

# Electrophysiological and therapeutic effects of amiodarone in patients with preexcited atrial fibrillation

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**Background:** Atrial fibrillation (AF) with fast ventricular response over an overt accessory pathway (AP) (preexcited AF) with a short anterograde refractory period is a potentially malignant arrhythmia. This study aimed to evaluate the safety and efficacy of amiodarone for preexcited AF management. **Materials and Methods:** This study enrolled 103 patients with evidence of AP in electrocardiography. Patients with preexcited AF were included in the study. Intravenous amiodarone (300 mg) was infused for 30 min for all patients in the AF rhythm. Electrophysiological parameters were evaluated before amiodarone injection and 2 h after pharmacological or electrical cardioversion. **Results:** Antegrade and retrograde refractory periods of the atrioventricular node (AVN) and AP, as well as antegrade and retrograde Wenckebach points of AVN, were increased significantly after amiodarone infusion. Furthermore, the mean of the shortest preexcited RR interval was increased during the monitoring period. Comparing the preexcited index at the beginning of the study and before cardioversion (2 h later) revealed that the QRS complexes changed to a wider pattern as the preexcitation index changed from 80.61 to 92.26 ( $P < 0.001$ ). Nineteen (18.4%) patients converted to the sinus rhythm with amiodarone infusion. No ventricular arrhythmia was detected during monitoring. **Conclusion:** Amiodarone could be considered a safe drug in patients with preexcited AF for rate control despite its relatively low efficacy in conversion to the sinus rhythm.

**Key words:** Accessory pathway, amiodarone, atrial fibrillation, electrophysiology

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## INTRODUCTION

The Wolff-Parkinson-White (WPW) syndrome, a disorder characterized by the presence of one or more accessory pathways (APs) may predispose patients to episodes of arrhythmia, usually, atrioventricular reciprocating tachycardia (AVRT) or preexcited atrial fibrillation (AF).<sup>[1]</sup> Episodes of AF are found in approximately half of the patients with WPW, especially young patients without structural heart diseases.<sup>[2]</sup> Besides, AVRT with a rapid ventricular rate may potentially degenerate to AF. As known,

AF conducting over an overt AP (preexcited AF) with the fast ventricular response is a potentially malignant rhythm in WPW syndrome due to possible deterioration into ventricular fibrillation (VF) and sudden cardiac death.<sup>[3]</sup> The preferred approach to the management of preexcited AF with a rapid ventricular rate is direct current (DC) cardioversion, especially in hemodynamic instability. However, in a stable situation, a medical attempt is tried to avoid cardioversion.

It is well-known that beta-blockers, calcium blockers, or adenosine, which slow or block atrioventricular (AV)

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nodal conduction, are avoided in this situation. The recommended antiarrhythmic drugs to prescribe in this situation are intravenous (IV) ibutilide or procainamide.<sup>[4]</sup> Amiodarone, as one of the frequently used antiarrhythmic drugs, has some challenges in this situation. Some studies have reported it as a safe drug in this setting, but there are also few case reports indicating the increased risk of degeneration to VF by amiodarone.<sup>[5-9]</sup> Although previous guidelines recommend amiodarone as one of the medical choices to control preexcited AF rate, the current guidelines recommend against amiodarone administration due to the risk of VF due to case reports of degeneration of arrhythmia to VF possibly due to amiodarone.<sup>[3,10]</sup> To the best of our knowledge, none of the previous studies were formal and perspective and mostly presented one or a few cases. They also had different endpoints and variable dosages and did not evaluate confounding variables. Thus, this study aimed to evaluate the safety and efficacy of amiodarone for preexcited AF in a relatively larger sample under a controlled situation and to assess the electrophysiological profile while using amiodarone in the electrophysiology (EP) laboratory.

## METHODS

This single arm before-after interventional study was conducted in the EP Department of Rajaie Medical and Research Cardiovascular Center from June 2017 to July 2021. The study population consisted of 103 patients with evidence of AP in electrocardiography (ECG) and evidence of retrograde AP conduction in EP study. Antiarrhythmic drugs were withdrawn before admission for at least five half-lives. No one had received amiodarone. Patients with spontaneous preexcited AF or accidentally induced AF during programmed atrial and ventricular stimulation in the laboratory were enrolled in the study. The study was approved by the Iran University Biomedical Research Ethics Committee (IR.IUMS.FMD.REC.1366.92111171009), and written informed consent was obtained from all the patients. The patients underwent a history-taking and physical examination. IV amiodarone (300 mg) was infused for 30 min for all patients in the AF rhythm. Those with spontaneous sinus rhythm or in need of immediate cardioversion (<30 min after amiodarone infusion) were excluded from the study. Prophylactic heparin was injected into all patients.

