Significant prolongation of atrial monophasic action potential duration: short-term reverse electrophysiological changes after internal cardioversion of atrial fibrillation

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Abstract

Objective: Since short action potentials and short refractory periods facilitate the induction of atrial reentry, this maladaptation has been proposed as the pathophysiological basis of the frequent immediate recurrences of atrial fibrillation (IRAF) after internal cardioversion. However, short-term reverse electrophysiological changes of the atria after cardioversion have not been studied in humans.

Methods: Thirty-seven patients with chronic atrial fibrillation of 16±19 months and ten patients with an atrial fibrillation duration ≤48 h underwent internal cardioversion. Antiarrhythmic medication was only continued in 10 patients (21%), who were on amiodarone before cardioversion. Atrial monophasic action potential duration at 90% repolarization (APD90), sinus rate, P wave duration and interatrial conduction times between high right atrium and coronary sinus were recorded at min 0, 1, 3, 5, 10, 15 and 20 after cardioversion.

Results: Internal cardioversion was successful in all patients, but twelve of the patients with chronic AF (32%) and three of the patients with intermittent AF (30%) had one to four episodes of IRAF after 16±28 s. There was a significant 52±30 ms APD90 prolongation, 83% of which occurred in min 0–3 (P<0.0001) and 17% in min 3–20 (P<0.05) after internal cardioversion. There was no significant temporal change in sinus rate, P-wave and interatrial conduction time during the time studied. APD90 prolongation and its time dependence did not show a detectable difference in subgroups with chronic AF, IRAF, left atrial size >40 mm and treatment with amiodarone.

Conclusions: There is a significant prolongation of action potential duration in min 0–3 after internal cardioversion of atrial fibrillation, whereas sinus rate and intra- and interatrial conduction time remain unchanged. APD90 prolongation in min 0–3 shows a temporal relationship to the high rate of immediate recurrences of atrial fibrillation during this time interval. The data imply that there is a transient recovery of atrial refractoriness after cardioversion and suggest a mechanism of the high rate of early recurrences of atrial fibrillation.

Keywords: Arrhythmia (mechanisms); Defibrillation; Ion channels; Remodeling; Supraventricular arrhythmia

1. Introduction

Immediate recurrence of atrial fibrillation (IRAF) within the first seconds and minutes after cardioversion remains as high as 13–29% [1–3] and is one factor determining unsuccessful electrical cardioversion.

The two components of wavelength, conduction velocity and atrial refractoriness, are basic determinants of AF onset and perpetuation. Wijffels et al. [4] have demonstrated in healthy goats that the artificial maintenance of AF by rapid atrial pacing induced progressive shortening of the atrial refractory period and that rate-related shortening of the effective refractory period was inverted, resulting in shorter refractoriness at lower rates. It was postulated that the loss of the normal increase in refractoriness with a decrease in rate could be an important factor favoring AF and might facilitate the induction of the arrhythmia by premature atrial beats during sinus rhythm. Allessie et al. [5] have proposed to differentiate between long-term reverse electrophysiological remodeling of the atria with alteration of gene expression, hibernation and irreversible structural changes, and short-term reverse

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electrophysiological (metabolic) changes with altered ion concentration, ion pump activity and phosphorylation of ion channels. A number of animal and humans studies have referred to long-term electrophysiological remodeling caused by atrial fibrillation and its correlation to AF recurrence [6–14]. The short-term reverse electrophysiological changes have been postulated as cause of immediate recurrence of AF but have not been studied after internal cardioversion in humans.

It was the aim of this study to analyze the short-term (metabolic) electrophysiologic changes of the atria in the first minutes after internal cardioversion of atrial fibrillation as potential mechanisms of immediate AF reinitiation and to look for predictors of AF reinitiation in a cohort of consecutive patients with chronic AF, and AF of recent onset.

