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Asymptomatic recurrences of atrial fibrillation after pulmonary vein isolation

Thomas Neumann*, Ali Erdogan, Thorsten Dill, Harald Greiss, Alexander Berkowitsch, Johannes Sperzel, Malte Kuniss, Klaus Kurzidim, Christian W. Hamm, and Heinz-Friedrich Pitschner

Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany

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Aims The purpose of this study was to determine the occurrence of asymptomatic episodes of atrial fibrillation (AF) and wrong AF perception after pulmonary vein isolation (PVI). We evaluated the success of ablation by using the following measurements: (i) clinical symptoms and duration of symptoms noticed by patients and (ii) synchronous event recording (ER).
Methods and results Eighty patients with paroxysmal AF underwent PVI and were provided repeatedly with a portable ER upon discharge and every 3 months for a year. The ER automatically detects arrhythmias by a detection algorithm and can also be manually triggered by the patient. In 46/80 patients (57.5%), episodes of AF were documented. Asymptomatic AF was detected in 21.3%. In 9/80 patients (11.3%), who reported clinical AF recurrence, no AF could be shown by ER. We compared patients' perception to have suffered AF episodes with the ERs and found a sensitivity of 75% and a specificity of 92%.
Conclusion Reliance on perception of AF by patients after PVI results in an underestimation of recurrence of the arrhythmia. We observed a maximal occurrence of silent AF or wrong perception of AF in 26/80 (32.6%) patients.

Introduction

Pulmonary vein isolation (PVI) has been shown to be an effective strategy in eliminating highly symptomatic paroxysmal, drug refractory atrial fibrillation (AF).[1] Irrespective of the reported strategies for electrical isolation of the pulmonary veins, most of the published studies[2–6] have documented the success rate of the therapy by performing occasional Holter ECG or event recording (ER).

Only few data with continuously ECG monitoring systems, which excluded the detection of silent AF episodes, are available.[7]

We hypothesized that patients' subjective reports of clinical AF relapses, as the only criterion for success of ablation allows mistakes in the interpretation of the success of PVI: (1) sinus tachycardia or single supraventricular premature beats could be classified as AF relapse and (2) silent AF could be unrecognized.

During the last decade, several investigators have reported on the occurrence of asymptomatic AF in patients with symptomatic paroxysmal AF,[8–10] but there are only few data available about the occurrence of asymptomatic AF episodes after PVI.

Methods

Study population

Starting in April 2000, we prospectively enrolled 80 consecutive patients (55 ± 9 years, 27 female) with highly symptomatic paroxysmal AF refractory to more than three antiarrhythmic drugs, including class-I agents, sotalol, and amiodarone. Medical history was obtained from patient interview and review of the medical records including ECGs and Holter ECGs depicting episodes of AF. The duration and number of AF episodes during the last 3 months before the ablation procedure were documented according to history and ECG recordings. The risks of ablation were discussed in detail and all patients gave written informed consent before the procedure.

Electrophysiological study and radiofrequency ablation

All procedures were performed under general anaesthesia. During the catheter procedure, an infusion of heparin was maintained to achieve an activated clotting time >300 s.

A diagnostic quadripolar catheter (Biosense Webster, Diamond Bar, CA, USA) was positioned in the coronary sinus. In addition, one mapping catheter (Lasso™, 10 polar, Biosense Webster) and one saline cooled ablation catheter (Cool tip™, Chilli, Cardiac

* Corresponding author: Department of Cardiology/Electrophysiology, Justus-Liebig-University of Giessen, Klinikstraße 35, 35392 Giessen, Germany. Tel: +49 641 9942112, fax: +49 600 3828990.
E-mail address: tneuman1@aol.com

Pathways, Sunnyvale, CA, USA) were placed in the pulmonary veins, using a transeptal approach (SL-1™, St Jude Medical Inc., Daig Division, St Paul, MN, USA). The ablation catheter was placed proximal to the mapping catheter at the atrial side of the pulmonary vein ostium. Primary ablation sites were the ostial region with verification by fractionated signals of myofibrils.

The aim of the ablation strategy was the electrical disconnection of the pulmonary veins in which we could find the described signals. PVI was verified by proof of entrance- and exit-block of each treated PV.

Clinical follow-up and ER

The event recorder (CardioRec™, AD Elektronik, Wetzlar, Germany) is a continuously functioning, single-channel system. The device permanently registers the cardiac frequency of the patient via detection of the R-peak. In the case of cardiac arrhythmia, the digital recording of the ECG starts automatically. After the analysis of a R-peak distance compared with the dynamic mean value of preceding five intervals, a recording of 20 s starts if this interval does not lie within the adjustable tolerance limits of the mean value (trigger thresholds maximum $>+60\%$, minimum $<-40\%$). Permanent detection allows every recording automatically to contain the data which occurred 20 s before the actual start of the arrhythmia. The start and the end of automatic recordings could not be noticed by the patients.

