical data set, so clinical data are limited and blood- or tissue-based biomarkers are not available. Our

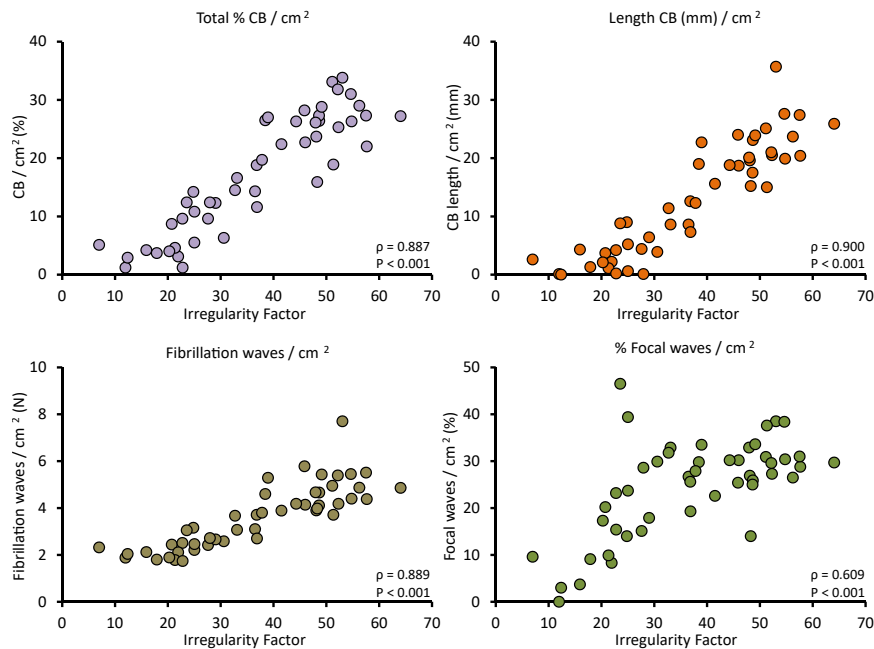


Figure 6

Scatter plots demonstrating the relation between the irregularity factor and a high prevalence of longitudinal dissociation in conduction (*upper left panel*), long lines of conduction block (CB) (*upper right panel*), a high number of fibrillation waves (*lower left panel*), and a high prevalence of focal waves (*lower right panel*).

measurements were performed during cardiac surgery in specific patient groups, and the value has not been investigated in patients with AF and without structural heart disease. However, based on data from the literature, there is no reason to assume that the relation between activation patterns and Δ -AFCL is different in patients with LSPAF and without structural heart disease. Also, only the RA was mapped in patients with induced AF.

Competency in medical knowledge

The hallmark of the most common arrhythmia AF is the spatiotemporal irregularity in AFCL. However, the exact mechanism underlying *beat-to-beat* irregularities in AFCL have so far not been understood. This study was the first to (1) investigate the nature of *beat-to-beat* irregularities in AFCL by relating temporal variation in fibrillation intervals with quantified *beat-to-beat* changes in patterns of activation and (2) test whether the IF, a novel measure of *beat-to-beat* irregularities in AFCL, is indicative of the complexity of the underlying arrhythmogenic substrate. *Beat-to-beat* irregularities in AFCL are caused by Δ -CV, propagation direction of fibrillation waves, shortening or lengthening of the path length of fibrillation waves by focal waves and lines of conduction block, respectively. The IF is a novel, easy-to-calculate, objective electrical biomarker of the complexity of the arrhythmogenic substrate that can be used for personalized AF therapy.

Translational outlook

The IF derived from *beat-to-beat* irregularities in AFCL is a strong indicator of the complexity of the activation patterns

during AF and may therefore be a suitable novel electrical biomarker of the “stage” of AF. In patients with LSPAF, the IFs in the RA and LA are comparable. The IF is the SD of the Δ -AFCL histogram and can therefore be easily calculated from fibrillation electrograms only. Consequently, any mapping technology can be used for calculation of the IF during a period as short as 10 seconds. The next step is to demonstrate that the IF determined before AF ablation therapy is a predictor of treatment outcome, for example, AF recurrences after pulmonary vein isolation. Subsequently, it has to be determined whether the IF can be used to provide patient-tailored (ablation) therapy by, for example, stratifying patients to pulmonary vein isolation only or additional substrate-based ablation approaches. For example, a low IF indicates a limited arrhythmogenic substrate and hence pulmonary vein isolation could suffice. In contrast, an intermediate IF could indicate that a substrate-based approach is beneficial, whereas a high IF indicates that the arrhythmogenic substrate is too extensively present and additional ablation procedures may therefore not be successful. Instead, rate control should be chosen.