2. Methods

2.1. Study population

Low-energy internal cardioversion of AF was performed in consecutive patients with either chronic AF or AF of recent onset ≤48 h. Cardioversion to sinus rhythm was performed for a clinically indicated restoration of sinus rhythm or indicated during an ablation procedure. Evaluation of the patients included clinical history, physical examination, routine laboratory (including T3, T4 and TSH), 12-lead ECG, and transthoracic and transesophageal echocardiography. Class I antiarrhythmic drugs and Sotalol were interrupted five half-times before cardioversion. If patients were on amiodarone, medication was continued. The investigation conforms with the principles outlined in the Declaration of Helsinki, all patients gave informed consent.

2.2. Internal cardioversion protocol

Internal cardioversion was performed by placement of a newly designed steerable cardioversion electrode (TC3+1DT, 7-French, VascoMed) in the coronary sinus and one cardioversion electrode in the anterolateral right atrium (TC2+1JO, 7-French, VascoMed) with insertion in the right femoral vein, respectively (Fig. 1). In eight patients (17%) the coronary sinus could only be cannulated using a

Fig. 1. Right oblique fluoroscopic projection of the position of the defibrillation electrodes in the anterolateral right atrium (RA) and coronary sinus (CS) and the catheter for recording of monophasic action potentials in the right atrial appendage (RAA). A quadripolar electrode is positioned at the right ventricular apex (RV) for synchronized shock delivery.
specially designed 8-French introduction sheath (SL1, Daig). A quadripolar 6-French electrode (Josephson, Bard) was placed in the right ventricle for triggering shock delivery to the R-wave. Using the coronary sinus catheter as the anode and the right atrial catheter as the cathode, a biphasic cardioversion shock was delivered from an external defibrillator (Ventak ECD, CPI Guidant). Shocks were delivered starting at 15 J, following a 5-J step-up protocol until cardioversion of AF was successful. The time interval between shocks was 3 min. Intravenous application of hypnomidate (0.5 mg/kg) was used for sedation. If no sinus rhythm was achieved with a maximum 35-J shock for internal cardioversion or >4 IRAF occurred cardioversion was declared unsuccessful.

2.3. **Electrophysiological parameters**

A 12-lead surface ECG, endocardial recordings of monophasic action potentials at the right atrial appendage, and endocardial signals at the coronary sinus, the high right atrium and the right ventricular apex were acquired continuously in digital format using a Prucka electrophysiology system (CardiaLab, Prucka Engineering). An example of the simultaneous recordings at internal cardioversion is shown in Fig. 2.

At min 0, 1, 3, 5, 10, 15 and 20 after internal cardioversion of AF monophasic action potential duration at 90% repolarization (APD<sub>90</sub>) during sinus rhythm, sinus rate and P-wave duration were determined.

Monophasic action potentials were recorded at the right atrial appendage with a 6-French fractually coated, steerable electrode (MAPCath, Biotronik). Measurements of APD<sub>90</sub> were performed by two independent observers manually (T.K., G.B.) at a paper speed of 200 mm/s according to the standard method [15]. Mean APD<sub>90</sub>, derived from the first three signals of sinus beats at min 0, 1, 3, 5, 10, 15 and 20 after cardioversion was determined. Intra- and interobserver variations were <5%. In patients with immediate recurrence of atrial fibrillation measurements were performed after successful cardioversion and persistence of sinus rhythm so that temporal changes could be evaluated. Patients with incomplete MAP recordings or a signal amplitude <10 mV were considered a dropout. A representative example of MAP recording at min 0, 1 and 3 after cardioversion is given in Fig. 3.

Interatrial conduction times were measured at min 1, 3, 5, 10, 15 and 20 by pacing from the right atrial and the coronary sinus cardioversion electrodes for 5 beats at a cycle length of 500 ms, respectively.

