ORIGINAL ARTICLE

Changes in Electrocardiographic P Wave Parameters after Cryoballoon Ablation and Their Association with Atrial Fibrillation Recurrence

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Background: Changes in P wave parameters after circumferential pulmonary vein isolation (CPVI) have been previously identified. In this study, we aimed to determine the changes in P wave parameters surface electrocardiogram (ECG) after cryoballoon ablation (CBA) for atrial fibrillation (AF) and evaluate their relationship with AF recurrence.

Methods: Sixty-one patients (mean age 53 ± 11 years, 50.8% male) with paroxysmal AF who underwent CBA were enrolled. A surface ECG was obtained from all patients immediately before the procedure, and repeated 12 hours after the procedure. P wave amplitude (Pamp), P wave duration (Pwd), and P wave dispersion (Pdis) values in preprocedural and postprocedural ECGs were measured and compared. Recurrence rates of AF in 3, 6, and 9 months following ablation were recorded for all patients. Changes in P wave parameters were compared between patients with and without AF recurrence.

Results: Compared to preprocedural measurements, Pamp (from 0.58 ± 0.18 mV at baseline to 0.48 ± 0.17 mV, $P < 0.001$), Pwd (from 109.72 ± 18.43 ms at baseline to 91.36 ± 22.53 ms, $P < 0.001$), and Pdis (from 55.44 ± 20.45 ms at baseline to 45.30 ± 15.31 ms, $P < 0.001$) were significantly decreased after CBA. The difference in Pamp between pre- and postprocedural values (ΔPamp) was significantly higher in patients without AF recurrence compared to those with recurrence (0.10 ± 0.06 mV vs 0.04 ± 0.01 mV, $P = 0.002$). There was no difference in Pwd difference (ΔPwd) and Pdis difference (ΔPdis) between patients with and without AF recurrence ($P > 0.05$).

Conclusion: Pamp, Pwd, and Pdis parameters exhibited significant decrease after CBA compared to preprocedural measurements. Decreased Pamp was shown to be a predictor for good clinical outcomes following CBA.

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atrial fibrillation; electrophysiology; atrial arrhythmias; noninvasive techniques; electrocardiography

Pulmonary vein isolation (PVI) is a cornerstone in atrial fibrillation (AF) treatment.[1–3] PVI isolates the electrical connection between pulmonary veins (PVs) and left atrium (LA), and also shows beneficial effects on triggered activity as well as autonomic modulation.[4,5] Cryoballoon ablation (CBA) is a safe and effective PVI method alternative to radiofrequency catheter ablation by delivering ultracold energy.[6–8] P wave duration (Pwd) is a reliable marker indicating atrial conduction, and

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prolonged P wave is associated with electromechanical dysfunction leading to atrial conduction disturbance.[9,10] Circumferential pulmonary vein isolation (CPVI) was previously reported to be associated with changes in P wave parameters as a consequence of reduced atrial electrical burden by ablation, and these changes were suggested to be an indicator of procedural success in several studies.[11–13] Technical differences between CBA and CPVI might have played role in the formation of distinct postprocedural electrical activity and electrocardiogram (ECG) P wave parameters due to different inflammatory reactions and necrotic lesions induced by ablation.

In this study, we aimed to evaluate P wave changes on surface ECG following CBA, and investigate the relationship between these changes and AF recurrence after ablation.

METHODS

Study Population

We enrolled 78 patients with paroxysmal AF (PAF) who were refractory or intolerant to antiarrhythmic drug (AAD) therapy. A 256-slice computerized tomography (CT) and three-dimensional reconstruction of LA-PV was performed in order to visualize the PV anatomy and variation before the CBA. Complex PV anatomy was defined as the presence of two more PV ostia on each side (right or left). Patients with complex PV anatomy (n = 17) were excluded. Sixty-one patients (mean age 53 ± 11 years, 50.8% male) were scheduled for CBA.

Patients with PAF were defined as those with normal sinus rhythm on admission ECG and AF episode lasting longer than 30 seconds in 24-hour ambulatory Holter ECG or in an ECG recorded within the last 12 months.

Exclusion criteria were defined as follows; anemia (Hb <10 g/dL), renal dysfunction (creatinine >2 g/dL), moderate to severe valvular heart disease, impaired left ventricle systolic function (EF <50%), active infection, malignancy, or acute coronary syndrome.

Echocardiographic Measurements

All echocardiographic measurements were performed according to the American Society of Echocardiography Guidelines.[14]

Ablation Procedure

The CBA procedure was performed similar to the CBA technique described elsewhere.[15,16] Right femoral vein, left femoral vein, and left femoral artery punctures were performed with Seldinger technique in patients who had CBA. A 6-French (F) decapolar catheter was placed in coronary sinus (CS) via the left femoral vein. A diagnostic catheter was advanced to aortic root via left femoral artery in order to mark aorta during transseptal puncture. A 7-F-long sheath was advanced to superior vena cava over a 0.38-inch guide wire from the right femoral vein. Transseptal puncture was performed with a Brockenbrough needle (St. Jude Medical, St. Paul, MN, USA) under fluoroscopic guidance. Transesophageal echocardiography was used for selected patients with difficult puncture. A steerable 12-F sheath (FlexCath, Medtronic, Brampton, Canada) was advanced to LA.

