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Prediction of early recurrence of atrial fibrillation after external cardioversion by means of P wave signal-averaged electrocardiogram

Erkennung frührezidiv-gefährdeter Patienten nach externer Kardioversion von Vorhofflimmern mittels signalgemitteltem P-Wellen EKG

Zusammenfassung Die Therapie von Vohofflimmern mittels elektrischer Kardioversion (CV) ist durch eine hohe Rate von Rezidiven limitiert. Frührezidive innerhalb der ersten Stunden nach CV treten in einer Subpopulation von Patienten auf, deren klinische Charakteristika nur wenig untersucht sind. Diese prospektive Untersuchung wurde durchgeführt, um den Wert des signalgemittelten P-Wellen EKGs (PSAECG) zur Erkennung der Patienten zu erforschen, die einem erhöhten Risiko eines Frührezidivs nach Kardioversion ausgesetzt sind. Es wurden 111 Patienten nach erfolgreicher Kardioversion untersucht und PSAECG nach 1/2, 1, 24 Stunden und 1 Woche registriert. Die Wertigkeit verschiedener PSAECG Parameter (signalgemittelte P-Wellen-Dauer, „root mean square“ Spannung der terminalen 20, 30 und 40 ms der P-Welle, RMS 20, 30, 40) zur Identifizierung von Patienten mit Frührezidiv (prospektiv definiert als Rezidiv innerhalb von vier Stunden nach CV) wurde untersucht. Innerhalb des Kollektivs trat bei sieben Patienten ein Frührezidiv auf, bei 30 Patienten trat ein Rezidiv innerhalb der ersten Woche nach CV auf. Die Patienten mit Frührezidiv wiesen eine signifikant verlängerte P-Wellen-Dauer auf im Vergleich zu denjenigen, die im Sinusrhytmus verblieben (194 ± 16 ms vs. 139 ± 3 ms nach 30 Minuten, $p < 0.001$). Eine P-Wellen-Dauer von ≥ 154 ms 30 Minuten nach CV wies die akkurateste Vorhersagekraft auf (Sensitivität 100%, Spezifität 82%, positiv prädiktiver Wert 33%, negativ prädiktiver Wert 100%). Andere PSAECG Parameter wiesen keine Unterschiede zwischen Patienten mit und ohne Frührezidfiv auf. *Schlussfolgerung* Die Ergebnisse dieser Studie zeigen, dass die P-Wellen Signalmittelung ein sensitives, nichtinvasives Verfahren darstellt, mittels dessen das Erkennen von Patienten mit erhöhtem Risiko für ein Frührezidiv bereits 30 Minuten nach erfolgreicher CV möglich erscheint. Bei diesen Patienten könnte mittels antiarrhythmischer Therapie ein Rezidiv verhindert werden.

Schlüsselwörter Vorhofflimmern – Kardioversion – Frührezidiv – Signalmittelung

Summary *Background* Therapy of atrial fibrillation by electrical cardioversion (CV) is limited by the high rate of recurrences. Early recurrence of atrial fibrillation (ERAF) occurs in a subgroup of patients whose characteristics are poorly defined. This prospective study was performed to evaluate if the P wave signal-averaged ECG (PSAECG) is able to identify patients with an increased risk of ERAF after CV. *Methods* Patients with an indication for elective external CV were enrolled. After successful CV, PSAECGs were recorded at 0.5, 1, 24 h and 1 week. The ability of PSAECG parameters (signal-averaged P wave

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duration, PWD; root-mean-square of the voltage of the terminal 20, 30, and 40 ms of the signal-averaged P wave; RMS20, RMS30, RMS40) to predict ERAF (prospectively defined as AF recurrence within 4 h after CV) was assessed. *Results* Of 111 consecutive patients, 7 experienced ERAF, 30 patients had AF recurrence later during the 1-week follow-up. Patients with ERAF had a significantly prolonged signal-averaged PWD compared to patients who remained in SR (194 ± 16 ms vs 139±3 ms at 0.5 h, $p < 0.001$). As ROC analysis revealed, a PWD ≥154 ms at 30 mmin after CV had the highest predictive accurracy for ERAF (sensitivity 100%, specificity 82%, positive predictive value 33%, negative predictive value 100%). Other parameters of the PSAECG did not reveal significant differences between patients with and without ERAF. *Conclusions* The PSAECG provides a sensitive noninvasive tool for detection of patients at risk of ERAF. Thus identified, tailored pharmacological therapy is conceivable to prevent ERAF.