2.4. **Predictor analysis**

In case of significant temporal changes of the measured electrophysiological parameters (APD<sub>90</sub>, sinus rate, P-wave duration and interatrial conduction times) additional subgroup analysis of patients with chronic AF vs. AF of recent onset, occurrence vs. no occurrence of IRAF, left atrium >40 mm and treatment with vs. without amiodarone was performed.

2.5. **Definitions**

AF has been described before [16,17]. IRAF was defined as the resumption of AF within 3 min after an internal defibrillation shock that resulted in sinus rhythm for at least one beat [1]. Chronic AF was defined as an AF...
duration of >48 h, and AF of recent onset as an AF duration of ≤48 h.

2.6. Statistical analysis

Continuous variables are expressed as mean±S.D. To assess differences in the course of APD\textsubscript{90}, sinus rate, P-wave duration and conduction time between right atrium and coronary sinus in min 0–20, a multivariate repeated measures analysis of variance was used. For comparison of APD\textsubscript{90} prolongation in min 0–3 and min 3–20, the paired Student’s t-test was performed. For the subgroup comparison of APD\textsubscript{90} prolongation in min 0–3, the unpaired Student’s t-test was used. Nominal values were evaluated by the \(\chi^2\) test. \(P<0.05\) was considered statistically significant.

3. Results

3.1. Clinical characteristics and acute results of internal cardioversion

Internal cardioversion was performed in thirty-seven patients with chronic AF of 16±19 (1–84) months and ten patients with AF of recent onset and a duration of 10±16 (0.1–48) h. Internal cardioversion was successful in all patients after an application of 21±10 (15–35) J. Table 1 shows the characteristics of the study group. No significant difference was found between the groups with chronic AF vs. AF of recent onset with regard to gender, age, heart...

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All patients (n=47)</th>
<th>Patients with chronic AF (n=37)</th>
<th>Patients with AF of recent onset (n=10)</th>
<th>Patients without IRAF (n=32)</th>
<th>Patients with IRAF (n=15)</th>
</tr>
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<tbody>
<tr>
<td>Men/women (n)</td>
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<td>35/2</td>
<td>7/3</td>
<td>31/1</td>
<td>13/2</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>58±10</td>
<td>60±9</td>
<td>58±10</td>
<td>61±8</td>
</tr>
<tr>
<td>Duration of cAF (min)</td>
<td>16±19</td>
<td>16±19</td>
<td>–</td>
<td>37±67 (n=24)</td>
<td>15±19 (n=12)</td>
</tr>
<tr>
<td>Duration of iAF (h)</td>
<td>10±16</td>
<td>–</td>
<td>10±16</td>
<td>24±14 (n=6)</td>
<td>23±6 (n=3)</td>
</tr>
<tr>
<td>Lone AF (n)</td>
<td>23 (49%)</td>
<td>18 (49%)</td>
<td>5 (50%)</td>
<td>14 (44%)</td>
<td>9 (60%)</td>
</tr>
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</table>

Structural heart disease

| Ischemic (n)                    | 9 (19%)            | 7 (19%)                        | 2 (20%)                               | 7 (22%)                     | 2 (13%)                 |
| Cardiomyopathy (n)              | 6 (13%)            | 5 (14%)                        | 1 (10%)                               | 5 (16%)                     | 1 (7%)                  |
| Hypertension (n)                | 7 (15%)            | 7 (19%)                        | 0                                     | 5 (16%)                     | 2 (13%)                 |
| WPW/AVNRT (n)                   | 2 (4%)             | 0                              | 2 (20%)                               | 1 (3%)                      | 1 (7%)                  |
| Number of AA (n)                | 1.5±0.8            | 1.4±0.8                        | 1.7±1                                 | 1.6±0.7                     | 1.3±0.9                 |
| Amiodarone at IC (n)            | 10 (21%)           | 9 (24%)                        | 1 (10%)                               | 7 (22%)                     | 3 (20%)                 |
| LA diameter (mm)                | 44±6               | 45±6                           | 40±7                                  | 43±7                        | 47±5                    |
| LVEF (%)                        | 59±13              | 58±14                          | 63±9                                  | 59±12                       | 57±16                   |

