Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional comparison of patients enrolled in two large clinical trials†

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Aims

Despite its high clinical relevance, few studies have investigated depression in patients with atrial fibrillation (AF). We aimed to assess whether depressed mood was more common in persistent or paroxysmal AF patients in controlled models and report frequencies of major depressive disorder.

Methods and results

Cross-sectional data from two contemporary clinical trials were used to compare paroxysmal (n = 310) and persistent (n = 392) AF patients’ depressed mood severity (measured by the Major Depression Inventory) with each trial including only one patient type. A four-category outcome of depressed mood severity was chosen as exposure variable. Ordinal logistic regression was applied to analyse the association of AF type with depressed mood in a crude model and a confounder control model. In the study sample, 8.4% were classified as having major depressive disorder [10.5% of persistent and 5.8% of paroxysmal patients; odds ratio (OR) = 1.89; 95% confidence interval (CI): 1.07–3.37], according to the diagnostic and statistical manual of mental disorders [(diagnostic and statistical manual of mental disorders (DSM-IV)] criteria. In both the age and sex adjusted crude model and in the confounder control model, the association of persistent AF with more severe depressed mood was significant (OR confounder controlled model = 1.44; 95% CI: 1.13–1.75, P = 0.007).

Conclusion

Persistent AF patients may suffer from more severe depressed mood than paroxysmal AF patients with similar symptom burden after controlling for relevant factors.

Keywords

Atrial fibrillation • Depression • Prevalence • Mental health

Introduction

Atrial fibrillation (AF) is the most common heart arrhythmia in adult populations1 with serious implications including increased risk of stroke, heart failure, thromboembolic complications,1 – 3 severely impaired health related quality of life (HRQoL),4 – 6 and significant patient-related attributable costs.7 Although the relationships between measures of psychological distress and a myriad of heart conditions including heart failure and coronary heart disease (CHD) have been thoroughly demonstrated8,9 few studies have applied psychosomatic concepts to patients with AF so far.10 It has, however, been shown that AF patients have higher rates of depression than healthy controls.11,12 Evidence suggests that depression is a relevant factor in AF research both as a risk factor for negative health outcomes in AF patients,13 as a relevant outcome of its own14 and as a mediator of HRQoL,14,15 which has become an important factor when considering treatment options.14,16 – 19

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Cardioversion Trial from the Targeted Pharmacological Reversal of Electrical Remodelling after HRQoL improvement after ablation.23 Dorian et al.24 found that patients with longstanding persistent AF exhibit worse material online, patterns, overlap of enroling centres (43 centres, see Supplementary material online). In addition, we aimed to identify cases of major depressive disorder (MDD) in the AF patient population and to compare these to frequencies shown in population-based studies.

Methods

Setting
The AFNET recruits AF patients from across Germany from medical wards, outpatient clinics, and via office-based physicians (internists and general practitioners) for a nationwide patient register, which, to date, has included more than 10,000 patients, with the aim of creating a representative sample of AF patients in Germany.16 We pooled the individual, patient-level baseline data of two large, recent controlled AF trials, the Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation Trial (ANTIPAF) (NCT 00098137)28,29 and patients from the Targeted Pharmacological Reversal of Electrical Remodelling after Cardioversion Trial (Flec-SL) (NCT 00215774).30,31 Both trials were conducted within the German AFNET, thereby supporting similar enrolment patterns, overlap of enroling centres (43 centres, see Supplementary material online, Appendices) and identical procedures and questionnaires. Patients were recruited from medical wards, outpatient clinics, and via office-based physicians (internists and general practitioners). Informed consent was obtained from all patients and the study protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Baseline data in the present study were collected from 2005 to 2009 for Flec-SL and from 2005 to 2008 for ANTriPAF. Patient management remained at the discretion of local physicians.

Baseline data on paroxysmal AF patients were taken from the ANTriPAF trial.28,29 In ANTriPAF, patients were eligible for inclusion if they were aged 18 years or older and had a confirmed diagnosis of AF (via electrocardiogram (ECG) or Holter ECG recording ≤ 1 year old, with documented AF; an episode of AF in any ECG recording lasting longer than 30 s) and documented paroxysmal AF (defined as: the ECG recordings within five consecutive days after initial detection of AF show both documented AF and sinus rhythm).