Key words Atrial fibrillation – cardioversion – early recurrence – signal averaging

Introduction

Although electrical CV is effective and widely used for termination of persistent atrial fibrillation (AF) (13), its therapeutic efficacy is limited by a high incidence of AF recurrences. Most recurrences occur during the first few days after CV (21, 24). Some patients may experience AF relapse within minutes to hours after CV (22, 23, 25). These incidents have been termed "immediate" or "early relaspses of AF" (22, 23, 25).

Efforts to prospectively identify patients at risk of relapse have been moderately effective at best. Results from studies evaluating clinical parameters are inconsistent owing to differences in patient characteristics. Assessment of the P wave signal-averaged ECG (PSAECG) has been introduced into clinical practice in an experimental attempt to identify patients at risk of developing AF (6, 26). Some PSAECG studies have been performed aiming at identification of patients at particular risk for relapses after CV within weeks to months after CV (2, 14–16, 18). These studies comprised only small patient cohorts and yielded contradictory results. Thus, the present prospective study was designed to specifically address the issue of prediction of AF relapses within 4 h after external CV since during this time period patients are still under close medical supervision and thus may be amenable to preventive therapeutic measures.

Methods

Patient population

Consecutive patients referred for elective CV of AF were asked for their participation and were included after successful cardioversion. If relapses occurred after a few beats of sinus rhythm, patients were cardioverted again and then included. Patients with pacemakers were excluded from the study unless the rhythm after CV was intrinsic sinus rhythm. Patients undergoing emergency CV of AF or patients on intensive care units were not included. Prior to enrollment, all patients signed informed consent. The study protocol had been approved by the institutional ethical committee. The investigation conforms with the principles outlined in the Declaration of Helsinki.

ECG recording and PSAECG

After CV, 12-lead ECGs were recorded. P wave signal-averaging was performed utilizing the MAC 5000™ system (Marquette-Hellige, Germany). All recordings were performed in a quiet atmosphere in order to reduce ambient noise. The system used utilizes a special software (PHiRES™, Marquette-Hellige, Germany) to perform time-domain analysis. P waves were recorded until a target noise level of < 0.3 μV was achieved in the TP segment of the ECG, or until 500 beats were analyzed. Before signal-averaging, a P wave template was created over a period of 9 seconds and measured P waves were correlated with that template. Unless a ≥95% match was present, P waves were rejected in order to exclude atrial premature beats. Signals from each lead were amplified and digitized at a sampling rate of 4 kHz. Spectral filtering with a band-width of 40–250 Hz was applied to the averaged P wave using fast Fourier transform. Signal-averaged P waves taken from Frank's orthogonal lead system were summed to a vector magnitude (VM = square root of $(X^2 + Y^2 + Z^2)$). Onset and offset of P waves were automatically determined and manually reassessed by two individual investigators. Parameters assessed comprised signal-averaged P wave duration (PWD) and root mean square voltage (RMS) of the terminal 40, 30 and 20 ms of the signal-averaged P waves.

Study protocol

Patients were on oral anticoagulation with a target INR of 2 to 3 for at least 3 weeks prior to CV. Serum potassium levels were determined and had to be within normal range (3.5 to 5.3 mmol/l) on the day of CV. Antiarrhythmic drug therapy was left at the preference of the treating physician and remained unchanged during the entire observation period. Echocardiography was performed within one month prior to CV. External R-wave triggered CV was performed under mild sedation according to accepted guidelines (7). Energy was delivered by means of monophasic shocks in a step-up fashion using 100, 200, 300, and 360 joules. All patients were continuously monitored by telemetry and automatic blood pressure measurements for a period of 4 h after CV.