Internal cardioversion

| Energy (J)                      | 21±10              | 21±9                           | 17±12                                 | 19±8                        | 25±12                   |
| Voltage (V)                     | 492±136            | 507±127                        | 438±162                               | 487±126                     | 504±166                 |
| Resistance (Ω)                  | 59±9               | 61±8                           | 53±7                                  | 58±8                        | 62±10                   |

\(cAF\), chronic atrial fibrillation; \(iAF\), intermittent atrial fibrillation; WPW, Wolff–Parkinson–White syndrome; AVNRT, AV-nodal reentrant tachycardia; AA, antiarrhythmic drugs; IC, internal cardioversion; LA, left atrium; LVEF, left ventricular ejection fraction.
disease, left atrial diameter, left ventricular ejection fraction and internal shock delivery. No thrombi were detectable during TEE and T3, T4 and TSH were in the normal range in all of the patients studied.

3.2. Patients with IRAF

Fifteen patients (32%) had 1.1±2.0 (1–4) episodes of IRAF after delivery of 25±12 J. The time interval between the termination of AF and reinitiation was 16±28 (3–128) s. The earliest atrial endocardial activation time recorded from the defibrillation catheters was always after the beginning of the P wave of the initiating atrial premature beat. Thus, these atrial premature beats did not seem to originate from the defibrillation catheters. There was no significant difference in the clinical characteristics of the patients with and without IRAF (Table 1).

3.3. Electrophysiological parameters after cardioversion

The electrophysiological study protocol was completed in thirty patients. Seventeen patients were dropouts because of low quality or incomplete MAP recordings. Of the thirty patients with completed electrophysiological protocol, twenty-one (70%) had chronic atrial fibrillation, ten patients (33%) had at least one episode of IRAF, six patients (20%) were on amiodarone at cardioversion and twenty-two patients (73%) had an atrial size >40 mm.

3.3.1. Monophasic action potentials

Fig. 4 demonstrates the temporal changes of APD 90 in min 0–20 after internal cardioversion with a APD 90 prolongation of 52±33 ms (0–118). Of this APD 90 prolongation 83% occurred in min 0–3 with 44±25 ms (2–100). The temporal effect was highly significant in min 0–3 (P<0.0001) and much less pronounced in min 3–20 (P=0.046). The return cycle to the first sinus beat after successful cardioversion was 1279±530 ms (265–2510) and had no significant effect on APD 90 at min 0.

3.3.2. Sinus rate and intra- and interatrial conduction times

Fig. 5a–c shows the temporal changes in sinus rate, intra- and interatrial conduction time from the high right atrium to the coronary sinus and from the coronary sinus to
As measured by the P wave duration and conduction between high right atrium and coronary sinus.

4.2. Atrial refractoriness and its temporal recovery after termination of atrial fibrillation

High-density mapping studies of AF in humans suggest that a determinant of AF is the presence of a critical number of wandering reentrant atrial wavelets [18,19]. The two components of wavelength, conduction velocity and atrial refractoriness, are thus basic determinants of AF (APD) in min 0–3 versus min 3–20 after internal cardioversion for all patients and patients with chronic atrial fibrillation (cAF), immediate recurrence of atrial fibrillation (IRAF), amiodarone treatment (Amio) and a left atrial size >40 mm (LA >40). The significant APD increase in min 0–3 was not different between subgroups (P >0.05).

Fig. 6. Percent increase in action potential duration at 90% repolarization (APD_90) in min 0–3 versus min 3–20 after internal cardioversion for all patients and patients with chronic atrial fibrillation (cAF), immediate recurrence of atrial fibrillation (IRAF), amiodarone treatment (Amio) and a left atrial size >40 mm (LA >40). The significant APD_90 increase in min 0–3 was not different between subgroups (P >0.05).