Patients with persistent AF were obtained from the Flec-SL trial database.30 In Flec-SL, the inclusion/exclusion criteria were similar to those described above for the ANTriPAF patients. ‘In Flec-SL the mean duration of AF prior to enrolment was 28 months. In all patients, persistent AF was documented by at least one ECG at enrolment and one 24 h Holter ECG showing continuous AF prior to enrolment. Details of the study protocol and results have been published.30,31 All Holter ECGs were centrally adjudicated by an independent committee who were masked to treatment allocation’.

Both studies exclude severe concomitant cardiovascular diseases, thus reducing potential confounding a priori and increasing the comparability of the two clinical studies. The inclusion and exclusion criteria are summarized in Appendix C.

Study population
The total study population consisted of 770 AF patients for whom HRQoL and clinical data were available (Figure 1). A total of 68 patients with missing values in the Major Depression Inventory (MDI) were excluded. Excluded patients with missing values in the MDI were more likely to be female, more likely to have hypertension, and more likely to have hyperlipidaemia than patients with no missing values.

The remaining 702 patients formed the study sample for which descriptive data are provided, and from which criteria for inclusion in the regression models were evaluated.

Outcome: depression
Depression was measured by the validated and widely used MDI scale32–35 consisting of 10 items rated on a 6-point Likert scale.

First, the MDI scale may be applied as a rating scale.34 The rating scale algorithm produces a sum score ranging from 0 to 50. Patients are considered to have mild depressed mood if they have a score of 20–24, moderate depressed mood with a score of 25–29, and severe depressed mood with a score of 30 or more.34

Secondly, the MDI scale may be applied to diagnose MDD according to the diagnostic and statistical manual of mental disorders (DSM-IV).35 For this purpose an algorithm is used whereby the 10 items are summarized into 9 symptoms. Patients who have at least five symptoms of which at least one must be a ‘core’ symptom, are diagnosed with MDD.35

Exposure: atrial fibrillation type
The principal inclusion criteria in ANTriPAF and Flec-SL called for an assessment of the type of AF. ANTriPAF required that the investigator classified AF as paroxysmal, while Flec-SL enrolled only patients which were classified as persistent AF by the investigator. The type of AF was verified in the two trials by the following ECG definitions, in line with outcome definitions;36,37 Paroxysmal AF: ECG recordings within seven consecutive days after initial detection of AF show both documented AF and sinus rhythm. Persistent AF: continuous AF in all ECGs recorded during the current episode and continuous AF in a Holter recording recorded prior to cardioversion.
Covariates

The following sociodemographic variables were analysed in this study: age, sex, and employment status (unemployed = students, housewives, unemployed; employed = full time, part time, and other). The clinical factors which were analysed in this study included: diabetes, dilated left atrium (LA), family risk for CHD, hyperlipidaemia, smoking (index = current smokers), physical inactivity (index = respondents who exercise less than three times a week), high alcohol consumption (index = regular to excessive users), obesity (index = body mass index ≥ 30), AF-related symptom burden (as measured by the Atrial Fibrillation Symptom Check-list), NYHA state (dichotomous with index = NYHA states 2–4), and hypertension. In addition, data on the following comorbidities were ascertained and included: valve disease, cancer, thromboembolic complications (including: stroke, transitory ischaemic attack, peripheral/pulmonary emboli), chronic obstructive pulmonary disease (COPD), syncope, CHD, and finally, whether patients received an electrical cardioversion (ECV) and/or pharmaceutical cardioversion in the last 12 months.

Statistical analyses

For descriptive analyses, regarding associations of variables with AF type and depressed mood, differences of continuous variables were assessed by the t-test; in case of ordinal variables, the Mann–Whitney U test was applied. The significance of associations between categorical variables was derived from the χ² test.

For multivariate analyses, ordinal regression models with a cumulative logit link function and multinomial distribution function were applied to assess the association between the exposure AF type and the outcome depressed mood, which was classified in four categories. Besides a crude model, a confounder control model was estimated with confounder selection based on the change-in-estimate (CIE) approach following Maldonado et al. As CIE criterion, we chose first the common 10% CIE criterion following Maldonado et al. (selection method 1). Secondly, a backward selection approach using CIE criterion was applied (selection method 2), whereby variables whose exclusion resulted in a CIE > 10% were selected. All regression models satisfied the proportional odds assumption (P > 0.34). The odds are cumulated over the lower ordered values. Thus, the calculated odds ratios (ORs) represent the change in likelihood of suffering from a more severe depressed mood state for persistent vs. paroxysmal AF patients.