The essential mechanism of the device is the detection of the R-wave. It distinguished (dx/dt) of the original signal. The slope and amplitude of the flanks concerning the QRS-complex differ considerably in comparison with the T-wave. A corresponding time period guaranteed that both flanks of the QRS-complex were analysed for recognizing the R-wave. Artefacts, mostly high frequency, were excluded by this analysis.

We tested the ER device especially for AF in a pilot study and used a Holter monitoring system as the gold standard in our intensive care unit. Concordance between ER and Holter was found in 240 cases from a total of 244 cases (52 patients) resulting in a positive predictive accuracy of 100% and a negative predictive accuracy of 98%.

In the case of clinical symptoms, the patients can start the recording at any time by tapping on the housing of the device.

ER contains date, time, and details of the trigger mode. During monitoring, about 1000 events can be recorded. That means 666.7 min at maximum can be stored with one event lasting 40 s. All patients received the described ER at discharge as well as 3, 6 and 9 months after the procedure for a period of 3 weeks each, total 12 weeks. For evaluation of clinical recurrences of AF, we asked about recurrence of symptoms which were described by the patients before the ablation procedure.

An episode of AF was defined as palpitations described by the patient, or AF documented for at least 30 s recorded by ER in the absence of clinical symptoms.

Patients were asked to keep a protocol with their annotation of time, number, and duration of clinical symptoms judged as AF during evaluation with the ER.

The interpreting physician for ER analysis was blinded to patient data.

Statistical analysis

All associations between dependent samples represented in 2×2 table were analysed using McNemar-χ^2 test. The non-paired 2×2 tables were analysed using Fisher's exact test. The $N \times M$ contingency tables were analysed using χ^2 test.

All continuous variables were tested for normality using Kolmogorov–Smirnov test. The normally distributed variables were analysed using paired and unpaired *t*-test (two-groups analysis) and ANOVA (N-groups analysis). In case of non-normal distribution, the continuous variables were analysed using Wilcoxon's matched pairs test/Mann–Whitney *U* test (two-groups analysis) and Kruskal–Wallis *H* test/Friedman test (N-groups analysis).

The percentage of patients with event-free, asymptomatic, mixed, and symptomatic AF recurrences and 95% confidence interval were calculated. The continuous data were described in mean, SD, median, lowest (Q25), and highest (Q75) quartiles.

Results

Thirty-four patients had lone AF and 46 patients had mild heart disease, including hypertensive cardiomyopathy and CAD with normal ejection fraction and normal atrial dimensions. Symptomatic AF occurred over a mean of 6.9 years.

In 94.8% (272/287) of the ablated pulmonary veins, we achieved a complete disconnection of the pulmonary vein from the left atrium.

In our patients, AF occurred 40 ± 36 (median = 20, Q25 = 10, Q75 = 90) times within 3 months before the procedure vs. 7 ± 21 (median = 0, Q25 = 0, Q75 = 2) times during the last 3 months of follow-up. The mean duration of symptomatic AF before the ablation procedure was 14.7 ± 24 h (median = 7.5, Q25 = 2, Q75 = 24) vs. 2.7 ± 6.7 h (median = 0, Q25 = 0, Q75 = 0.5) during the last 3 months of follow-up. Regarding the AF burden, a product of duration and number of AF episodes within the last 3 months before the procedure ($26\,485 \pm 40\,326$ min, median = 8640, Q25 = 1890, Q75 = 27 900) vs. during the last 3 months of follow-up ($4140 \pm 20\,466$ min, median = 0, Q25 = 0, Q75 = 240), we observed a drastic reduction after ablation in the total group ($P < 0.01$). The reduction was more pronounced at the end of the observation time compared with the beginning.

All patients with asymptomatic AF relapses were not receiving antiarrhythmic medication. Eleven patients with clinical symptomatic AF relapses after PVI received an antiarrhythmic drug during the period of observation. A prophylactic antiarrhythmic drug therapy after PVI was not scheduled. In the case of symptomatic AF, the medication was adjusted on an individual basis.

A correlation between clinical reports of episodes of AF and episodes documented during ER was confirmed ($P < 0.01$). Compared with the documented episodes of AF, patients' reports of clinical episodes showed a sensitivity of 75% and a specificity of 92%.

During follow-up of 12 months after ablation in 80 patients, the mean observation time of ER per patient was 83 days. We analysed a total of 316 ERs and associated symptoms of the patients over the time of ER. Four ERs were excluded from analysis because of technical reasons. The results of the perception of underlying rhythm given by the patients vs. objective results of the ER's are shown in *Table 1*.