3.3.3. Variables with potential influence on prolongation of monophasic action potentials

The influence of four clinical variables on the prolongation of APD_90 was analyzed (Fig. 6). APD_90 prolongation in min 0–3 was not significantly different in patients with chronic AF vs. patients with AF of recent onset (P = 0.948), patients with vs. patients without IRAF (P = 0.731), patients with vs. patients without amiodarone at cardioversion (P = 0.567) and patients with a left atrial size >40 mm vs. patients with normal atrial size (P = 0.304) (due to a low patient number in the studied subgroups and a high common standard deviation, power <20%, respectively).

4. Discussion

4.1. Main findings

The main finding of the study is that there is a significant right atrial prolongation of APD_90 after internal cardioversion in patients with both chronic AF and AF of recent onset, and that most of the temporal recovery of APD_90 prolongation occurs within 3 min. There is a temporal relationship between the changes in action potential prolongation and the high rate of immediate recurrence of AF in min 0–3 after internal cardioversion. APD_90 prolongation in min 0–3 is independent of sinus rate, which does not show a significant temporal change during the studied time period. In addition, there is no significant change in intra- and interatrial conduction time as measured by the P wave duration and conduction between high right atrium and coronary sinus.

4.2. Atrial refractoriness and its temporal recovery after termination of atrial fibrillation

High-density mapping studies of AF in humans suggest that a determinant of AF is the presence of a critical number of wandering reentrant atrial wavelets [18,19]. The two components of wavelength, conduction velocity and atrial refractoriness, are thus basic determinants of AF onset and perpetuation. In AF, if the atrial wavelength is long, reentry may not be maintained and AF may self-terminate. However, if atrial wavelength is relatively short because of short refractory period or depressed conduction, or both, then a greater number of wave fronts can circulate through the atria and AF may be sustained [20–22]. Daoud et al. [23] and others [24] have demonstrated that brief episodes of pacing-induced AF shorten the atrial refractory period following spontaneous AF termination, thereby shortening the wavelength. Temporal changes recovered within 5–10 min after spontaneous AF termination. No information is given about changes in atrial conduction velocity and the influence of rate on refractoriness after AF termination.

As demonstrated in this study, similar short-term changes of atrial refractoriness as measured by action potential duration, occur in min 0–3 after internal cardioversion of both chronic AF and AF of recent onset. In contrast to the study by Daoud et al. [23] we did not perform repeated ERP measurements and measured action potentials during sinus rhythm to exclude possible effects of extensive pacing on the temporal changes in refractoriness. This method also enabled us to monitor sinus rate which showed no significant change during the time analyzed. Thus the temporal changes in refractoriness seem to be independent of sinus node recovery after cardioversion. Furthermore, we demonstrate that the early changes in refractoriness are not accompanied by a temporal change in intra- and interatrial conduction time.

4.3. Occurrence of IRAF

In their study Daoud et al. [23] report on frequent induction of secondary episodes of AF after a primary episode of pacing-induced AF supporting the hypothesis that the AF-induced shortening of the atrial ERP promotes perpetuation of AF. As other investigators [1] we found a high rate (32%) of immediate recurrences of AF within min 0–3 after cardioversion. Thus, there also is a clear temporal relationship between the changes of atrial refractoriness and the propensity for reinduction of AF after internal cardioversion. Consistent with others [1], we could not find a clinical parameter (AF duration, amiodarone treatment, atrial size) predicting IRAF, suggesting that the short-term changes in refractoriness and the propensity of
very early AF reinitiation is independent of these variables. Furthermore, this study was not able to demonstrate a direct relationship between the extent of APD\textsubscript{90} prolongation and AF duration, occurrence of IRAF, amiodarone treatment and atrial size. This might be explained by the small patient number studied in the subgroups. In particular, the impact of APD\textsubscript{90} prolongation on the occurrence of IRAF has to be studied in greater patient cohorts. Other early changes in atrial electrophysiology such as dispersion of repolarization may also facilitate the induction of secondary episodes of AF immediately after cardioversion.