All statistical analyses were run in SAS (Version 9.2, SAS-Institute Inc.). The significance level α was set at 0.05. The analysis and the description in this paper follow the STROBE guidelines for cross-sectional studies.

Results

Description of study population

The study population consisted of 702 patients (Figure 1), of whom 392 (55.8%) patients had persistent AF and 310 (44.2%) had paroxysmal AF. Table 1 shows sociodemographic variables, clinical factors, and comorbidities stratified by persistent and paroxysmal patients.
Persistent AF patients were more likely older, to have received an ECV in the past 12 months, to have hypertension, valve disease, and COPD. Risk of CHD in the family was a trait associated with paroxysmal patients. Forty-three patients had comorbid CHD, with no difference between the AF types. Patients under investigation were relatively healthy, with ≏ 80% having no symptoms of heart failure.

### Association of atrial fibrillation type and covariates with depressed mood and major depressive disorder—bivariate analysis

In the whole sample, 38.8% of patients experienced mild, 19% moderate, and 14.8% severe depressed mood. Table 2 shows sociodemographic variables, clinical factors, and comorbidities stratified by depressed mood severity. As can be seen, NYHA class, AF symptom severity, hypertension, and cancer were significantly associated with depressed mood.

Persistent AF patients were more likely to suffer a more severe depressed mood state across the four possible classifications \( [\text{OR} = 1.69; 95\% \text{ CI: } 1.29–2.22] \). Furthermore, frequencies of MDD were calculated. A total of 59 (8.4%) patients were diagnosed with MDD \( [10.5\% \text{ of persistent patients}; 5.8\% \text{ of paroxysmal patients} \ (\text{OR} = 1.89; 95\% \text{ CI: } 1.07–3.37)] \). Figure 2 shows frequencies of depressed mood states and MDD, stratified by AF type and \( P \) values for associations of AF type with depressed mood using different cut-off points.

### Association of atrial fibrillation type with depressed mood—multivariate analysis

Table 2 shows the values for the CIE of each covariate being added to the crude model. After backward selection, NYHA state met the criteria for inclusion as a confounder. One hundred and four patients with missing data were deleted for the purposes of the regression model. Excluded patients were less likely to have hypertension and hyperlipidaemia. No differences were found with regard to the remaining variables.

After controlling for potential confounders, persistent AF patients were significantly more likely to suffer a more severe state of depressed mood than paroxysmal patients in the crude model \( (\text{OR} = 1.63; 95\% \text{ CI: } 1.33–1.92, P = 0.001) \). The first confounder selection method included NYHA and pharmaceutical cardioversion as confounders and the second method selected NYHA only. In both models, the association between persistent AF and depressed mood severity remained significant \( \text{(OR}^2 = 1.44; 95\% \text{ CI: } 1.13–1.75, P = 0.007) \) \( \text{(OR}^2 = 1.44; 95\% \text{ CI: } 1.14–1.75, P = 0.007) \). Figure 3 summarizes these results. Interaction terms were tested in
the crude model for age, sex, and NYHA state. None of the interaction terms were significant (all \( P \) values > 0.66).

**Discussion**

Here, we report for the first time that depressed mood tends to be more severe in patients with persistent AF than in patients with paroxysmal AF. Specifically, persistent AF patients were more likely to report more severe states of depressed mood, as measured by a widely accepted and reproducible measure of depression, than paroxysmal patients in this study. Although it is unclear to what extent the patients’ characteristics reflect those of all persistent and paroxysmal patients, various commonly used measures of disease severity, including symptom burden, could not explain the observed differences. This is the first study to show a significant difference in suffering from depressed mood and MDD between persistent and paroxysmal AF patients. However, although the present investigation takes into account one of the most extensive datasets to study mental health aspects in over 700 AF patients, further studies are needed to replicate these analyses and to further test the relationship between types of AF and their related characteristics with longitudinal study designs. The present study adds to the findings of Peinado et al., who showed that persistent and paroxysmal AF patients have significantly lower psychological HRQoL (as measured by the AF-QOL instrument) than permanent AF patients. That study did not find differences in depression between patients with persistent and paroxysmal AF, but the cohort size may not have been large enough. Dabrowski et al. found no significant differences in depression levels between paroxysmal, persistent nor permanent AF patients. The findings of Peinado and Dabrowski, however, relied on notably smaller and less homogeneous populations (\( n = 341 \), \( n = 150 \), respectively).

