Title: Personalized monitoring of electrical remodelling during atrial fibrillation progression via remote transmissions from implantable devices.

J.M. Lillo-Castellano, PhD[1,2]; J.J. González-Ferrer, MD, PhD*[3,4]; M. Marina-Breysse, MD*[1,5]; J.B. Martínez-Ferrer, MD[6]; L. Pérez-Álvarez, MD[7]; J. Alzueta, MD[8]; J.G. Martínez, MD[9]; A. Rodríguez, MD[10]; J.C. Rodríguez-Pérez, MD[11]; I. Anguera, MD[12]; X. Viñolas, MD[13]; A. Alberola, MD[14]; J. G. Quintanilla, MScEng, PhD[1,3,4]; J.M. Alfonso-Almazán, MSc[1]; Javier García, MD[15]; L. Borrego, MD[3]; V. Cañadas-Godoy, MD, PhD[3,4]; N. Pérez-Castellano, MD, PhD[3,4]; J. Pérez-Villacastín, MD, PhD[2,3,4]; J. Jiménez-Díaz, MD[16]; J. Jalife, MD[4,17]; D. Filgueiras-Rama, MD, PhD[1,3,4]

* Both authors contributed equally.

Affiliations:

[1]Advanced Development in Arrhythmia Mechanisms and Therapy Laboratory. Centro Nacional de Investigaciones Cardiovasculares (CNIC). Madrid, Spain.

[2]Fundación Interhospitalaria para la Investigación Cardiovascular (FIC), Madrid, Spain.

[3]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC). Cardiovascular Institute. Madrid, Spain.

[4]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV). Madrid, Spain.

[5]Agencia Española de Protección de la Salud en el Deporte (AEPSAD). Madrid. Spain.

[6]Hospital Universitario de Araba. Vitoria, Spain.

[7]Hospital Universitario A Coruña. La Coruña, Spain.

[8]Hospital Universitario Virgen de la Victoria. Málaga, Spain.

[9]Hospital General Universitario de Alicante. Valencia, Spain.

[10]Hospital Universitario de Canarias. Santa Cruz de Tenerife, Spain.

[11]Hospital Insular de Gran Canaria. Las Palmas, Spain.

[12] Hospital de Bellvitge. Barcelona, Spain.

[13] Hospital Santa Creu i san Pau. Barcelona, Spain.

[14]Hospital Universitario Virgen de la Arrixaca. Murcia, Spain.

[15] Hospital Universitario de Getafe, Madrid, Spain.

[16]Hospital General Universitario de Ciudad Real. Castilla la Mancha, Spain.

[17]Cardiac Arrhythmia Laboratory. Centro Nacional de Investigaciones Cardiovasculares (CNIC). Madrid, Spain.

Address for correspondence: David Filgueiras-Rama, Centro Nacional de Investigaciones Cardiovasculares (CNIC). Melchor Fernández Almagro 3, 28029, Madrid, Spain. Tel: +34 914531200 (Ext. 1510). Fax: +34 914531265. Email: david.filgueiras@cnic.es.

ABSTRACT

Aims: Atrial electrical remodelling (AER) is a transitional period associated with the progression and long-term maintenance of atrial fibrillation (AF). We aimed to study the progression of AER in individual patients with implantable devices and AF episodes.

Methods: Observational multicentric study (51 centres) including 4618 patients with implantable cardioverter defibrillator+/-resynchronization therapy (ICD/CRT-D) and 352 patients (2 centres) with pacemakers (median follow-up: 3.4 years). Atrial activation rate (AAR) was quantified as the frequency of the dominant peak in the signal spectrum of AF episodes with atrial bipolar electrograms. Patients with complete progression of AER, from paroxysmal AF episodes to electrically remodelled persistent AF, were used to depict patient-specific AER slopes.

Results: A total of 34712 AF tracings from 830 patients (87 with pacemakers) were suitable for the study. Complete progression of AER was documented in 216 patients (16 with pacemakers). Patients with persistent AF after completion of AER showed ~30% faster AAR than patients with paroxysmal AF. The slope of AAR changes during AF progression revealed patient-specific patterns that correlated with the time-to-completion of AER (R^2=0.85). Pacemaker patients were older than patients with ICD/CRT-Ds (78.3 vs. 67.2 year-olds, respectively, p<0.001) and had a shorter median time-to-completion of AER (24.9 vs. 93.5 days, respectively, p=0.016). Remote transmissions in patients with ICD/CRT-D devices enabled the estimation of the time-to-completion of AER using the predicted slope of AAR changes from initiation to completion of electrical remodelling (R^2=0.45).

Conclusion: AF progression shows patient-specific patterns of AER, which can be estimated using available remote monitoring technology.

Keywords: atrial fibrillation; implantable cardiac defibrillators; eHealth; telemedicine; mobile health.

CONDENSED ABSTRACT

Remote monitoring technology and a digital cloud-based big data storage of intracardiac electrograms enabled demonstration that atrial electrical remodelling during atrial fibrillation progression follows patient-specific patterns. Time-to-completion of atrial electrical remodelling can be estimated using the computed individual slope of atrial activation rate changes and the underlying cardiac condition.

What is new?

- Current remote monitoring technology in implantable devices enables identification of patient-specific slopes of atrial electrical remodelling during atrial fibrillation (AF) progression.
- Time-to-completion of atrial electrical remodelling can be estimated using the computed patient-specific slope of atrial activation rate changes and the underlying cardiac condition.
- The results represent a step forward in monitoring the progression of atrial electrical remodelling, which may further assist physicians in the stratification and personalized care of patients with AF.

INTRODUCTION

Atrial fibrillation (AF) is currently considered a growing and inevitable worldwide epidemic with important economic and social burden.[1, 2] AF diagnosis is simple when using non-invasive surface electrocardiographic (ECG) recordings,[3] although can also be obtained from intracardiac atrial recordings in patients with implantable devices and atrial leads.[4] Characteristically, both surface and intracardiac AF tracings will show fast atrial activation rate (AAR) and irregular activity.[3, 4]

AF is often a progressive cardiac arrhythmia from short-lasting episodes to long-standing persistent episodes,[3] which increases the risk of hospitalization and adverse cardiovascular events.[5] AF itself induces progressive functional and structural changes in the atrial myocardium that facilitate long-term perpetuation of the arrhythmia.[6] Concomitant genetic and cardiovascular conditions also establish an underlying substrate favouring AF initiation and perpetuation,[2] although they do not provide information about individualized progression of AF remodelling as the arrhythmia persists.

Initially, AF provokes ion channel changes leading to shortening of the action potential duration and progressively faster AAR until reaching a complete electrically remodelled state.[6, 7] As AF evolves other mechanical and structural changes also progressively develop,[6] which further decrease the probability of achieving a successful rhythm control strategy.[8] Interestingly, in translational animal models of persistent AF, the time-course of atrial electrical remodelling (AER) has been shown to present distinct progression from animal to animal,[6] whose remodelling slopes are sensitive to the effect of pharmacological treatment.[7] Although monitoring AER may have diagnostic and therapeutic implications in the clinic, it has not been demonstrated that AER also follows patient-specific patterns.

We tested the hypothesis that AAR changes during AF progression show patient-specific patterns that can be estimated using clinical variables and remote-monitoring tracings from implantable devices. We aimed to study AARs and the time-course of AER progression using bipolar AF recordings obtained from two populations of patients with implantable cardioverter defibrillator+/-

resynchronization therapy (ICD/CRT-D) and pacemaker devices. We also aimed to study the effect of the underlying clinical conditions on the AER process of AF.

METHODS

Study design

ICD/CRT-D data were obtained from an observational multicentre registry from 51 Spanish centres included in the UMBRELLA study (NCT01561144 at clinicaltrials.gov). This database is supported by the scientific cooperation platform, which is a cloud-based big-data tool that enables automatic and non-invasive data transmission with digitally structured storage. The database consisted of 4618 patients undergoing a Medtronic (Tolochenaz, Switzerland) ICD/CRT-D implantation from August 2011 to November 2017. A total of 2074 patients with dual chamber ICD/CRT-D devices and remote monitoring transmissions were considered for the study. Pacemaker data were obtained from a retrospective observational study in two Spanish centres. All patients undergoing a dual-chamber Microport (Clamart, France) pacemaker implantation from December 2009 to December 2018 were considered for the study. Atrial leads were routinely implanted in the right atrial appendage. Figure 1 shows the study flow-chart.