Table 1 All performed ERs

Perception of rhythm vs. ER	*n*
SR (clinical) vs. SR (ER)	202
SR (clinical) vs. AF (ER)	24
AF (clinical) vs. AF (ER)	73
AF (clinical) vs. SR (ER)	17

During 202 ERs without documented AF relapses, the patients had no clinical symptoms of AF. However, in 24 ERs with documented AF, the patients had no clinical symptoms.

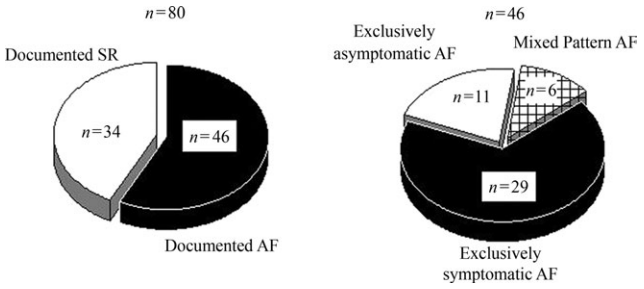

Figure 1 The left circle depicts the distribution of all patients divided into documented sinus rhythm (SR) and AF. The right circle illustrates the distribution of patients with exclusively asymptomatic AF and patients with symptomatic AF. Six patients demonstrated a mixed pattern of clinically recognized and asymptomatic episodes of AF during the time of ER.

Table 2 Characteristics of AF episodes

Characteristics	Asymptomatic AF	Symptomatic AF
Number	33	156
Circardian distribution (7 a.m.–7 p.m.)	24	119
Mean of minimal/maximal frequency (bpm)	69–140	98–149

A total of 6/80 patients (7.5%) demonstrated a mixed pattern of clinically recognized and asymptomatic episodes of AF during the time of ER. In 11/80 (13.8%) patients, we observed only episodes of asymptomatic AF and no symptomatic AF (*Figure 1*).

Regarding the 17 patients with asymptomatic AF, we observed 33 episodes. In 13 of these patients with asymptomatic AF, the episodes were documented during daytime between 7 a.m. and 7 p.m. We observed a minimum of 13.8% (patients with exclusively asymptomatic episodes) and a maximum of 21.3% (patients exclusively asymptomatic episodes and a mixed pattern) suffered from asymptomatic AF episodes. The maximum rate is limited by the uncertainty of sleep periods. There was no discernible pattern either in duration or in the mean, minimal, or the maximal frequency of these asymptomatic AF episodes (*Table 2*).

The point estimate and 95% confidence intervals for patients with asymptomatic AF, mixed pattern of AF (asymptomatic and symptomatic AF), symptomatic AF, and no AF, validated by repeated ER are shown in *Figure 2*.

Discussion

This article reports on the efficacy of PVI for patients with highly symptomatic paroxysmal AF. It provides information regarding the assessment of efficacy, in that patient's symptoms may not reflect the entire burden of AF as well as the