Conclusion

Beat-to-beat irregularities in AFCL are caused by Δ -CV, propagation direction of fibrillation waves, shortening or lengthening of the pathlength of fibrillation waves by focal waves and lines of conduction block, respectively. The IF, a measure of *beat-to-beat* differences in AFCL, assessed during LSPAF in patients with coronary and/or valvular heart disease, is considerably higher than that assessed during acute AF in young patients with normal atria. The IF is indicative of the

complexity of patterns of activation during AF, irrespective of the AF mechanism, and may therefore be a suitable novel electrical biomarker of the “stage” of AF and to guide personalized AF therapy.

Funding Sources: Dr de Groot was funded by Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO) through the CIRCULAR project (NWA.1389.20.157).

Disclosures: The authors have no conflicts of interest to disclose.

Address reprint requests and correspondence: Dr Natasja M.S. de Groot, Department of Cardiology, Unit Translational Electrophysiology, Erasmus University Medical Center, PO Box 616, Dr Molenwaterplein 40, 3015GD Rotterdam, The Netherlands. E-mail address: nmsdegroot@yahoo.com

References

- de Groot NMS, Shah D, Boyle PM, et al. Critical appraisal of technologies to assess electrical activity during atrial fibrillation: a position paper from the European Heart Rhythm Association and European Society of Cardiology Working Group on eCardiology in collaboration with the Heart Rhythm Society, Asia Pacific Heart Rhythm Society, Latin American Heart Rhythm Society and Computing in Cardiology. *Europace* 2022;24:313–330.
- Kleber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. *Physiol Rev* 2004;84:431–488.
- Di Marco LY, Raine D, Bourke JP, Langley P. Characteristics of atrial fibrillation cycle length predict restoration of sinus rhythm by catheter ablation. *Heart Rhythm* 2013;10:1303–1310.
- Nakamura H, Niwano S, Fukaya H, et al. Fibrillation cycle length predicts cardiovascular events in patients with long-standing persistent atrial fibrillation. *Heart Vessels* 2022;37:1027–1033.
- Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res* 2002;54:204–216.
- de Groot NMS, Kleber A, Narayan SM, et al. Atrial fibrillation nomenclature, definitions, and mechanisms: position paper from the international Working Group of the Signal Summit. *Heart Rhythm* 2025;22:1480–1491.
- Sih HJ, Zipes DP, Barbari EJ, Adams DE, Olgin JE. Differences in organization between acute and chronic atrial fibrillation in dogs. *J Am Coll Cardiol* 2000;36:924–931.
- Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. *Circulation* 1994;89:1665–1680.
- Allessie MA, de Groot NM, Houben RP, et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol* 2010;3:606–615.
- de Groot NM, Houben RP, Smeets JL, et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation* 2010;122:1674–1682.
- van Schie MS, Talib S, Knops P, Taverne Y, de Groot NMS. Conduction velocity and anisotropic properties of fibrillation waves during acutely induced and long-standing persistent AF. *JACC Clin Electrophysiol* 2024;10:1592–1604.
- Allessie M, de Groot N. Wave-mapping as a guide for ablation of atrial fibrillation: a daydream? *Circ Arrhythm Electrophysiol* 2013;6:1056–1058.
- Yuen HC, Roh SY, Lee DI, et al. Atrial fibrillation cycle length as a predictor for the extent of substrate ablation. *Europace* 2015;17:1391–1401.
- Haissaguerre M, Lim KT, Jacquemet V, et al. Atrial fibrillatory cycle length: computer simulation and potential clinical importance. *Europace* 2007;9:vi64–vi70.
- Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation* 1995;92:1954–1968.
- Duytschaever M, Mast F, Killian M, Blaauw Y, Wijffels M, Allessie M. Methods for determining the refractory period and excitable gap during persistent atrial fibrillation in the goat. *Circulation* 2001;104:957–962.
- Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* 1999;100:87–95.
- Akar JG, Everett TH, Kok LC, Moorman JR, Haines DE. Effect of electrical and structural remodeling on spatiotemporal organization in acute and persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2002;13:1027–1034.
- Cervigon R, Moreno J, Reilly RB, Millet J, Perez-Villacastin J, Castells F. Entropy measurements in paroxysmal and persistent atrial fibrillation. *Physiol Meas* 2010;31:1011–1020.
- Sahadevan J, Ryu K, Peltz L, et al. Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. *Circulation* 2004;110:3293–3299.
- Yoo S, Rottmann M, Ng J, et al. Regions of highly recurrent electrogram morphology with low cycle length reflect substrate for atrial fibrillation. *JACC Basic Transl Sci* 2023;8:68–84.
- Zeemering S, van Hunnik A, van Rosmalen F, et al. A novel tool for the identification and characterization of repetitive patterns in high-density contact mapping of atrial fibrillation. *Front Physiol* 2020;11:570118.
- Mann I, Linton NWF, Coyle C, et al. RETRO-MAPPING: a new approach to activation mapping in persistent atrial fibrillation reveals evidence of spatiotemporal stability. *Circ Arrhythm Electrophysiol* 2021;14:e009602.