Repetitive PSAECGs were recorded after 0.5 and 1 h, 24 h and one week after CV. Three patient groups were defined. Group 1 consisted of a subgroup of patients with ERAF (prospectively defined to occur within ½ to 4 h after successful CV), group 2 comprised patients with AF relapse between 4 h and 1 week, and group 3 comprised patients in sinus rhythm throughout the study period.

Tab. 1 Patient characteristics

Parameter	Overall	Group 1	Group 2	Group 3
Patients	111	7 (6%)	30 (27%)	74 (67%)
Female gender	29 (26%)	0 (0%)	8 (27%)	21 (28%)
Age (years)	63 ± 1	54 ± 3	65 ± 2	62 ± 1
Median AF duration (days)	62	45	136**	41
BMI (kg/m^2)	27±1	29±2	27±1	27±1
LA (mm)	47±1	55±3*	47±1	46±1
LVEDD (mm)	52±1	54±3	52±2	52±1
LVEF (%)	51±2	53±6	52±3	50±2
CAD	26 (23%)	2 (29%)	6 (20%)	18 (24%)
HTN	46 (41%)	5 (71%)	16 (53%)	35 (47%)
Lone AF	17 (15%)	1 (14%)	5 (17%)	11 (15%)
Flecainide	7 (6%)	1 (14%)	2 (7%)	4 (5%)
Sotalol	17 (15%)	1 (14%)	3 (10%)	13 (18%)
Amiodarone	25 (23%)	1 (14%)	8 (27%)	16 (22%)
Digoxin	16 (14%)	1 (14%)	2 (7%)	13 (18%)
Betablocker	54 (49%)	5 (71%)	16 (53%)	33 (46%)
No antiarrhythmic drugs (incl. calcium antagonists)	21 (19%)	1 (14%)	3 (10%)	17 (23%)
Patients with prior CV	57 (51%)	3 (43%)	16 (53%)	38 (51%)

There were no statistically significant differences among groups except for larger left atrial diameter in patients with ERAF (* $p < 0.05$ vs group 2 and group 3) and a longer duration of AF before CV in patients within group 2 vs group 3 (** $p < 0.05$), but not vs group 1. *BMI* body mass index, *LA* left atrium, *LVEDD* left ventricular end-diastolic diameter, *LVEF* left ventricular ejection fraction, *LoneAF* lone atrial fibrillation, *HTN* arterial hypertension, *CAD* coronary artery disease

Statistical analysis

Data are presented as mean ± SEM. Measurements were compared by the Mann-Whitney U-test or Fisher's exact test as appropriate. Comparison of repeated measurements within patient groups was performed using ANOVA. Receiver operator characteristic (ROC) curve analysis as an objective means for determination of the utility of various P wave measurements for prediction of AF recurrence (10, 19). Correlations were analyzed using Pearson's correlation coefficient. Multivariate analysis with ERAF as the dependent variable was performed by binary logistic regression analysis. Software packages SPSS 9.0.1 and BiAS 7.0 were used for all calculations. Statistical significance was assumed at a two-sided p-value of < 0.05.

Results

Patient population

One hundred-eleven consecutive patients (29 females) were enrolled in the study (Table 1). AF relapse during the first week after CV occurred in 37 patients. There were 7 patients (6%) with ERAF (group 1) with ERAF occurring within one hour after CV in 3 of them. Group 2 consisted of 30 patients with AF relapse between 4 h and 1 week after CV. Seventy-four patients remained in sinus rhythm throughout the study period (group 3). Clinical characteristics of patients were comparable between all groups except for left atrial size which was significantly larger in group 1 patients, and AF duration prior to CV which was longer among group 2 patients (Table 1). Twenty-five patients were on chronic amiodarone therapy, 17 were on sotalol medication and 7 patients were taking flecainide. The remaining 62 patients were not on antiarrhythmic drug treatment except for beta blockers. The total incidence of AF relapse was 34% in patients with and without antiarrhythmic drug medication (p = n.s.). ERAF occurred in 4 patients without and in 3 patients with antiarrhythmic drug therapy. Furthermore, antiarrhythmic therapy with verapamil a calcium channel blocker that may influence tachycardia-induced remodeling (20) – was not taken by any patient. Diltiazem medication was taken by 16 patients (0 in group 1, 4 in group 2, 12 in group 3, p between groups = n.s.) without an obvious effect in relapse rate or PSAECG parameters.