The frequencies of MDD in this study population were alarmingly elevated in comparison with population-based estimates. Olsen et al. calculated a prevalence of 3.3% for MDD (using the MDI scale) in Denmark. In an elderly, German, population-based study (including persons aged 60–85 years), Glaesmer et al. estimated a prevalence of 6.6% for MDD (measured by the Patient Health Questionnaire). The questionnaires (MDI and PHQ-9) used in these studies ask for depressive symptoms in the past 2 weeks, as in the present analysis. In our population, 8.4% (± 2.5) of patients were diagnosed with MDD. Thus, this study adds to evidence that AF

### Table 2 Sociodemographic and clinical characteristics of the AF study population, stratified by severity of depressed mood (\( N = 702 \))

<table>
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<tr>
<th></th>
<th>Missing</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>( P )</th>
<th>CIE</th>
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<td>69.2</td>
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<td>36.6</td>
<td>30.8</td>
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<td></td>
<td></td>
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<td>Unemployed</td>
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<td></td>
<td></td>
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<td>AF symptom severity (median, IQR)</td>
<td>257</td>
<td>17 (9.5)</td>
<td>21 (12)</td>
<td>26 (12)</td>
<td>26.5 (12.5)</td>
<td>&lt;0.001</td>
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<td>Diabetes</td>
<td>0</td>
<td>7.8</td>
<td>8.8</td>
<td>9.7</td>
<td>11.5</td>
<td>0.278</td>
<td>1.3</td>
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<td>LA dilated</td>
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<td>50.5</td>
<td>34.5</td>
<td>37.1</td>
<td>28.9</td>
<td>0.091</td>
<td>8.6</td>
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<td>Family CHD risk</td>
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<td>29.1</td>
<td>20.2</td>
<td>28.5</td>
<td>23</td>
<td>0.590</td>
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<td>Hyperlipidaemia</td>
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<td>28.7</td>
<td>32.2</td>
<td>32.5</td>
<td>38</td>
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<td>74.6</td>
<td>70.2</td>
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<td>34.3</td>
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<td>9</td>
<td>11.5</td>
<td>0.247</td>
<td>1.7</td>
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<td>81.3</td>
<td>81.7</td>
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<td>1.1</td>
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<td>26</td>
<td>28.9</td>
<td>0.002</td>
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<td>0</td>
<td>54.7</td>
<td>57</td>
<td>65</td>
<td>65.4</td>
<td>0.025</td>
<td>7.5</td>
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<td>0</td>
<td>11</td>
<td>7.7</td>
<td>8.2</td>
<td>15.4</td>
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<td>0.5</td>
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<td>Cancer</td>
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<td>7.7</td>
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<td>0.5</td>
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<td>0.5</td>
<td>4.1</td>
<td>3</td>
<td>3.9</td>
<td>0.124</td>
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<td>26</td>
<td>4.4</td>
<td>5.3</td>
<td>9.9</td>
<td>8</td>
<td>0.073</td>
<td>5.6</td>
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<tr>
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<td>12.5</td>
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<td>23.1</td>
<td>18.3</td>
<td>0.044</td>
<td>8.8</td>
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<td>Pharmacological cardioversion</td>
<td>0</td>
<td>4.7</td>
<td>4</td>
<td>5.2</td>
<td>3.9</td>
<td>0.909</td>
<td>17.3</td>
</tr>
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</table>

CIE, change in estimate: change in estimate of the association between AF type and depressed mood severity resulting from including the covariates into the crude model. For categorical variables, column percentages are reported (e.g. 49% of patients with no depressed mood had persistent AF). Bold values indicate a \( P \) value, > 0.25.
Depression in paroxysmal and persistent AF patients

The main result of the present analysis is at first glance slightly counterintuitive, as paroxysmal AF patients tend to be more symptomatic. 

Hence, AF-related symptoms cannot fully explain depression in persistent AF patients, consistent with a prior review that suggests lower HRQoL in ‘asymptomatic’ AF. 

In the present analysis, it is unlikely that AF-related symptoms explain the difference in depressed mood severity, since the symptom burden was undistinguishable between the two patient groups.

Figure 2 Prevalences of states of depressed mood severity and cases of MDD. 

Figure 3 Odds ratios (OR) for the association of AF type with depressed mood severity in multivariate ordinal regression models. 