We obtained ethical committee approval for both ICD/CRT-D and pacemaker series in accordance with the Helsinki Declaration. All patients signed an informed consent. In patients with ICD/CRT-D devices, clinical baseline and demographic data were retrospectively collected at the time of device implantation using the official data collection sheet from the Spanish Society of Cardiology (see also Suppl. Material). In cases with device replacement during follow-up, the baseline data were selected using the data collection that was closest to the initiation of AF history. In pacemaker patients, clinical data and pharmacological history were obtained from electronic medical records during the follow-up period. In these patients left atrial (LA) diameter was also measured using transthoracic echocardiography and a parasternal long-axis view.

Data selection and rhythm classification

The UMBRELLA scientific committee initially reviewed and classified 27461 ICD/CRT-D stored episodes registered in a digital two-channel electrogram format. Three independent investigators used a custom-made Java-based software tool (Standard Edition 8, Oracle. Redwood, CA, USA) to further review and classify 31672 tracings obtained from remote monitoring transmissions. Stored pacemaker tracings obtained at the time of regular device interrogations were reviewed using the same software tool. Poor signal quality tracings were excluded from the study during the review process. Then, all AF tracings with a bipolar lead configuration (tip-ring) (Figure 2A), overt irregular and fast activation rates >3 Hz, and ≥3-s long recordings were included in the study. Manual selection of AF segments was performed in tracings with documented AF termination at the end of the tracing. Signal artefacts were manually excluded if necessary.

Selected AF tracings were further classified as paroxysmal or persistent AF based on the recorded episode duration. In pacemaker patients further confirmation of AF classification was obtained from clinical records. AF episodes lasting <7 days were classified as paroxysmal AF and episodes lasting ≥7 days as persistent AF.[3] In ICD/CRT-D patients, AF tracings without episode duration were classified using subsequent recordings in a way that two or more consecutive remote transmissions documenting AF, at least 7 days apart, were considered as persistent AF.

Computation of atrial activation rates

Atrial signals from stored episodes (ICD/CRT-Ds and pacemakers) were obtained at 128 Hz and data from remote transmissions (ICD/CRT-Ds only) were obtained at 256 Hz. Signals were high-pass filtered with cut-off frequency of 0.5 Hz. The median duration of AF tracings per patient was 9.6 [5.03, 10.00] s in ICD/CRT-D devices and 14.6 [10.6, 19.7] s in pacemakers. Local right AAR was computed using spectral analysis and the fast Fourier transform (FFT) to convert the tracing into the frequency domain as reported elsewhere.[6] Specifically, we used the non-parametric Welch method for power spectrum estimation with a median spectral resolution per patient of 0.10 [0.06, 0.24] Hz and 0.07 [0.05, 0.09] Hz in ICD/CRT-Ds and pacemakers, respectively. Spectral information below 10 Hz was normalized to the amplitude of the highest spectral peak within this band. The dominant frequency (DF) was defined as the frequency with the highest power within this

band. The DF value for each AF tracing was reviewed to detect potential harmonic peaks, and if needed, it was manually corrected to the estimated average local AAR using a custom-made Java tool. Thus, the DF peak provided a robust and rapid calculation of the reciprocal average local activation intervals (estimated average cycle length (ms) = [*(1/DF) *1000*]) (Figure 2B, C, D).

Time-course analysis of atrial electrical remodelling

DF-derived AARs were ordered by date to depict any changes during the follow-up period (Figure 2B). Then, patients with progression of AER from paroxysmal AF episodes (AER remodelling not present or incomplete) to persistent AF episodes with complete electrical remodelling were used to plot remodelling slopes. Pre- and post-electrical remodelling segments were manually selected using a custom-made Java tool. Because of the fact that atrial activations during AF are irregular and DF values may slightly vary during consecutive tracings, we used median DF values during the pre- and post-remodelling phases to compute the difference between the two stages. Then, the slope of AER was computed automatically by fitting the DF values to a linear regression function dependent on both the median DF values and the documented date of initiation and completion of AER (Figure 2B).

Statistical analysis

All data are presented as median and interquartile range [25^{th}, 75^{th} percentiles], except where noted. Normal distribution of variables was assessed with the Shapiro-Wilk test. Statistical significance was assessed by the T-test or the Mann-Whitney-Wilcoxon test, as appropriate. The ANOVA or the Kruskal-Wallis test was used for three- four-group comparisons according to data distribution. Categorical variables were compared using the Chi-squared test. The log(·) function was used to transform the exponential nature of the time-to-completion of AER distribution to a normally distributed variable. The Pearson's correlation coefficient (R^2) was used for correlation analysis between continuous variables and DF values during persistent AF. A $p<0.05$ was considered statistically significant.

The large series of patients with ICD/CRT-D devices was used to study the predictive value of clinical variables to establish the time-to-completion of AER, by means of univariate analysis and a multivariate stepwise linear regression model. Then, we developed a computational method using remote monitoring tracings to estimate patient-specific times-to-completion of AER. First, all variables statistically associated with DF values during persistent AF were included in a multivariate stepwise linear regression model to predict AAR during persistent AF after completion of AER. Then, for each patient, the time-to-completion of AER was estimated using the predicted values of AAR after completion of the AER process and the computed slope at 25% of the expected change in AAR from paroxysmal AF to complete electrical remodelling in persistent AF. The analyses were carried out using SPSS v21 (IBM Corp, New York, US) and custom Matlab (MathWorks Inc., Natick, US) scripts for mathematical assistance.

RESULTS

A total of 34712 AF tracings from 830 patients (87 with pacemakers) were suitable for the study. Patients with pacemakers showed a similar follow up period to ICD/CRT-D patients (3.4 [1.7, 5.3] and 3.4 [1.9, 4.3] years, respectively), although the former were significantly older (78.3 [73.1, 85.3] vs 67.2 [59.3, 73.7] year-olds, $p<0.001$, respectively) and had a predominant left ventricular ejection fraction (LVEF) >35%. Table 1 shows baseline clinical characteristics and comparisons between pacemaker and ICD/CRT-D populations. Complete progression of AER from pre-remodelling to complete remodelling in persistent AF was documented in 216 patients (16 with pacemakers). Other 543 patients in the ICD/CRT-D population and 71 patients in the pacemaker population were classified as paroxysmal (no progression to persistent AF during the follow-up) or persistent AF (repeated transmissions in AF during the follow-up) (Figure 1). ICD/CRT-D indication was for primary prevention in the majority of patients (71.7%) and the underlying myocardial substrates were mainly ischemic cardiomyopathy (ICM, 50.6%) and non-ischemic dilated cardiomyopathy (DCM, 33.2%), with a left ventricular ejection fraction (LVEF) ≤35% in 73.4% of patients (Table 2).

Atrial fibrillation stage determines atrial activation rates and structural changes

Patients with paroxysmal AF showed slower AAR than patients with persistent AF. Two representative cases are shown in Figure 3A, B. Overall, AAR was ~30% higher after completion of AER compared with pre-remodelling stages in paroxysmal AF (Figure 3C). The data reflect the presence of two electrical remodelling stages with an intermediate period between them. This increase in AAR was present in both pacemaker and ICD/CRT-D populations, although pacemaker patients showed slower AAR during paroxysmal AF episodes compared with ICD/CRT-D patients (4.12 [3.64, 4.53] Hz vs. 4.63 [4.07, 5.34] Hz, respectively, $p<0.001$). These differences were not documented after completion of AER in persistent AF (Figure 3C). Moreover, in the pacemaker population, echocardiography data showed a progression in structural remodelling reflected by a significantly larger LA diameter after completion of AER compared with early electrical remodelling stages (50 [40, 56] mm vs. 38 [41, 45] mm, $p=0.006$. Figure 3D).

More specific analysis of AARs in patients with an ICD or CRT-D device and complete monitoring of AER (n=200) showed that AARs during paroxysmal AF episodes were significantly slower in CRT-D patients compared with ICD patients (4.15 [3.48, 4.80] Hz vs. 4.45 [3.81, 5.25] Hz, respectively, $p=0.005$). However, these differences were not statistically significant after completion of AER in persistent AF (Suppl. Figure 1). Biventricular capture in CRT-D patients was 95.4 [89.3, 99.0] %. In the pacemaker population we also documented a trend to lower AARs under Class I/III antiarrhythmic drugs (Suppl. Figure 2).