PSAECG analysis

On average, 268 ± 8 beats were analyzed to achieve a median noise level of 0.38 μV. Analysis of P wave measurements comparing patients within the three groups revealed significantly prolonged signal-averaged PWD at 0.5 and 1 h measurements among patients with ERAF (group 1). Signal-averaged PWD at 0.5 and 1 h was also prolonged in patients of group 2 compared to group 3 (Fig. 1). The mean PWD among group 1 was 194 ± 16 ms at 0.5 h and 188 ± 24 ms at 1 h compared to 139 ± 3 ms at both measurements in group 3 ($p < 0.001$ and $p = 0.003$, respectively) and 156 ± 4 ms and 154 ± 4 ms in group 2 ($p=0.001$ and $p=0.004$, respectively). Mean PWD was furthermore significantly prolonged in patients in group 2 compared to group 3 (Fig. 1).

A significantly lower terminal P wave amplitude was observed in group 1 compared to both other groups at 0.5 h after CV. This difference was still present at 1 h after CV, however, without reaching statistical significance. There was only a trend towards lower P wave voltage parameters (RMS 40, 30 and 20 ms) among group 2 patients compared to group 3 (Table 2).

Evolution of signal-averaged P wave measurements over time

There were no significant changes of P wave parameters during the entire observation period. Within each group, the mean PWD was similar at all recordings. Also the analysis of voltage parameters revealed no significant changes over time in all groups (Table 2).

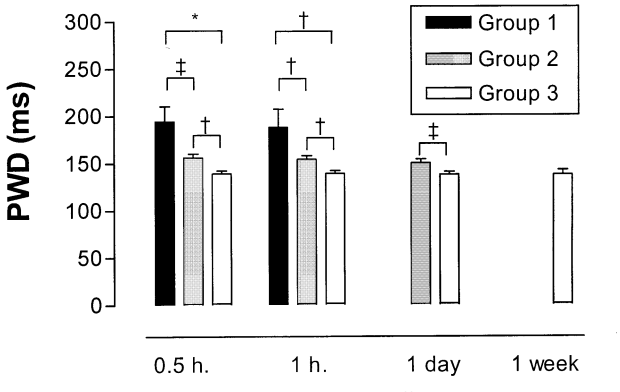

Fig. 1 Mean signal-averaged PWD in the three different groups in comparison. *: $p < 0.0001$, †: $p < 0.005$ and ‡: $p < 0.05$

Tab. 2 Results of PSAECG measurements

	Group	Measurement			
		0.5 h	1 h	24 h	1 week
PWD (ms)	1	194 ± 16*	188 ± 24**	n.a.	n.a.
	2	156 ± 4***	154 ± 4***	150 ± 4****	n.a.
	3	139 ± 3	139 ± 3	138 ± 3	138 ± 3
RMS 40 ms (mV)	1	3.0 ± 0.7*	3.3 ± 1.3	n.a.	n.a.
	2	5.8 ± 0.4	5.5 ± 0.5	5.6 ± 0.4	n.a.
	3	6.4 ± 0.4	6.1 ± 0.3	6.5 ± 0.5	5.5 ± 0.4
RMS 30 ms (mV)	1	2.6 ± 0.8*	3.3 ± 1.3	n.a.	n.a.
	2	5.0 ± 0.3	4.9 ± 0.5	5.3 ± 0.6	n.a.
	3	5.8 ± 0.4	5.4 ± 0.3	5.7 ± 0.4	5.0 ± 0.4
RMS 20 ms (mV)	1	2.6 ± 0.8*	3.3 ± 1.3	n.a.	n.a.
	2	4.9 ± 0.3	4.8 ± 0.5	5.2 ± 0.6	n.a.
	3	5.7 ± 3.3	5.3 ± 0.3	5.7 ± 0.4	4.9 ± 0.3

* $p < 0.005$ vs. group 2 and group 3, ** $p < 0.005$ vs group 3 and n.s. vs group 2, ** $p < 0.005$ vs group 3, **** $p < 0.05$ vs group 3, *n.a.* not applicable

Influence of clinical parameters on AF recurrence

Upon multivariate analysis, no clinical parameter including duration of AF prior to CV and left atrial diameter was found to be independently associated with ERAF or AF recurrence within one week, whereas signal-averaged P wave duration measured 0.5 h after CV was independently associated.