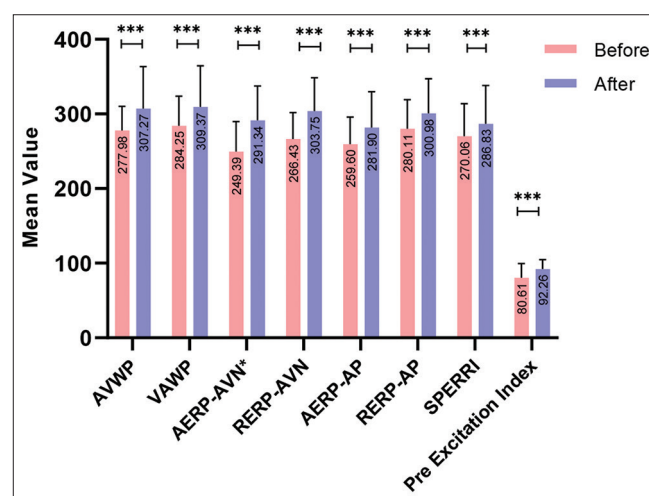
Venous accesses were obtained under local anesthesia, and the procedure was performed under conscious sedation. Baseline measurements including basic cycle length, PR interval, QRS duration in the sinus rhythm, QT interval, and AP localization were recorded. Incremental atrial and ventricular pacing began at rates just above the sinus rate and continued until AV Wenckebach point (AVWP)

and ventriculoatrial Wenckebach point (VAWP) had been achieved, or the cycle length had reached 200 m. Thereafter, the extra stimulus method was used to measure the antegrade effective refractory period of the AV node (AERP-AVN), retrograde effective refractory period of the AV node (RERP-AVN), AERP-AP, and RERP-AP. These parameters were evaluated before amiodarone injection and 2 h after pharmacological or electrical cardioversion. The preexcitation index was defined as the percentage of widened QRS ( $\geq 120$  m) in 100 beats of preexcited AF rhythm. The shortest preexcited RR interval (SPERRI) was also measured.

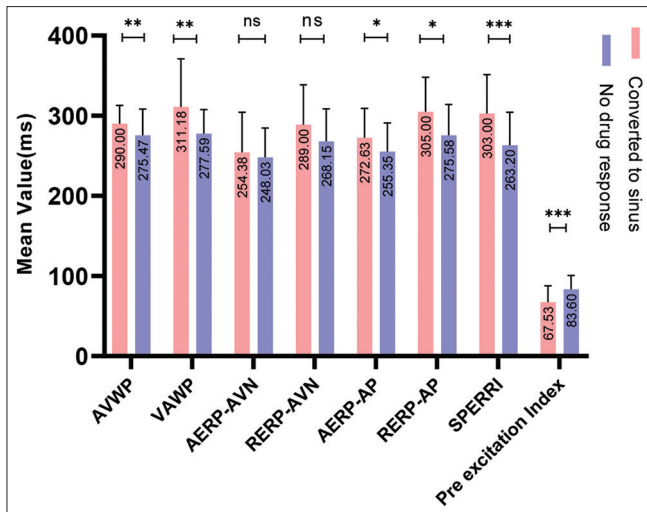
All the patients were monitored for 2 h, provided that spontaneous or medical cardioversion did not achieve. If VF or hemodynamic instability was happened electrical cardioversion would be performed. Radiofrequency ablation was performed for all eligible patients after cardioversion.

## Statistical analysis

We used SPSS 18.0 (PASW Statistics for Windows, Version 18.0. SPSS Inc., Chicago, Illinois, USA) for all statistical analysis. Continuous and categorical variables are presented as mean  $\pm$  standard deviation and count (percentages), respectively. The paired-sample *t*-test was used to compare the quantitative variables in the same group [Figure 1 and Table 1] and independent-sample *t*-test was used to compare quantitative variables in different groups [Figure 2]. A *P* < 0.05 was considered statistically significant.



**Figure 1:** Electrophysiology measurements before and after amiodarone infusion. Data are presented as mean  $\pm$  SD. \*For 16 patients with AV nodal RP greater than AP before amiodarone administration, this measurement was not possible, \*\*\* *P* < 0.001. AVWP = Atrioventricular Wenckebach point; VAWP = Ventriculoatrial Wenckebach point; AERP-AVN = Antegrade effective refractory period of the atrioventricular node; RERP-AVN = Retrograde effective refractory period of the atrioventricular node; AERP-AP = Antegrade effective refractory period of the accessory pathway; RERP-AP = Retrograde effective refractory period of the accessory pathway; SPERRI = Shortest preexcited RR interval; SD = Standard deviation