Prediction of atrial activation rates after completion of atrial electrical remodelling

In ICD/CRT-D patients with complete monitoring of AER, there was a statistically significant correlation between AARs during paroxysmal AF and at the completion of AER in persistent AF ($R^2=0.424$, $p<0.001$. Figure 4A). Thus, the slower the AAR during paroxysmal AF, the slower the expected AAR will be after completion of AER. Moreover, AARs after completion of AER were significantly lower in patients with ICM compared to patients with DCM or other structural cardiomyopathies (6.30 [5.60, 6.70] vs 6.48 [5.96, 7.20] Hz, and vs 6.93 [5.61, 7.45] Hz, respectively, $p=0.015$ and $p=0.036$, respectively. Figure 4B). LVEF ≤35% was also associated with lower AARs compared with LVEF>35% (6.30 [5.61, 6.79] vs. 6.84 [5.72, 7.38] Hz, respectively,

p=0.013). Table 3 shows the univariate analysis of baseline clinical characteristics and any statistically significant association with AAR values during persistent AF after completion of AER. Importantly, a predictive model using the underlying cardiac condition and the AAR during early stages of AER in paroxysmal AF significantly correlated with AAR values after completion of AER in persistent AF (Table 4. R^2=0.460).

Atrial fibrillation progression shows patient-specific patterns of electrical remodelling

The log(slope) of AARs during AF progression showed patient-specific patterns that strongly correlated with the log(time-to-completion of AER), both in the ICD/CRT-D and pacemaker populations (R^2=0.852 and R^2=0.853, respectively. p<0.001. Figure 4C and Suppl. Figure 3). Using the large population of patients with ICD/CRT-D devices, univariate analysis of baseline clinical variables showed that only the presence of left bundle branch block (p=0.036) was associated with the time-to-completion of AER (Suppl. Table 1). However, multivariate analysis did not identify any statistically significant association of clinical variables with the time-to-completion of AER.

Importantly, patient-specific time-to-completion of AER could be estimated in a subset of the ICD/CRT-D population (n=51) with remote-monitored AF tracings. Thus, the predicted value of AARs at the completion of the AER process and the computed slope at 25% of the expected change in AARs, from paroxysmal AF to complete electrical remodelling in persistent AF, correlated with the time-to-completion of AER (R^2=0.458. Figure 4D, E and Suppl. Figure 4). Error quantification of the estimated log(time-to-completion of AER) showed a median value of 33.56% [12.72, 57.06].

Further comparisons between the pacemaker population and patients with ICD/CRT-D devices showed that the time-to-completion of AER was significantly shorter in patients with pacemakers (24.9 [14.3, 108.2] d vs. 93.5 [36.6, 190.5] d, respectively, p=0.016. Figure 4F). Despite limitations to identify the underlying causes of such differences, older ages in the pacemaker population may be involved (Table 1).

DISCUSSION

We studied the time-course of AER in two populations of patients with implantable devices during AF progression. Patients with paroxysmal and persistent AF showed significantly different AARs, with faster activation rates during persistent AF after completion of AER. We have identified that AAR after completion of AER could be predicted using the underlying cardiac condition and the AAR during paroxysmal AF. Moreover, we have documented patient-specific patterns of time-to-completion AER, which were significantly faster in the older population of patients with pacemakers compared with the ICD/CRT-D population. Individual patterns of AER progression could be estimated using the predicted values of AAR at the completion of the AER process and the computed slope at 25% of the expected change in AAR from the initiation to complete electrical remodelling in persistent AF.

The influence of the underlying cardiac condition and therapies (e.g. CRT-D) on AARs may represent different predominant mechanisms affecting atrial electrophysiology. Yoshida *et al.* have reported a direct relationship between LA pressure and the DF of AF at the LA appendage.[9] Thus, atrial stretch in the presence of increased intracavitary pressures may lead to faster AARs as we have documented in patients with DCM. Slower AARs during paroxysmal AF episodes in patients with CRT-D compared with ICD patients may also reflect an improvement in cardiac hemodynamic status upon resynchronization therapy. Interestingly, the majority of patients with other structural cardiomyopathies had hypertrophic cardiomyopathy, which is also associated with atrial diastolic dysfunction and increased LA pressures.[10] Therefore, atrial stretch may represent the cause of faster AARs in patients with other structural cardiomyopathies compared with patients with ICM. Although patients with ICM can also have increased intracavitary pressures,[11] infarct-related scar tissue may affect atrial activation and potentially decrease AAR. The latter would be consistent with the study by Swartz *et al.* showing an inverse correlation between LA fibrosis and LA activation frequencies.[12] This is also consistent with our data from patients with pacemakers; a more advanced age in this population justifies higher levels of underlying atrial fibrosis and significantly slower AAR during paroxysmal AF compared with the ICD/CRT-D population. At the cellular level, the

myofibroblast/myocyte ratio in two-dimensional cardiac monolayers has also shown an inverse relationship with activation frequencies of re-entrant activity.[13]

The data demonstrate the potential of personalized monitoring of AARs as a marker of electrical remodelling during AF progression. Moreover, regardless of the current classification of paroxysmal versus persistent AF, which does not provide accurate information about the underlying remodelling stage, our approach to assess the progression and stage of AER may have important therapeutic and prognostic implications. Lankveld *et al.* have documented that slower AARs on single surface ECG recordings of patients with persistent AF undergoing electrical cardioversion were associated with sinus rhythm maintenance after 1-year follow up.[14] Interestingly, the mean episode duration was 3 months in patients with and without AF recurrences, which suggests that within the same time period slower progression of AER will lead to slower AARs and higher probability of sinus rhythm maintenance. Bollman *et al.* have also shown that single ECG-derived atrial fibrillatory frequencies of 5.9 Hz in patients with persistent AF were associated with successful pharmacological cardioversion.[15] Conversely, mean atrial fibrillatory frequencies of 6.4 Hz did associate with unsuccessful pharmacological cardioversion, while mean episode duration (4 to 6 months) was not significantly different between the two groups. Data from ablation procedures have also documented the role of ECG-based parameters to predict AF termination during the procedure and long-term freedom from AF. Using a retrospective cohort of patients undergoing persistent AF ablation, Lankveld *et al.* could document that DF values <6.0 Hz were frequently associated with AF termination during the ablation procedure, along with long-term freedom from the arrhythmia.[16] Such DF values were mainly present in AF episodes with duration <12 months. The latter is consistent with our data in which the majority of patients in the ICD/CRT-D population (n=150, 75th percentile) showed complete electrical remodelling after 191 days of remodelling initiation.

Remote monitoring of different cardiac conditions has already demonstrated an impact on clinical outcomes, health care utilization and expenditures.[17] Continuous ECG monitoring with implantable cardiac monitors has also demonstrated that AF detection can be substantially improved in patients at high risk of both AF and stroke.[18] However, despite the potential impact of early AF detection on

clinical outcomes as rhythm control or stroke, data from trials with early therapeutic interventions are warranted. Our data represent one step forward on AF monitoring to detect both the electrical remodelling stage during AF episodes and the progression rate of AER as AF evolves. These two aspects may potentially assist physicians in personalized care of patients with AF and implantable devices; e.g. adjusting medical therapy and further monitoring its effects or proposing an early interventional ablation procedure before completion of AER.

We have obtained AARs from intracardiac bipolar tracings, which provided local activation rates from the right atrium. However, remodelling progression could also be monitored using single lead ECG tracings after QRS-T subtraction as it has been performed in animal models of long-standing persistent AF.[6] The latter opens new diagnostic options for monitoring AF progression using non-invasive long-term recording devices as smart watches or wearable holter ECG, which would require implementing appropriate algorithms for QRS-T subtraction and optimization of remote transmissions once AF is detected. Importantly, AF is an irregular rhythm with variations in local AAR within specific time windows.[4] Therefore, a single ECG tracing or DF value may not represent an accurate measurement of AAR compared with repeating measurements for the same day. In patients with complete monitoring of AER in the ICD/CRT-D population we have used a median of 64 [34, 122] AF tracings per patient, which minimized this potential limitation. Moreover, estimated slope calculations were performed using median DF values for repeating tracings from the same day. The latter could be further improved using algorithms that can store reliable DF values or average atrial activation cycle lengths using repeating samples from the same day. DF values will have the advantage of providing a rapid measurement with no need for detecting individual activations, which may be challenging in the presence of fragmented electrograms or low amplitude signals.[19, 20] In fact, low fibrillatory wave amplitudes are commonly present in long-standing AF episodes.[16] Conversely, DF values may be affected by harmonic peaks, which may require improved algorithms or additional revision by the physician using representative tracings that could be transmitted to a cloud-based data tool and avoid compromising devices´ battery longevity.