Statistical descriptors for AF relapse

For discrimination of patients with AF relapse during 1 week (group 2) from patients in SR (group 3), ROC analysis revealed that a signal-averaged PWD ≥ 145 ms measured at 0.5 h after CV separated both groups with a sensitivity of 68% and 64% specificity (positive and negative predictive values 42% and 84%, respectively). At the 1 h measurement, sensitivity and specificity were 69% and 72% (for PWD ≥ 145 ms) with a PPV of 50% and a NPV of 85%. Integrated areas under the curve were 0.723 and 0.686 for measurements at 0.5 and 1 h ($p < 0.001$ and $p < 0.005$, respectively).

For discrimination between patients with ERAF and sinus rhythm by means of ROC analysis, a signal-averaged PWD ≥ 154 ms measured at 0.5 h yielded a sensitivity, specificity, PPV and NPV of 100, 82, 33, 100%, respectively. The area under the curve was 0.931 ($p < 0.005$). Since three patients already had a relapse at the 1 h measurement, the differences in the signal-averaged PWD measured at 1 h were smaller although still significant (Fig. 1). Analyzing differences in signal-averaged PWD of patients between group 1 and all other patients (group 2 + 3) by ROC method revealed that a PWD ≥ 154 ms

measured at 0.5 h after CV had sensitivity, specificity, PPV and NPV of 100, 71, 19 and 100%, respectively. For this analysis, the area under the curve was 0.894 ($p = 0.0005$).

Discussion

The results of this prospective study indicate that a signal averaged P wave duration ≥ 154 ms measured 30 min after external CV may be predictive of ERAF within the first 4 h following restoration of sinus rhythm. Thus, PSAECG provides a sensitive noninvasive tool to identify patients at high risk of ERAF.

PWD as a predictor of AF relapse after CV

The signal-averaged PWD assessed from the surface ECG has been examined previously with respect to its potential value as a predictor of AF relapse. Methodological differences and small patient populations, however, have yielded inconsistent results (2, 14–16, 18) (Table 3). The present study was therefore prospectively designed to examine the predictive power of PSAECG for ERAF defined as AF recurrence within 4 h after successful external CV, on the basis of serial recordings of signal-averaged P wave parameters at predefined time points. The rationale for this study was based on the consideration that AF recurrence within the first hours after CV may be amenable to pharmacological interventions while patients are still under medical supervision.

A cutoff value for signal-averaged PWD of ≥154 ms (measured at 30 min after CV) was found to best separate patients with ERAF from those who remain in sinus rhythm. This resulted in a positive predictive value of 33% and, more importantly, in a negative predictive value of 100%. Other clinical factors that differed between study groups were not independently associated with AF relapse upon multivariate analysis.

Raitt et al. measured the signal-averaged PWD after CV in 32 patients and found a significantly prolonged PWD among 11 patients with AF relapses during the first 3 months after CV in the absence of antiarrhythmic drug therapy (16). The mean value of the signal-averaged PWD of 148 ± 17 ms in their study is similar to the PWD of patients with AF relapse during 1 week in the present study. In another study, Aytemir et al. observed prolonged PWDs measured within 2 h after CV in patients who had a relapse of the arrhythmia within 6 months (2). However, their study protocol called only for a single measurement of PWD after CV within a randomly chosen time interval; thus, no specific consideration was given to relapses within hours after CV in both of these prior studies (2, 16). In contrast to these studies, Stafford and colleagues failed to demonstrate predictive power of the signal-averaged PWD for AF recurrence after CV (18). In their study in 31 patients with 75 CVs, serial P wave parameters were measured at 3 and 24 h after CV and early relapse was defined to occur within 1 week after CV. However, these patients had had a recurrence of persistent AF after CV before study inclusion and may represent a selected group of patients with a much higher propensity to AF relapse which occurred after 53 of 75 CVs (71%) within the study period of 4 weeks.