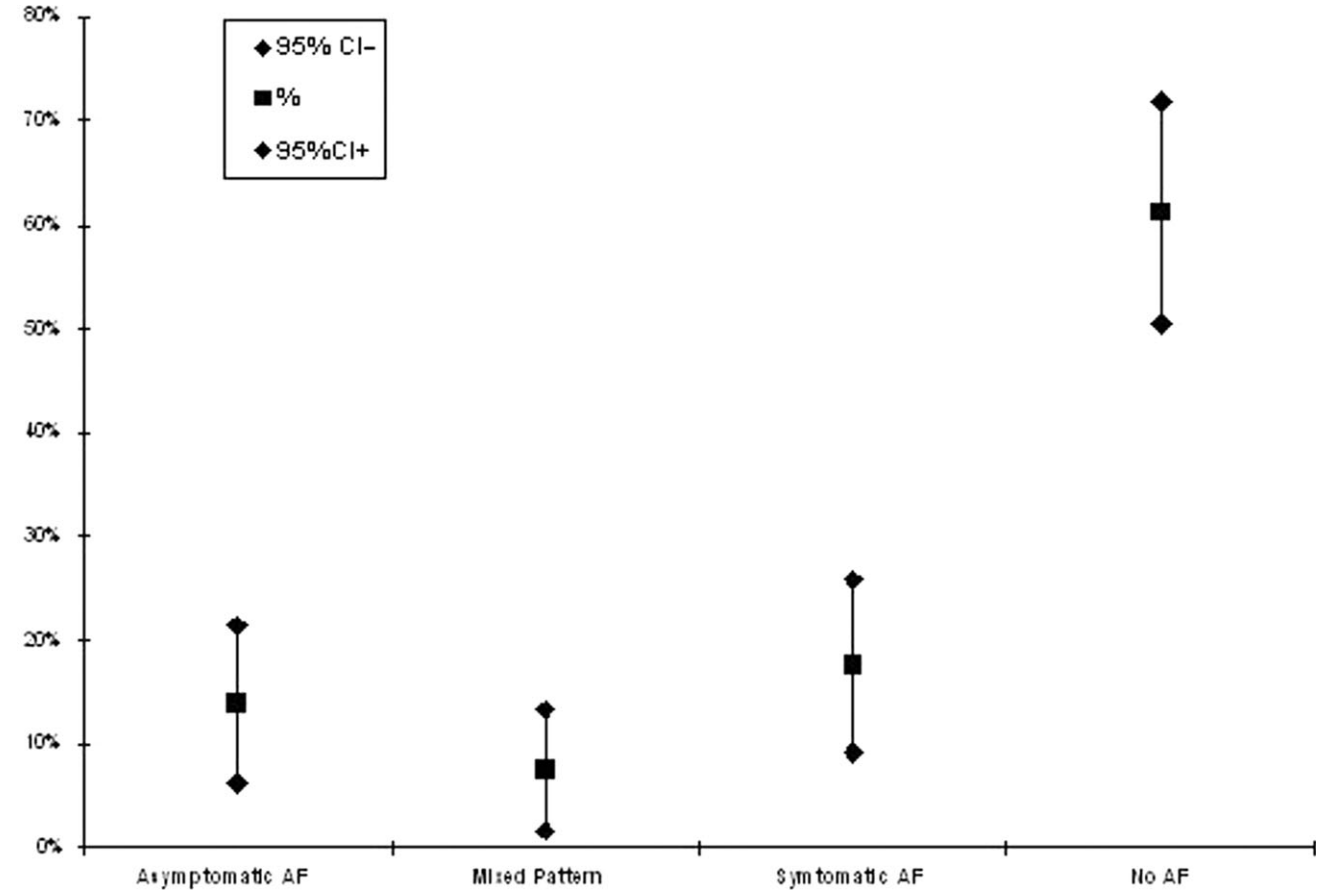

Figure 2 Point estimate and 95% confidence intervals for patients with asymptomatic AF, mixed pattern of AF (asymptomatic and symptomatic AF), symptomatic AF, and no AF, validated by repeated ER.

fact that patient's symptoms may suggest arrhythmia recurrence when no arrhythmias exist.

The prevalence of asymptomatic AF in general is not clearly known.

Some data are available from prospective studies which estimated the prevalence of asymptomatic AF.[11,12] Rose *et al*.[12] reported that among 18 403 British male civil servants, AF was found in 70, and in 33 (47%) it was totally silent. Benjamin *et al*.[13] published data from the Framingham Study reporting asymptomatic AF relapses in 40.5% of all AF cases.

Recently published studies on success rates after catheter ablation of drug refractory AF have not reported data about systematic follow-up over a period of 12 months, using a continuous functioning ER system with automatic detection of AF. Most of the studies described the performance of several cursory Holter-ECGs, patients' clinical perception of AF, and only the sporadic performance of ER.[2–4] However, recently published studies have shown that the ER systems with automatic detection of arrhythmias are superior in the detection of AF compared with Holter-ECGs.[14]

The recently published prospective study of Roche *et al*.[14] reported an overall incidence of AF episodes in 20/65 (31%) consecutive patients with negative 24-h Holter ECG. Eleven (55%) of these 20 patients were asymptomatic and would not have been diagnosed without the automatic mode of the event recorder. These results support the published data on a superior detection of arrhythmias using ER systems compared with standard 24- or 48-h Holter-ECG recordings.[15,16]

We observed an AF burden reduction of 84.4% in the total cohort of which only 11 were treated with antiarrhythmic drug therapy after ablation due to highly symptomatic recurrences. This clearly documents the clinical effectiveness of the approach. Although the clinical success rate in patients who felt free of AF during the last 3 months was 68.8% in our cohort, the analysis of recurrence of AF was much higher than purely clinical follow-up might have suggested. A purely clinical follow-up is associated with underestimation of AF. We showed that 21.3% of patients with documented AF suffered from asymptomatic AF in our study. Nine patients (11.3%) reported AF episodes without documentation on ER.

Unfortunately, we did not perform an ER before PVI. Therefore, we are unable to give any information on whether this phenomenon already exists before PVI. A further limitation of this study is that the portable ER system was only used for a limited time period of the whole clinical follow-up. Therefore, we can only speculate if the percentage of asymptomatic AF recurrences is the true number, or only the 'tip of the iceberg'.

Conclusion and perspectives

Reliance on perception of AF by patients after PVI results in an underestimation of recurrence of the arrhythmia. We observed a maximal occurrence of asymptomatic AF or wrong perception of AF in 26/80 (32.6%) patients.

In order to obtain reliable information about success of PVI, repeated ER with automatic detection of arrhythmias seems to be necessary.

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