Limitations

The design of the study did not enable us to obtain remote monitoring transmissions using specific criteria, which could have improved the estimation of AER slopes. This limitation was more relevant in pacemaker devices, in which remote transmissions were not available and AF tracings were only obtained from stored AF episodes. Representative cases are shown in Suppl. Figure 4.

The study was focused on monitoring AER using a large number of tracings during a long follow-up. However, other remodelling changes as structural remodelling were not thoroughly evaluated because of study design limitations to obtain such data in ICD/CRT-D patients. Pharmacological history was not included in the official datasheet at the time of ICD/CRT-D implantation, which precluded us from obtaining more meaningful data about specific drug effects on both AAR and the progression of AER. Slower progression of AER in patients with ICD/CRT-D devices may be related to a high percentage of these patients taking upstream therapies (based on historical series with ICD/CRT-D devices) compared with pacemaker patients (Suppl. Figure 2). However, this study shows that regardless the underlying pharmacological effects on remodelling slopes, AER could be efficiently monitored and estimated using current technology. The methodology used in this study is not available in clinical practice and would require further implementation in implantable devices or remote monitoring platforms to validate the impact in prospective series.

CONCLUSION

AF progression shows patient-specific patterns of AER, which can be estimated using the computed individual slope of atrial activation rate changes and the underlying cardiac condition.

ACKNOWLEDGMENTS

We thank the UMBRELLA study (NCT01561144 at clinicaltrials.gov) and the scientific cooperation platform for providing a valuable source of data to independent investigators in Spain. We thank Dr. Stuart Pocock for his statistical advice.

COMPETING INTERESTS

None

FUNDING

The Centro Nacional de Investigaciones Cardiovasculares (CNIC) is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia, Innovación y Universidades (MCNU) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505). This study was supported by grants from the Fondo Europeo de Desarrollo Regional (CB16/11/00458) and the Spanish MCNU (SAF2016-80324-R). The study was also partially supported by the Fundación Interhospitalaria para la Investigación Cardiovascular (FIC, Madrid, Spain) and the Heart Rhythm Association of the Spanish Society of Cardiology (DFR, JJGF). Dr. Jalife is supported by R01 Grant HL122352 from the National Heart Lung and Blood Institute, USA National Institutes of Health.

REFERENCES

[1] Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011; **4**: 313-20.

[2] Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B, et al. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation. *Circulation* 2018; **137**: 1027-38.

[3] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016; **18**: 1609-78.

[4] Isa R, Villacastin J, Moreno J, Perez-Castellano N, Salinas J, Doblado M, et al. [Differentiating between atrial flutter and atrial fibrillation using right atrial bipolar endocardial signals]. *Rev Esp Cardiol* 2007; **60**: 104-9.

[5] de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010; **55**: 725-31.

[6] Martins RP, Kaur K, Hwang E, Ramirez RJ, Willis BC, Filgueiras-Rama D, et al. Dominant frequency increase rate predicts transition from paroxysmal to long-term persistent atrial fibrillation. *Circulation* 2014; **129**: 1472-82.

[7] Takemoto Y, Ramirez RJ, Yokokawa M, Kaur K, Ponce-Balbuena D, Sinno MC, et al. Galectin-3 Regulates Atrial Fibrillation Remodeling and Predicts Catheter Ablation Outcomes. *JACC Basic to translational science* 2016; **1**: 143-54.

[8] Quintanilla JG, Alfonso-Almazan JM, Perez-Castellano N, Pandit SV, Jalife J, Perez-Villacastin J, et al. Instantaneous Amplitude and Frequency Modulations Detect The Footprint of Rotational Activity and Reveal Stable Driver Regions as Targets for Persistent Atrial Fibrillation Ablation. *Circ Res* 2019.

[9] Yoshida K, Ulfarsson M, Oral H, Crawford T, Good E, Jongnarangsin K, et al. Left atrial pressure and dominant frequency of atrial fibrillation in humans. *Heart rhythm* 2011; **8**: 181-7.

[10] Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. *Circulation* 2007; **116**: 2702-8.

[11] Kyhl K, Vejlstrup N, Lonborg J, Treiman M, Ahtarovski KA, Helqvist S, et al. Predictors and prognostic value of left atrial remodelling after acute myocardial infarction. *Open heart* 2015; **2**: e000223.

[12] Swartz MF, Fink GW, Lutz CJ, Taffet SM, Berenfeld O, Vikstrom KL, et al. Left versus right atrial difference in dominant frequency, K(+) channel transcripts, and fibrosis in patients developing atrial fibrillation after cardiac surgery. *Heart Rhythm* 2009; **6**: 1415-22.

[13] Zlochiver S, Munoz V, Vikstrom KL, Taffet SM, Berenfeld O, Jalife J. Electrotonic myofibroblast-to-myocyte coupling increases propensity to reentrant arrhythmias in two-dimensional cardiac monolayers. *Biophys J* 2008; **95**: 4469-80.

[14] Lankveld T, de Vos CB, Limantoro I, Zeemering S, Dudink E, Crijns HJ, et al. Systematic analysis of ECG predictors of sinus rhythm maintenance after electrical cardioversion for persistent atrial fibrillation. *Heart Rhythm* 2016; **13**: 1020-7.

[15] Bollmann A, Binias KH, Toepffer I, Molling J, Geller C, Klein HU. Importance of left atrial diameter and atrial fibrillatory frequency for conversion of persistent atrial fibrillation with oral flecainide. *Am J Cardiol* 2002; **90**: 1011-4.

[16] Lankveld T, Zeemering S, Scherr D, Kuklik P, Hoffmann BA, Willems S, et al. Atrial Fibrillation Complexity Parameters Derived From Surface ECGs Predict Procedural Outcome and Long-Term Follow-Up of Stepwise Catheter Ablation for Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2016; **9**: e003354.

[17] Piccini JP, Mittal S, Snell J, Prillinger JB, Dalal N, Varma N. Impact of remote monitoring on clinical events and associated health care utilization: A nationwide assessment. *Heart Rhythm* 2016; **13**: 2279-86.

[18] Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, et al. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. *JAMA cardiology* 2017; **2**: 1120-7.

[19] Oral H, Chugh A, Good E, Wimmer A, Dey S, Gadeela N, et al. Radiofrequency catheter ablation of chronic atrial fibrillation guided by complex electrograms. *Circulation* 2007; **115**: 2606-12.

[20] Kuklik P, Zeemering S, Maesen B, Maessen J, Crijns HJ, Verheule S, et al. Reconstruction of instantaneous phase of unipolar atrial contact electrogram using a concept of sinusoidal recomposition and Hilbert transform. *IEEE Trans Biomed Eng* 2015; **62**: 296-302.

Figure legends

Figure 1. Study flowchart. AF: atrial fibrillation. CRT-D/P: cardiac resynchronization therapy plus defibrillator/Pacemaker. ICD: implantable cardioverter defibrillator.

Figure 2. Sample signal processing and representation of the time-course of atrial electrical remodelling. A, Schematic representation of a dual-chamber implantable cardioverter defibrillator to obtain atrial bipolar electrograms during atrial fibrillation (AF) episodes. **B,** Sample time-course of atrial activation rate (AAR) during AF progression from early stages of atrial electrical remodelling (AER, light green background colour) with paroxysmal AF episodes to completion of AER in persistent AF (red light background colour). **C,** Sample tracings from downward arrows in ***B*** that represent different stages of AER. **D,** Power spectra and dominant frequency values associated with the samples tracings in ***C***.

Figure 3. Atrial activation rates during paroxysmal and persistent atrial fibrillation and associated structural changes. A and **B,** Left panels, show the time-course of atrial activation rate (AAR) during paroxysmal and persistent atrial fibrillation (AF). Right panels show sample AF tracings at downward arrows. Light green and red background colours indicate early and complete atrial electrical remodelling (AER) stages, respectively. **C,** Box-plots and comparisons of AAR during paroxysmal (pre-AER) and persistent AF (complete AER) between patients with implantable cardioverter defibrillator+/-resynchronization therapy (ICD/CRT-D) and pacemaker devices. **D,** Box-plots and comparison of left atrial diameters between pre-AER and complete AER stages. Box-plot data show median and interquartile ranges. Central dots inside the box-plots show the mean.

Figure 4. Monitoring and prediction of time-to-completion of atrial electrical remodelling. A, Scatter-plot of atrial activation rate (AAR) during paroxysmal (pre-AER stage) atrial fibrillation (AF) and after completion of atrial electrical remodelling (AER) in persistent AF. Each black dot represents an individual patient. The diagonal dashed line represents the line of equality. **B,** Box-plots and comparisons of AAR during persistent AF among patients with ischemic cardiomyopathy (ICM), non-ischemic dilated cardiomyopathy (DCM) and other structural cardiomyopathies (SCM).