Clinical factors associated with AF relapse

Previous studies have examined the value of clinical factors in predicting recurrences of AF after initially successful CV. Only the duration of AF prior to CV (4, 5) and the patient age (12, 17) appear to correlate with the incidence of AF relapse after electrical CV. However, these studies evaluated AF recurrence within weeks or months after CV. More recently,

Tab. 3 Synopsis of studies on signal-averaged PWD after CV

Study	Patients	AF duration (months)	Relapse within	P wave measurement at	PWD AF (ms)	PWD SR (ms)	P-value
Raitt, 2000 (16)	32	2.1 ± 1.9	3 months	1 to 5 h	146 ± 14	122 ± 18	0.005
Masaki, 2000 (14)	16	32 ± 12	3 months	1 h	171 ± 1	147 ± 18	< 0.05
Aytemir, 1999 (2)	73	4.3 ± 2	6 months	< 2 h	138 ± 13	112 ± 12	0.001
Stafford, 1998 (18)	31	12.7	1 week	3 h	155 ± 3	157 ± 3	n.s.
Opolski, 1997 (15)	35	5 ± 4.6 (AF) 4 ± 3.9 (SR)	6 months	2 h	145 ± 12	130 ± 11	< 0.001

PWD AF P wave duration in patients with AF relapse after cardioversion; PWD SR: P wave duration in patients who remained in sinus rhythm throughout the study period

early AF relapses minutes to hours after initially successful CV have been the focus of clinical research (22, 23). In accordance with the observations of the present study, no clinical differences between patients with ERAF and those remaining in sinus rhythm have been identified in these studies (22, 23).

Pathophysiological considerations

One factor involved in AF re-initiation is the development of atrial ectopic beats with short coupling intervals (21, 22) which will not be detected or predicted by the signal-averaged ECG. However, experimental data indicate that a reduction of atrial conduction velocity induced by atrial electrical remodeling due to AF may play an important role in the development of ERAF, possibly induced by a decrease in sodium current density in remodeled atria (8, 9). This transiently reduced atrial conduction velocity may be reflected by a prolonged PWD after CV which was observed in the present study in patients with ERAF. On the other hand, other clinical factors may influence the signal-averaged PWD. Atrial interstitial fibrosis, which occurs regularly during aging, may decrease conduction velocity and thus also lead to prolonged PWD (1, 3, 6). Whereas there was no such correlation in our study, previous work has indicated that age influences PWD (3). Left atrial size could also play a role in determining PWD. In the study population which included patients with AF and various underlying pathological cardiac substrates, we found a correlation between echocardiographically determined LA size and signal-averaged PWD. In contrast, a recent study using magnetic resonance imaging to measure left and right atrial size showed no correlation between PWD and atrial size among 38 patients with paroxysmal AF (11). The reasons for these discrepant findings are not evident but may include different techniques to assess LA size or, more importantly, differences in the patient populations examined.

Limitation of the study

ERAF occurs only in a small percentage of patients successfully cardioverted from AF (25). Therefore, as expected, the number of patients in the ERAF group reported in this study was small (6%) and this may limit the descriptive power of the observations. The aim of this study was to determine the role of PSAECG for discrimination of patients with ERAF within hours after CV. As patients with relapses within 0.5 h post CV were not studied, we cannot address the value of PSAECG in detecting patients at risk for relapses within seconds to minutes.

The patients were treated with various antiarrhythmic drugs since drug treatment was not prespecified by the study protocol. Although there was no difference in relapse rates in patients on and off antiarrhythmic drug therapy, no firm conclusion can be drawn regarding the effects of antiarrhythmic agents on the occurrence of ERAF.

In order to fully assess the value of a prospectively defined PWD (≥154 ms) to differentiate patients with ERAF from those without and the potential of a pharmacological intervention, a prospectively performed study is necessary.

Conclusion

Results from the present study suggest that a P wave duration ≥154 ms measured in the signal-averaged ECG may predict AF recurrence within the next few hours. This information may enable the physician to select patients in whom an intervention to prevent AF relapse (e.g., administration or dosage increase of an antiarrhythmic drug) can be initiated and its success to prevent ERAF can be monitored while the patient is still under close supervision.

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