Study limitations

The major strength of this study is the large sample size (n = 702) and the homogeneous setting of inclusion within the AFNET study umbrella. The cross-sectional nature of this study is a major limitation. Furthermore, a limitation is that only one patient type was available in each trial. Despite this, patients recruited by the AFNET for both the Flec-SL and ANTIPAF trial have been recruited from a range of clinical populations around Germany including both hospitals and clinics, thus increasing the generalizability in comparison with a host of other clinical studies. Identical enroling centres and procedures for both trials make the two trials comparable and minimize potential centre effects. Nonetheless, some differences in inclusion and exclusion criteria do exist. For example, effective anticoagulation for 3 weeks or the exclusion of the presence of thrombi via transesophageal echocardiogram (TEE) was an inclusion criterion in Flec-SL only. Flec-SL also allows the inclusion of patients with a pacemaker. However, only two patients in the study population had any implanted pacemaker or defibrillator. Full details on the inclusion and exclusion criteria are available in Appendix C. The anticipation of cardioversion in persistent patients may also have affected their mood, although the MDI should represent chronic rather than acute conditions, and thus be robust against state-related adversities.

No data were available on marriage status and financial stability. Data on treatment of patients with pharmacological therapies, which may influence mood were not available. The patients observed in the present study are relatively healthy; 80% of patients suffer no heart failure. Generalizability to patients with a greater burden of comorbidities may be limited.

Implications

The observed association of persistent AF with depression appears suggestive that the increased duration and regularity of being in arrhythmia is responsible for the association. However, symptom perception and perception of being in arrhythmia have been shown to be unrelated to device detected episodes. A plausible cause could be that persistent patients perceive themselves to have a more severe disease condition. It has been shown that patients, who report a good understanding of their illness have less negative emotions and fewer symptoms. 

Evidence so far suggests that depression plays a role in mortality, in AF patients and risk for recurrence of AF after therapy. This is not surprising given the importance of depression in cardiovascular disease research. Lange and Herrmann-Lingen suggest that heightened adrenergic tone and pro-inflammatory states pose plausible mechanisms through which this takes place. Combined with the fact that this study and others confirm elevated levels of depression in AF patients, the importance of analysing depression specifically in AF research is highlighted.

Future aims

Future work should aim to further elucidate the predictors for depression in AF patients. In future studies, we aim to analyse the causation of the observed differences in depression risk.

Conclusions

Persistent AF patients may be more likely to suffer from more severe states of depressed mood than paroxysmal AF patients, after
adjustment for potential confounders. The observed differences are not explained by symptoms nor commonly measured clinical variables. Observed frequencies of MDD (i.e. clinically relevant) are elevated in comparison with various estimations of the prevalence of MDD in European countries.

Supplementary material

Supplementary material is available at Europace online.

Acknowledgements

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Funding

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Adenosine reveals dormant conduction of an arrhythmogenic thoracic vein despite the absence of previous ablation

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A 60-year-old man with paroxysmal atrial fibrillation (AF) underwent pulmonary vein (PV) isolation. Repeat procedure was performed due to immediate clinical recurrence. None of the previously isolated PVs were found to have reconnected. Adenosine challenge induced a burst of atrial tachycardia (AT) initiating a self-terminating episode of AF (Panel A). Based on the 12-lead electrocardiogram (ECG) morphology and after ruling out a left atrial origin, a focus arising from either the superior vena cava (SVC) or the high crista terminalis was suspected. At baseline, no potentials were recorded from the Lasso catheter positioned in the SVC. However, a repeated adenosine injection exposed a dormant conduction from the right atrium to the vein despite the absence of any previous ablation in that area (Panel B, black arrows). It triggered repetitive SVC ectopies (Panel C left, black stars), at times concealed, that reproduced the 12-lead ECG morphology of the AT initiating AF (Panel C right).

The present case thus further expands the field of application of adenosine challenge in patients with recurrent paroxysmal AF despite PV isolation. Until now, adenosine has been shown to restore dormant conduction of arrhythmogenic thoracic veins in the acute and, more recently, chronic post-ablation period. The present case demonstrates that adenosine can also provoke conduction in electrically silent connections between atrium and veins despite the absence of previous ablation.

This finding suggests that some venous muscular sleeves may spontaneously alternate between electrical quiescence and phases of recovered excitability leading to intermittent venoatrial conduction. This hypothesis is further substantiated by reports showing that the sites of PV conduction gaps observed during a third ablation procedure can differ from those observed during the second procedure.