C, Log(slope) correlation with log(time-to-completion AER). **D,** Correlation of predicted and actual log(time-to-completion of AER). **E,** Sample case with the predicted and actual times-to-completion of AER. **F,** Blox-plots and comparison of time-to-completion of AER between the ICD/CRT-D and pacemaker populations. All panels, but panel **F** show data from the ICD/CRT-D population. ICD/CRT-D as in Figure 3.

Table 1. Baseline clinical and demographic characteristics of ICD/CRT-D and pacemaker populations.

Clinical characteristics	ICD / CRT-D (n=743)	Pacemaker (n=87)	p-value
Age (years), n (median [IQR])	67.2 [59.3, 73.7]	78.3 [73.1, 85.3]	**< 0.001**
Male, n (%)	609 (82.0)	51 (58.6)	**< 0.001**
Cardiomyopathy, n (%)			**< 0.001**
ICM	376 (50.6)	19 (21.8)	
DCM	247 (33.2)	1 (1.1)	
Other SCM: HCM, ARVC, VHD, or CHD	97 (13.1)	3 (3.4)	
Non-structural arrhythmogenic disease	23 (3.1)	0 (0.0)	
Non-cardiomyopathy	0 (0)	64 (73.6)	
LBBB, n (%)	334 (45.6)	12 (13.8)	**< 0.001**
LVEF (≤35%), n (%)	544 (73.4)	4 (4.6)	**< 0.001**
Functional class, n (%)			**< 0.001**
NYHA I	119 (18.2)	34 (39.5)	
NYHA II	288 (44.0)	41 (47.7)	
NYHA III	235 (35.9)	10 (11.6)	
NYHA IV	12 (1.8)	1 (1.2)	
Clinical history, n (%)			
Hypertension	434 (59.9)	77 (88.5)	**< 0.001**
Diabetes mellitus	227 (31.2)	25 (28.7)	0.641
Hyperlipidaemia	388 (54.6)	50 (57.5)	0.608
Current smoking	206 (30.2)	5 (5.7)	**< 0.001**
Chronic renal failure	143 (20.0)	12 (13.8)	0.168
Previous stroke or TIA	50 (7.5)	6 (6.9)	0.852
Medications during the AF period, n (%)			
β-blocker	-	40 (46.0)	
ACE-inhibitor / ARB	-	61 (70.1)	
Verapamil / diltiazem	-	6 (6.9)	
Mineralocorticoid receptor antagonist	-	9 (10.3)	
Statins	-	52 (59.8)	
Class I antiarrhythmic drug	-	8 (9.2)	
Class III antiarrhythmic drug	-	9 (10.3)	
Anticoagulant	-	58 (66.7)	

Table 1 continuation. ACE: angiotensin-converting-enzyme. AF: atrial fibrillation. ARB: angiotensin-receptor blocker. ARVC: arrhythmogenic right ventricular cardiomyopathy. CHD: congenital heart disease. DCM: non-ischemic dilated cardiomyopathy. ICD/CRT-D: implantable cardioverter defibrillator+/-resynchronization therapy. ICM: ischemic cardiomyopathy. HCM: hypertrophic cardiomyopathy. LBBB: left bundle branch block. LVEF: left ventricular ejection fraction. SCM: structural cardiomyopathy. TIA: transient ischemic attack. VHD: valvular heart disease.

Table 2. Baseline clinical and demographic characteristics of patients with ICD/CRT-D devices in different atrial fibrillation groups.

Clinical characteristics	Paroxysmal AF (n=427)	Complete AER progression (n=200)	Persistent AF (n=116)	p-value
Age (years), median [IQR]	66.2 [58.1, 72.9]	67.9 [58.1, 74.5]	69.3 [62.7, 75.3]	**0.005**
Male, n (%)	334 (78.2)	178 (89.0)	97 (83.6)	**0.004**
Cardiomyopathy, n (%)				0.575
ICM	214 (50.1)	101 (50.5)	61 (52.6)	
DCM	141 (33.0)	68 (34.0)	38 (32.8)	
Other SCM: HCM, ARVC, VHD, or CHD	55 (12.9)	29 (14.5)	13 (11.2)	
Non-structural arrhythmogenic disease	17 (4.0)	2 (1.0)	4 (3.4)	
LBBB, n (%)	195 (46.5)	84 (42.0)	55 (48.7)	0.444
LVEF (≤35%), n (%)	303 (71.1)	147 (73.5)	94 (81.7)	0.073
Functional class, n (%)				0.073
NYHA I	79 (21.6)	30 (16.8)	10 (9.1)	
NYHA II	156 (42.7)	80 (44.7)	52 (47.3)	
NYHA III	124 (34.0)	67 (37.4)	44 (40.0)	
NYHA IV	6 (1.6)	2 (1.1)	4 (3.6)	
Clinical history, n (%)				
Hypertension	244 (59.2)	120 (61.2)	70 (60.3)	0.891
Diabetes mellitus	134 (32.5)	57 (28.5)	36 (31.0)	0.601
Hyperlipidaemia	220 (55.1)	110 (55.0)	58 (51.8)	0.812
Current smoking	127 (32.5)	53 (28.8)	26 (24.5)	0.253
Chronic renal failure	73 (18.0)	44 (22.6)	26 (22.6)	0.312
Previous stroke or TIA	24 (6.3)	16 (8.7)	10 (9.1)	0.464
Clinical presentation, n (%)				
Asymptomatic	184 (44.0)	92 (46.5)	44 (39.3)	0.473
Syncope	68 (16.3)	32 (16.2)	18 (16.1)	0.999
Sudden cardiac death	40 (9.6)	15 (7.6)	7 (6.3)	0.459
Primary prevention, n (%)	305 (71.4)	143 (71.5)	85 (73.3)	0.923
Device type (ICD), n (%)	229 (53.6)	91 (45.5)	41 (35.3)	**< 0.001**

Abbreviations as in Table 1.

Table 3. Univariate analysis of variables potentially associated with atrial activation rates during persistent atrial fibrillation.

Clinical characteristics	No	Yes	p-value / R^2
Age			**0.002** / 0.047
Male, n (Hz)	22 (6.29)	178 (6.40)	0.925 / -
Cardiomyopathy, n (Hz)			**0.008** / -
ICM		101 (6.30)	
DCM		68 (6.48)	
Other SCM: HCM, ARVC, VHD, or CHD		29 (6.93)	
Non-structural arrhythmogenic disease		2 (7.76)	
LBBB, n (Hz)	116 (6.40)	84 (6.28)	0.536 / -
LVEF (≤35%), n (Hz)	53 (6.84)	147 (6.30)	**0.013** / -
Functional class, n (Hz)			0.194 / -
NYHA I		30 (6.60)	
NYHA II		80 (6.39)	
NYHA III		67 (6.30)	
NYHA IV		2 (5.26)	
Clinical history, n (Hz)			
Hypertension	76 (6.31)	120 (6.39)	0.930 / -
Diabetes mellitus	143 (6.40)	57 (6.30)	0.314 / -
Hyperlipidaemia	90 (6.47)	110 (6.28)	0.136 / -
Current smoking	131 (6.28)	53 (6.50)	0.169 / -
Chronic renal failure	151 (6.30)	44 (6.43)	0.671 / -
Previous stroke or TIA	167 (6.30)	16 (6.86)	0.242 / -
Clinical presentation, n (Hz)			
Asymptomatic	106 (6.27)	92 (6.42)	0.263 / -
Syncope	166 (6.40)	32 (6.30)	0.900 / -
Sudden cardiac death	183 (6.36)	15 (6.50)	0.787 / -
Primary prevention, n (Hz)	57 (6.32)	143 (6.40)	0.926 / -
Device type (ICD), n (Hz)	109 (6.30)	91 (6.44)	0.118 /-
AAR during Paroxysmal AF			**< 0.001** / 0.424

Data are shown as the number of patients (n) and the median atrial activation rate (AAR) during persistent AF after completion of atrial electrical remodelling (in Hz). Abbreviations as in Table 1

Table 4. Predictive model of atrial activation rates during persistent atrial fibrillation after completion of atrial electrical remodelling.