**Figure 2:** Comparison of baseline electrophysiologic parameters in patients converted to sinus rhythm by amiodarone versus no drug response group. Data are presented as mean ± SD. ns  $P > 0.05$ , \*  $P \leq 0.05$ , \*\*  $P \leq 0.01$ , \*\*\*  $P \leq 0.001$ . VAWP = Ventriculoatrial Wenckebach Point; AERP-AVN = Antegrade effective refractory period of the atrioventricular node; RERP-AVN = Retrograde effective refractory period of the atrioventricular node; AERP-AP = Antegrade effective refractory period of the accessory pathway; RERP-AP = Retrograde effective refractory period of the accessory pathway; SPERRI = Shortest preexcited RR Interval; AVWP = Atrioventricular Wenckebach point; SD = Standard deviation

**RESULTS**

Data were collected from 103 patients. The mean age of the participants was 34.67 years, with male dominance. Right posteroseptal and left lateral APs were more prevalent (35.9% and 35%, respectively). Other demographic characteristics, localization of AP, and baseline ECG indices are summarized in Table 2. During the monitoring period, only 19 (18.4%) patients converted to the sinus rhythm with amiodarone infusion. No ventricular arrhythmia was detected during the monitoring period.

The results of the EP study are detailed in Figure 1. As shown, AVWP, VAWP, AERP-AVN, AERP-AP, RERP-AVN, and RERP-AP were increased significantly after amiodarone infusion. Furthermore, the mean of SPERRI was increased in the monitoring period. Recording and comparing the preexcited index at the beginning of the study and before cardioversion (2 h later) revealed that the QRS complexes changed to a wider pattern as the preexcitation index changed from 80.61 to 92.26 ( $P < 0.001$ ).

Table 1 presents the effect of amiodarone on refractory periods. As described, the AERP and RERP of AVN increased more compared with AP (42.40 vs. 23.20 and 37.63 vs. 18.50, respectively,  $P < 0.001$ ). Patients converted to the sinus rhythm compared with the no drug response group, as shown in Figure 2. Initial AVWP and VAWPs were longer in the converted to sinus group compared with no drug response group (AVWP:  $290 \pm 22.85$  vs.

**Table 1: Comparison of changes which was made by amiodarone in refractory periods**

Variable	Mean	P
$\Delta$ AERP-AVN	41.95±26.36	<0.001
$\Delta$ AERP-AP	22.30±30.90	
$\Delta$ RERP-AVN	37.32±38.68	<0.001
$\Delta$ RERP-AP	20.86±26.36	

Data are presented as mean±SD.  $\Delta$ =The difference between parameters before and after amiodarone infusion; AERP-AVN=Antegrade effective refractory period of the atrioventricular node; RERP-AVN=Retrograde effective refractory period of the atrioventricular node; AERP-AP=Antegrade effective refractory period of the accessory pathway; RERP-AP=Retrograde effective refractory period of the accessory pathway; SD=Standard deviation

**Table 2: Baseline characteristics**

Variable	n=103
Age	34.67±9.90
Sex (male)	72 (69.90)
Family history of sudden cardiac death	2 (1.90)
Ejection fraction	51.89±5.06
Localization of accessory pathway	
Right posteroseptal	37 (35.90)
Right lateral	3 (2.90)
Right anteroseptal	9 (8.70)
Right anterolateral	3 (2.90)
Left posteroseptal	10 (9.70)
Left lateral	36 (35)
Left posterolateral	2 (1.90)
Epicardial posteroseptal	2 (1.90)
Multiple	2 (1.90)
AF type	
Spontaneous	46 (44.70)
Induced	57 (55.30)
ECG parameters	
PR interval	95.45±11.55
QRS duration	135.26±15.22
QT interval	415.79±33.77

Data are presented as mean±SD or frequency (%). SD=Standard deviation; AF=Atrial fibrillation; ECG=Electrocardiography

$275.47 \pm 33.01$ ,  $P = 0.01$ ; VAWP:  $311.18 \pm 59.98$  vs.  $277.59 \pm 30.05$ ,  $P = 0.004$ , respectively). Although the value of baseline AERP-AVN did not differ significantly between the groups ( $254.38 \pm 50.06$  vs.  $248.03 \pm 36.70$ ,  $P = 0.71$ ), those who converted to the sinus rhythm had a longer antegrade refractory period of AP ( $272.63 \pm 36.49$  vs.  $255.35 \pm 35.78$ ,  $P = 0.03$ ). Other differences in EP measurements are also presented in Figure 2. No adverse effect including hemodynamic instability or VF was observed with the infusion of amiodarone during the monitoring period.