4.4. Mechanisms of prolongation of atrial refractoriness after AF termination

Allessie et al. [5] have proposed to differentiate between long-term reverse electrophysiological remodeling of the atria with alteration of gene expression, hibernation and irreversible structural changes, and short-term reverse electrophysiological (metabolic) changes, demonstrated in this study, with altered ion concentration, ion pump activity and phosphorylation of ion channels.

One likely short-term mechanism for AF-induced shortening of atrial refractoriness is the physiological, rate-dependent shortening of the action potential duration [23]. Activation and deactivation of gated outward potassium current during the action potential plateau phase can result in beat-to-beat potassium accumulation and shortening of the action potential duration and the ERP [25–29]. The reverse mechanism may occur after restoration of sinus rhythm. A second mechanism for shortening of the atrial ERP after AF might be ‘cardiac memory’, which has been described for T-wave changes after rapid ventricular pacing. It has been suggested that cardiac memory is also caused by changes in potassium current, i.e. the transient outward potassium channel [30–32]. A similar alteration in potassium current may occur as a result of AF, and might explain the alteration of post-AF atrial repolarization and its short-term reversal. As a third mechanism of the changes in atrial properties, anisotropic capacitive coupling has been proposed [32–33]. As cause of AF changes in cellular coupling and thus action potential duration may occur. After resumption of isotropic conduction during sinus rhythm, these coupling changes may persist and be reversible after a few minutes. Further studies are needed to more clearly define the ionic mechanisms and signal transduction pathways involved in the short-term electrophysiological changes after AF termination.

4.5. Prevention of IRAF by influencing early electrophysiological changes after AF

Prevention strategies of IRAF have only been studied in a few animal and human studies. Timmermanns et al. [1] reported on atropin or a type Ic antiarrhythmic drug to prevent further IRAF in three of five patients. Tieleman et al. [34] reported on significantly less shortening of the atrial effective refractory period after rapid atrial pacing in goats treated with verapamil. But there was only a minimal reduction in inducibility of AF. Daoud et al. [3] found a reduced recurrence of IRAF in patients with external cardioversion and intravenous administration of verapamil. Tieleman et al. [35] reported that digoxin aggravates tachycardia-induced atrial electrical remodeling in goats with a prolonged shortening of the atrial refractory period. Nakashima et al. [36] showed a complete inhibition of shortening of the atrial effective refractory period after rapid atrial pacing in dogs with angiotensin II antagonist treatment. Tse et al. [2] reported on the efficacy of right atrial pacing in 42% and administration of sotalol in 71% of patients with IRAF. Although our study was not able to show a correlation between the extent of prolongation of monophasic action potentials and IRAF occurrence it might be postulated that influencing the very early electrophysiological changes after internal cardioversion, i.e. atrial refractoriness due to the sudden rate drop might significantly reduce the number of IRAF occurrences.

4.6. Limitations

Atrial refractoriness could not be directly measured, because the short period of 20 min analyzed after cardioversion of atrial fibrillation did not allow extensive pacing protocols. Only monophasic action potentials from the right atrium were recorded to avoid transseptal puncture, and therefore changes of MAP potentials from the left atrium could not be analyzed.

5. Conclusions

Monophasic action potential duration at 90% repolarization significantly prolongs in min 0–3 after internal cardioversion of atrial fibrillation. Other electrophysiological parameters such as sinus rate and intra- and interatrial conduction time remain constant. APD\textsubscript{90} prolongation in min 0–3 shows a temporal relationship to the high rate of immediate recurrences of atrial fibrillation during this time interval. These data suggest recovery of atrial refractoriness as a mechanism of the high rate of early recurrences of AF after cardioversion.

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