	Estimate	Standard error	t-statistic	p-value
Intercept	2.947	0.270	10.923	<0.0001
Cardiomyopathy	0.258	0.071	3.6311	<0.0001
AAR during Paroxysmal AF	0.675	0.056	12.150	<0.0001
R^2	0.460			

AR: atrial activation rate. AF: atrial fibrillation.

Supplemental Material

Personalized monitoring of electrical remodelling during atrial fibrillation progression via remote transmissions from implantable devices

Authors: J.M. Lillo-Castellano, PhD[1,2]; J.J. González-Ferrer, MD, PhD*[3,4]; M. Marina-Breysse, MD*[1,5]; J.B. Martínez-Ferrer, MD[6]; L. Pérez-Álvarez, MD[7]; J. Alzueta, MD[8]; J.G. Martínez, MD[9]; A. Rodríguez, MD[10]; J.C. Rodríguez-Pérez, MD[11]; I. Anguera, MD[12]; X. Viñolas, MD[13]; A. Alberola, MD[14]; J. G. Quintanilla, MScEng, PhD[1,3,4]; J.M. Alfonso-Almazán, MSc[1]; Javier García, MD[15]; L. Borrego, MD[3]; V. Cañadas-Godoy, MD, PhD[3,4]; N. Pérez-Castellano, MD, PhD[3,4]; J. Pérez-Villacastín, MD, PhD[2,3,4]; J. Jiménez-Díaz, MD[15]; J. Jalife, MD[4,16]; D. Filgueiras-Rama, MD, PhD[1,3,4]

* Both authors contributed equally.

Author Affiliations:

[1]Advanced Development in Arrhythmia Mechanisms and Therapy Laboratory. Centro Nacional de Investigaciones Cardiovasculares (CNIC). Madrid, Spain.

[2]Fundación Interhospitalaria para la Investigación Cardiovascular (FIC), Madrid, Spain.

[3]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC). Cardiovascular Institute. Madrid, Spain.

[4]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV). Madrid, Spain.

[5]Agencia Española de Protección de la Salud en el Deporte (AEPSAD). Madrid. Spain.

[6]Hospital Universitario de Araba. Vitoria, Spain.

[7]Hospital Universitario A Coruña. La Coruña, Spain.

[8]Hospital Universitario Virgen de la Victoria. Málaga, Spain.

[9]Hospital General universitario de Alicante. Valencia, Spain.

[10]Hospital Universitario de Canarias. Santa Cruz de Tenerife, Spain.

[11]Hospital Insular de Gran Canaria. Las Palmas, Spain.

[12] Hospital de Bellvitge. Barcelona, Spain.

[13] Hospital Santa Creu i san Pau. Barcelona, Spain.

[14]Hospital Universitario Virgen de la Arrixaca. Murcia, Spain.

[15] Hospital Universitario de Getafe, Madrid, Spain.

[16] Hospital General Universitario de Ciudad Real. Castilla la Mancha, Spain.

[17]Cardiac Arrhythmia Laboratory. Centro Nacional de Investigaciones Cardiovasculares (CNIC). Madrid, Spain.

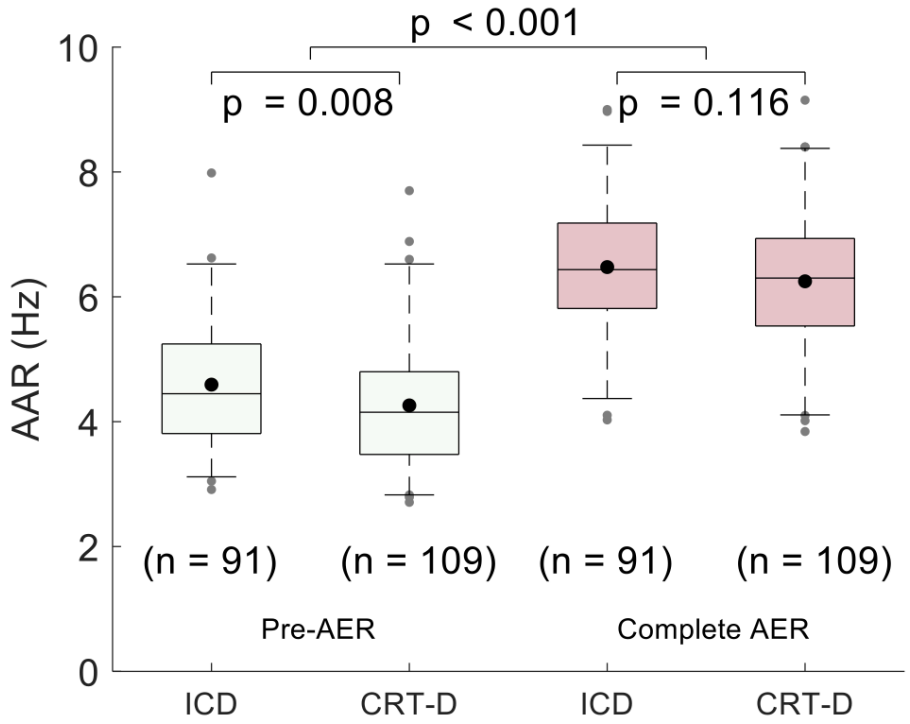
Supplemental Material

ICD/CRT-D database

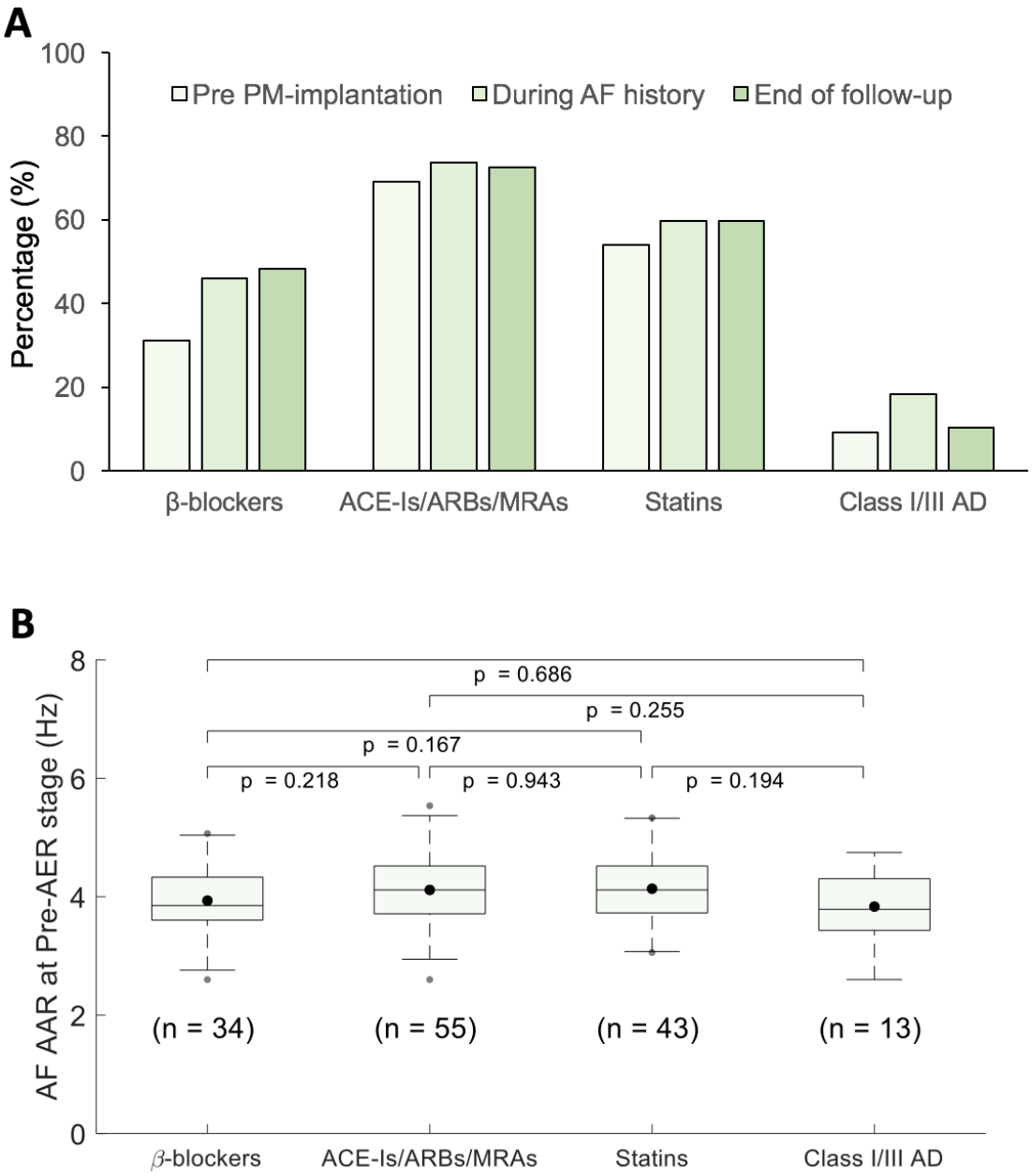
The Scientific COOperation Platform (SCOOP) is a Spanish cloud based big-data tool for generating cooperative knowledge in the field of cardiac implantable devices.[1, 2] The main property of SCOOP is its capability for remote monitoring and digital signal acquisition. The follow-up of each patient was incorporated into a database within an observational research study (UMBRELLA), ensuring the legal, normative, and scientific data exploitation. Clinical baseline and demographic data were retrospectively collected at the time of device implantation using the official data collection sheet from the Spanish Society of Cardiology: "http://secardiologia.es/images/stories/file/arritmias/registros-arritmias-hoja-datos-dai.pdf".