**DISCUSSION**

This study evaluated the safety and efficacy of amiodarone in preexcited AF with an emphasis on the electrophysiological features of AVN and AP before and after the drug administration. We revealed that IV amiodarone increases

the refractory periods of both AVN and AP. However, conduction through AVN was prolonged more than AP with amiodarone. Although the mean of SPERRI increased in preexcited AF, QRS complexes became wider and more bizarre after amiodarone administration. Approximately one-fifth of patients converted to the sinus rhythm with amiodarone, indicating that it could be effective for cardioversion in a minority of patients. No ventricular arrhythmia was detected in the monitoring period. Patients who converted to the sinus rhythm had differences in baseline electrophysiological criteria, for example, they had a longer AERP-AP.

Amiodarone is a widespread and effective antiarrhythmic drug with a broad spectrum of multichannel pharmacological effects. It seems to have a distinctive property of lengthening action potential duration and refractory periods in approximately all cardiac tissues.<sup>[11]</sup> Calcium channel blockade can depress AV node conduction, and potassium and sodium channel blockade can lengthen the antegrade refractory period of AP.<sup>[12]</sup> Data comparing its impact on AVN and AP are scarce.<sup>[13]</sup> In our evaluation of approximately 100 patients, we revealed that IV amiodarone administration lengthens both AV and AP refractory periods, but much more prolongation occurred in AVN than in AP. Therefore, IV amiodarone administration has a more prevalent effect on AV node conduction properties. These findings suggest that amiodarone has more effects on cardiac tissues with decremental properties (AVN) than on APs with nondecremental conduction (WPW syndrome). However, the difference in the acute IV phase and chronic use of oral amiodarone was also focused on in previous studies. In a study, evaluating the effects of IV and oral uses of amiodarone, the AV node was affected to the same degree, but the anterograde refractory period of the AP was more affected by chronic oral use than acute IV administration.<sup>[14]</sup> Therefore, the mechanisms of action for oral or IV administration of amiodarone may vary and may be the reason why IV administration was less effective for preexcited AF.

Preexcited AF manifests with a rapid, irregular ventricular rate and varying QRS morphology. The altering QRS morphology consequences from varying degrees of the width of the delta wave due to different levels of activation over both AP and AVN.<sup>[15]</sup> The risk of ventricular arrhythmia and sudden death is the reason for much more attention to this disorder. Some electrophysiological features are associated with the capacity of AP to allow rapid ventricular conduction. These parameters include the presence of multiple APs, SPERRI of  $\leq 250$  m at baseline or AERP-AP  $\leq 250$ , and the inducibility of AVRT during the study.<sup>[16-19]</sup> The preferred approach to managing AF with preexcitation is DC

cardioversion, although pharmacological management in hemodynamically stable patients may be an alternative option. The first recognized deterioration of AF to VF occurred after the administration of propranolol and digoxin in a patient with preexcited AF. Accordingly, these AVN blocking drugs (adenosine, beta-blockers, calcium channel blockers, or digoxin) are to be avoided in this situation.<sup>[3,20,21]</sup> Ibutilide and procainamide are the drugs of choice.<sup>[3]</sup> A review of previous studies and case reports found a small risk of VF due to the administration of amiodarone for rate or rhythm control in preexcited AF.<sup>[8]</sup> However, some studies also reported the safety of amiodarone when administered for preexcited AF management.<sup>[22]</sup> The conduction properties of APs may be accountable for amiodarone response in preexcited AF. A previous study verified that the prolongation of AERP-AP by amiodarone was reached more often in patients with initial AERP-AP  $> 270$  m than in those with shorter refractory periods.<sup>[13]</sup> In our study, the patients who had converted to the sinus rhythm had more prolonged initial AERP of AP and lower preexcited index. It seems that a lower preexcited index in ECG (intermittent wide QRS complexes) can be an indicator of amiodarone response in converting to the sinus rhythm.

The power of the study is a relatively large sample of patients with preexcited AF who were evaluated in the standard setting in an EP laboratory. The limitations include monitoring of the patients under a conscious sedation setting due to the probability of unstable condition, so the evaluation of sympathetic tone may be conferred. The other limitation was the inability of measuring AVN RP before amiodarone administration in those patients with AV nodal RP greater than AP. Single arm before-after interventional design could be another limitation.

## CONCLUSION

We found that IV amiodarone lengthens the refractory period of both AVN and AP. Therefore, the ventricular rate will not increase significantly, leading to VF degeneration and implying its safety. However, due to the more prolongation of AVN refractoriness than AP, QRS morphologies may be wider and more bizarre, leading to a worsening preexcited index. Therefore, amiodarone could be considered a safe drug in patients with preexcited AF for rate control despite its relatively low efficacy in conversion to the sinus rhythm.

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## Conflicts of interest

There are no conflicts of interest.

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