In this study we included 4618 patients undergoing a Medtronic implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy plus defibrillator (CRT-D) implantation, from August 2011 to November 2017. The following Spanish hospitals participated in the study:

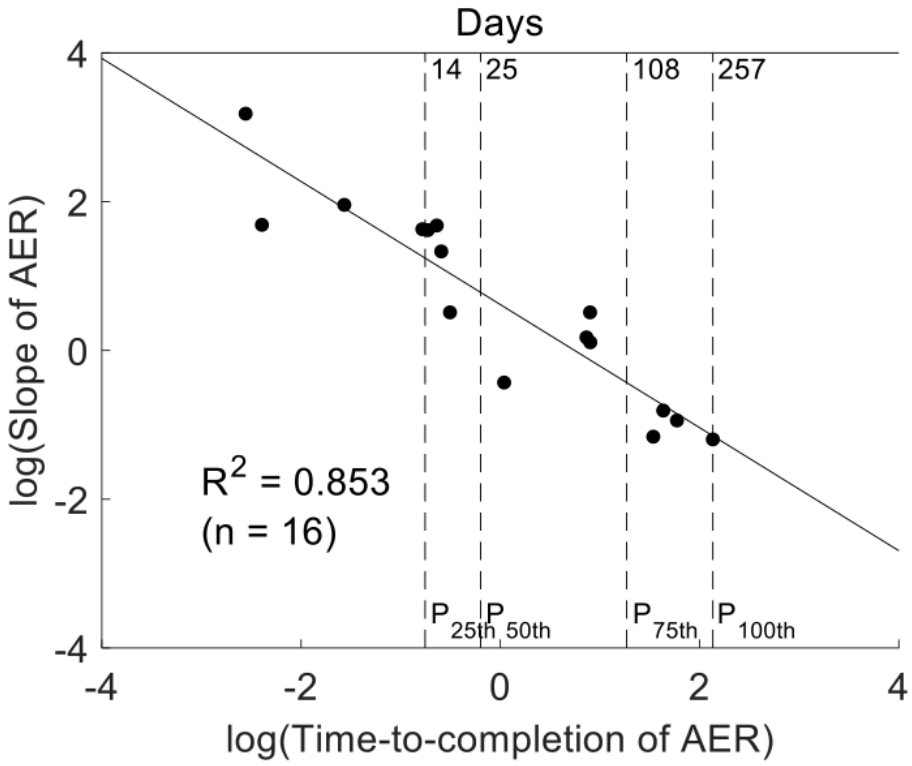
Hospital Clínico Universitario San Carlos, Hospital General Universitario de Ciudad Real, Hospital Universitario Puerta de Hierro-Majadahonda, Hospital Universitario de la Fe, Hospital de la Santa Creu i Sant Pau, Hospital General Universitario Guadalajara, Hospital General Universitario Alicante, Hospital Universitario Virgen de la Arrixaca, Hospital Virgen de la Victoria, Hospital Infanta Cristina, Hospital Universitario de Canarias, Hospital Virgen de las Nieves, Hospital Universitario Insular de las Palmas, Hospital Ntra. Señora de la Candelaria, Hospital Clínic de Barcelona, Hospital Universitario la Paz, Hospital San Juan de Alicante, Hospital de Cruces, Hospital Reina Sofía de Córdoba, Hospital Universitario Marqués de Valdecilla, Hospital Universitario Araba, Hospital Ntra. Señora de Valme, Hospital Universitario 12 de Octubre, Hospital de Donostia, Hospital General Universitario Gregorio Marañón, Hospital Infanta Leonor, Hospital San Pedro de Alcántara, Hospital Son Llátzer, Hospital Universitario Central de Asturias, Hospital de Basurto, Hospital Galdakao-Usansolo, Hospital Universitario Joan XXIII, Hospital General de Valencia, Hospital Universitario Virgen Macarena, Hospital Clínico de Valladolid, Hospital de Elche, Complejo Hospitalario Torrecárdenas, Hospital Universitario Burgos, Complejo Hospitalario Universitario de A Coruña, Hospital de Navarra, Hospital de Bellvitge, Hospital Trias i Pujol, Complejo Hospitalario Universitario de Vigo, Hospital Ramón y Cajal, Hospital del Ribera-Alzira, Complejo Universitario Asistencial de León, Hospital General Universitario Reina Sofía de Murcia, Hospital Ramón Méndez, Hospital Virgen de la Salud de Toledo, Hospital Clínico Universitario de Santiago de Compostela.



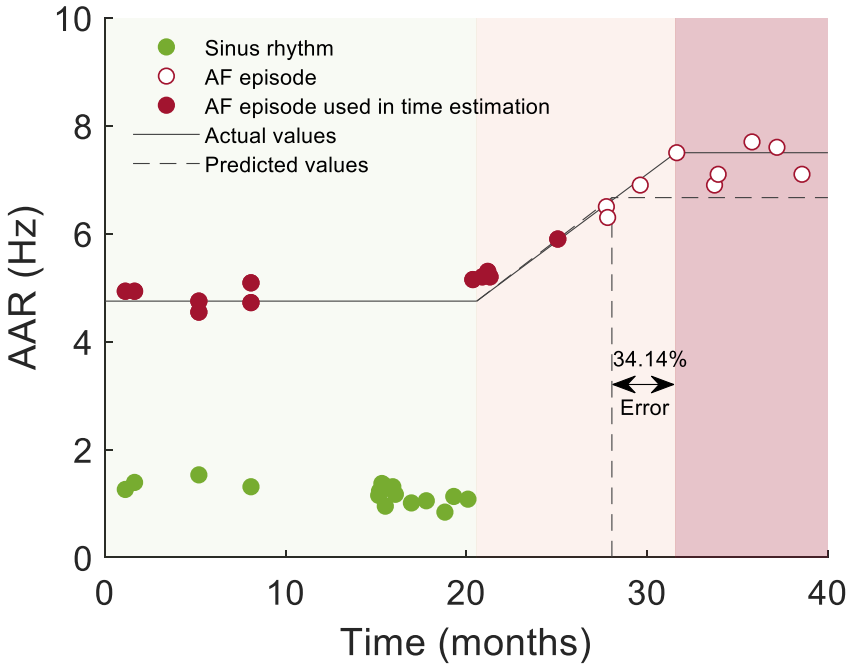
Supplemental Figure 1. Atrial activation rate comparisons among specific subsets of the study. Blox plots and comparisons of atrial activation rate (AAR) between patients with ICD and CRT-D devices. ICD/CRT-D: implantable cardioverter defibrillator+/- resynchronization therapy.



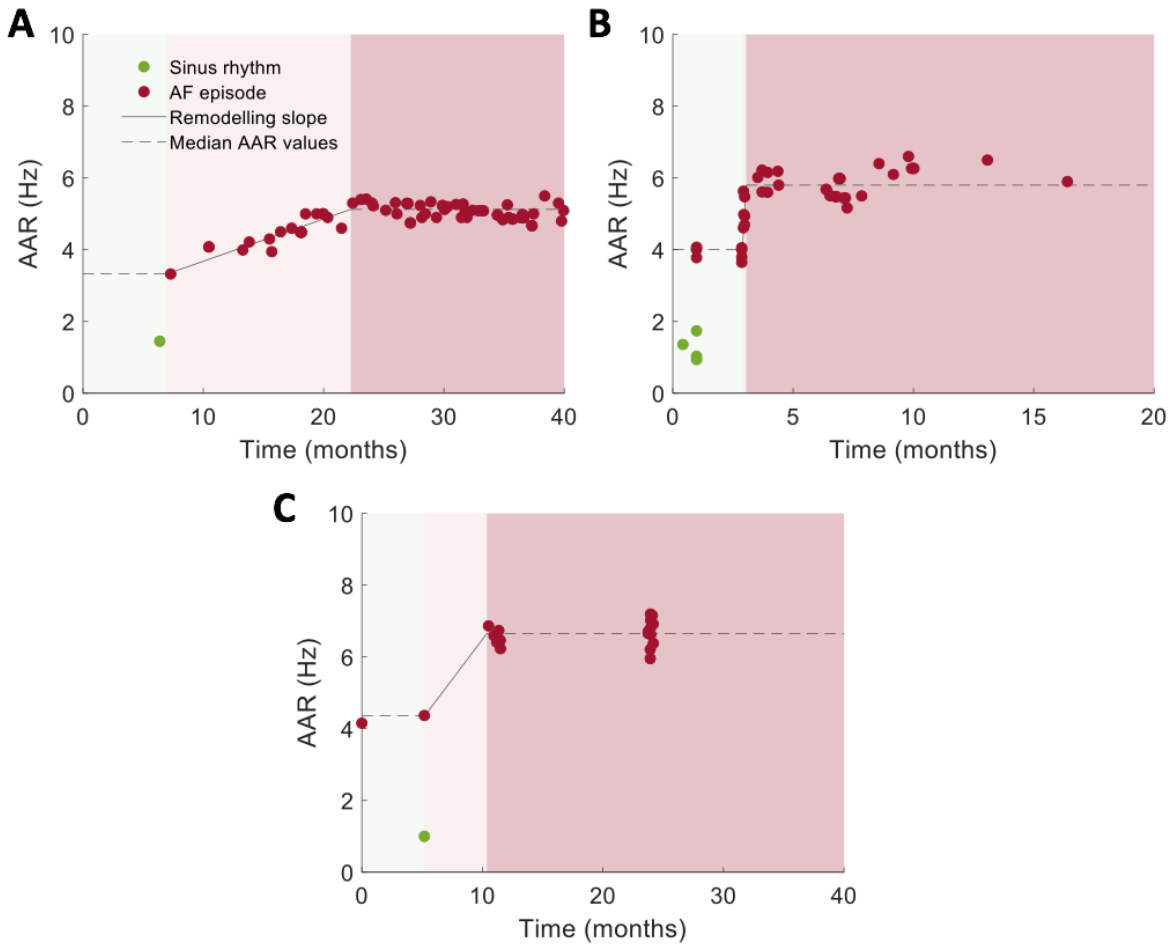
Supplemental Figure 2. Pharmacological therapy in patients with pacemaker and effects on atrial activation rate. A, Percentage of patients with upstream therapies and antiarrhythmic drugs (AD) in the pacemaker (PM) population (N=87). **B,** Blox plots and comparisons of atrial activation rate (AAR) among different pharmacological therapies. ACE-Is: angiotensin-converting-enzyme inhibitors. AER: atrial electrical remodelling. AF: atrial fibrillation. ARB: angiotensin-receptor blockers. MRAs: mineralocorticoid receptor antagonists.



Supplemental Figure 3. Log(slope) correlation with log(time-to-completion AER) in patients with pacemaker. AER: atrial electrical remodelling.



Supplemental Figure 4. Sample case with estimation of time-to-completion of atrial electrical remodelling. Estimation of time-to-completion of atrial electrical remodelling (AER) requires: (1) the median atrial activation rate (AAR) during paroxysmal AF episodes (early stages of AER), (2) the predicted AAR after completion of the electrical remodelling process, and (3) the computed slope at 25% of the expected change in AAR from paroxysmal AF to complete AER in persistent AF. In this case the actual progression of AER is represented with the continuous line. The oblique and horizontal dashed lines show the estimated progression of AER. Red dots indicate median AAR values during the AF episodes used to estimate the time-to-completion of AER. White dots indicate actual AAR values during AF episodes that are not used to estimate the time-course of AER. Green dots indicate AAR during sinus rhythm. Error quantifications of the predicted and actual time-to-completion of AER are shown between the vertical dashed line and the actual completion of AER (end of the pink light background colour). Early stages of AER are indicated with a light green background colour. Complete AER in persistent AF episodes is indicated with a red light background colour. AF: atrial fibrillation.



Supplemental Figure 5. Representative cases of atrial electrical remodelling progression as atrial fibrillation evolves. A and **B,** Sample cases from the ICD/CRT-D population using stored atrial fibrillation (AF) episodes and remote transmissions. In **A,** Time-course of atrial activation rate (AAR, red dots) during AF progression from early stages of electrical remodelling in paroxysmal AF (light green background colour), to completion of atrial electrical remodelling (AER) in persistent AF (red light background colour). Pink light background indicates the electrical remodelling period, which was gradual at 0.11 Hz/moth. In **B,** Representative case of fast progression (12.02 Hz/month) of AER. C, Sample case from the pacemaker population using only stored AF episodes. In patients with pacemakers is also evident the differences in AAR from paroxysmal to persistent AF episodes after completion of AER. Green dots indicate the AAR of sinus rhythm tracings. ICD/CRT-D: implantable cardioverter defibrillatosr+/- resynchronization therapy.

Supplemental Table 1. Univariate analysis of variables potentially associated with time-to-completion of atrial electrical remodelling.

Clinical characteristics	No	Yes	p-value / R^2
Age			0.248 / 0.007
Male, n (months)	22 (1.84)	178 (3.35)	0.152 / -
Cardiomyopathy, n (months)			0.394 / -
ICM		101 (3.63)	
DCM		68 (2.13)	
Other SCM: HCM, ARVC, VHD, or CHD		29 (3.39)	
Non-structural arrhythmogenic disease		2 (3.99)	
LBBB, n (months)	116 (3.61)	84 (2.13)	**0.036** / -
LVEF (≤35%), n (months)	53 (3.21)	147 (2.98)	0.757 / -
Functional class, n (months)			0.782 / -
NYHA I		30 (3.76)	
NYHA II		80 (3.50)	
NYHA III		67 (2.21)	
NYHA IV		2 (2.78)	
Clinical history, n (months)			
Hypertension	76 (2.49)	120 (3.44)	0.259 / -
Diabetes mellitus	143 (3.01)	57 (3.24)	0.871 / -
Hyperlipidaemia	90 (3.19)	110 (2.95)	0.864 / -
Current smoking	131 (3.14)	53 (3.48)	0.614 / -
Chronic renal failure	151 (3.01)	44 (3.57)	0.449 / -
Previous stroke or TIA	167 (3.40)	16 (1.55)	0.064 / -
Clinical presentation, n (months)			
Asymptomatic	106 (3.72)	92 (2.26)	0.123 / -
Syncope	166 (3.30)	32 (2.35)	0.731 / -
Sudden cardiac death	183 (3.14)	15 (3.72)	0.931 / -
Primary prevention, n (months)	57 (3.75)	143 (2.49)	0.112 / -
Device type (ICD), n (months)	109 (2.79)	91 (3.24)	0.929 /-
AAR during Paroxysmal AF			0.002 / 0.584

Data are shown as the number of patients (n) and the median time-to-completion of atrial electrical remodeling (in months). AAR: atrial activation rate. AF: atrial fibrillation. ARVC: arrhythmogenic right ventricular cardiomyopathy. CHD: congenital heart disease. DCM: non-ischemic dilated cardiomyopathy. ICD: implantable cardioverter defibrillator. ICM: ischemic cardiomyopathy. HCM: hypertrophic cardiomyopathy. LBBB: left bundle branch block. LVEF: left ventricular ejection fraction. SCM: structural cardiomyopathy. TIA: transient ischemic attack. VHD: valvular heart disease.

Supplemental References

[1]Lillo-Castellano JM, Marina-Breysse M, Gomez-Gallanti A, Martinez-Ferrer JB, Alzueta J, Perez-Alvarez L, et al. Safety threshold of R-wave amplitudes in patients with implantable cardioverter defibrillator. *Heart* 2016; 102: 1662-70.
[2]Fontenla A, Lopez Gil M, Martinez Ferrer J, Alzueta J, Fernandez Lozano I, Vinolas X, et al. Clinical profile and incidence of ventricular arrhythmia in patients undergoing defibrillator generator replacement in Spain. *Rev Esp Cardiol* 2014; 67: 986-92.