We used a 28-mm cryoballoon (Arctic Front Medtronic Cryocath and Aortic Front Advance) for the ablation procedure. The balloon was introduced into the PV ostium over an Achieve guide wire (Medtronic Ablation Frontiers, LLC, Carlsbad, CA, USA) utilized for mapping PV potentials before, during, and after cryo applications. Contrast medium was injected to the distal site of the balloon in order to visualize occlusion through the Arctic Front catheter. Cryothermic energy was delivered for 4 minutes per application, and two applications were performed for each PV. If PV potentials were still present, one extra cryoballoon application was attempted as needed. Before targeting the right PVs, the decapolar CS catheter was positioned in superior cava for continuous phrenic nerve stimulation during cryoapplication. After the procedure, exit and entrance block of all PVs were confirmed by pacing maneuvers.

ECG Recordings and Analysis

A 12-lead ECG was recorded both before and 12 hours after the procedure in all patients. The standard 12-lead ECG was initially recorded at a 25 mm/s paper speed and 1 mV/cm calibration. Thereafter, recordings were performed at a 50 mm/s paper speed and 2 mV/cm calibration in order to obtain more sensitive measurements. Scanning and digitizing of ECG signals from the paper recordings using an optical scanner were performed for all ECG recordings. Standard

12-lead ECGs were analyzed by two independent cardiologists in a blinded manner. Patients with documented AF on ECG were excluded from the study.

P Wave Parameters and Analysis

Pwd: The onset and end of the P wave was defined as the point of the first visible upward slope from the isoelectric line and the point of return to isoelectric line, respectively. The duration between those points were measured in aVF lead of 12-lead ECG as milliseconds.

P wave amplitude (Pamp): The vertical distance between the peak point of P wave and isoelectric line was measured in aVF lead of 12-lead ECG as millivolts.

P wave dispersion (Pdis): The difference between maximum and minimum Pwd on 12-lead ECG was defined as Pdis.

ΔPwd: The difference between Pwd measured on preprocedural ECG (PrePwd) and postprocedural ECG (PostPwd) was defined as ΔPwd.

ΔPamp: The difference between P waves measured on preprocedural ECG (PrePamp) and postprocedural ECG (PostPamp) was defined as ΔPamp.

ΔPdis: The difference between Pdis measured on preprocedural ECG (PrePdis) and postprocedural ECG (PostPdis) was defined as ΔPdis.

Follow-Up

Regular follow-up consisted of outpatient clinic visits at 3, 6, and 9 months after the procedure and included a detailed history for arrhythmia-related symptoms (palpitations, chest discomfort, fatigue, and dizziness), physical examination, 12-lead ECG, and 24-hour Holter monitoring. If symptoms occurred outside the recording period, patients were asked to contact our center or the referring physician to obtain ECG documentation. AF recurrence was defined as the presence of any AF episode lasting more than 30 seconds on 12-lead ECG or 24-hour ambulatory ECG monitoring after a 3-month postablation blanking period. Patients were treated with propafenone or amiodarone for 6 weeks following ablation. All patients were orally anticoagulated for 3 months following ablation, and those with a CHA_2DS_2VASc score ≥2 received continuous oral anticoagulant therapy. Procedural success was defined as absence of any atrial arrhythmia lasting longer than 30 seconds at 6 weeks after discontinuation of the AAD therapy.

Statistical Analysis

SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentage. The Kolmogorov-Smirnov test was used to test the normality of distribution of continuous variables. Group means for continuous variables were compared with the use of Student's *t*-test, the Mann-Whitney U test, as appropriate. Categorical variables were compared with the use of chi-square test. Variables with a P value of ≤0.05 were selected for logistic regression analysis. Logistic regression analysis was performed to find independent associates of postablation recurrence. Interobserver agreement of ECG P wave analysis data was calculated using the Bland-Altman analysis and intraclass correlation coefficient was used to assess intraobserver agreement. Receiver-operating characteristic (ROC) curve analysis was performed to detect the cutoff value of ΔPamp in prediction of postablation recurrence. Comparison of area under curve (AUC) values was performed by MedCalc software program, release 7.3.0.1 (MedCalc Software, Mariakerke, Belgium). A P value of ≤0.05 was considered statistically significant.

Reproducibility

Intra- and interobserver variability was calculated for PrePwd, PrePamp, and PrePdis, which were assessed based on the electrocardiographic data of a subgroup of 15 subjects. To assess interobserver variability, a second cardiologist who was unaware of the previous measurements performed the electrocardiographic analysis. One month later, the first cardiologist repeated the analysis to assess intraobserver variability. Agreement analysis of interobserver measurements for PrePamp, PrePwd, and PrePdis revealed a high level of agreement; a mean difference of 1.04 (95% limit of agreement 1.23, 0.86), 1.01 (95% limit of agreement 1.07, 0.95), and 1.00 (95% limit of agreement 1.15, 0.85), respectively. Intraobserver intraclass correlation coefficients of PrePwd, PrePamp, and PrePdis were 0.96 (95% CI 0.88–0.99), 0.97 (95% CI 0.93–0.99), and 0.97 (95% CI 0.91–0.99), respectively.

Table 1. Baseline Characteristics of Patients

	n = 61
Age (years)	53 ± 11
Gender, n (male %)	31(50.8%)
HT, n (%)	26(42.6%)
DM, n (%)	9(14.8%)
CAD, n (%)	8(13.1%)
LAD (cm)	3.3 ± 0.5
LVEF (%)	64.3 ± 2.6
ESD (cm)	2.8 ± 0.4
EDD (cm)	4.2 ± 0.4
Procedure time (mins)	79.4 ± 18.8
Fluoroscopic time (mins)	22.3 ± 6.8
Energy delivery time (mins)	43.8 ± 7.5
PrePamp (mV)	0.58 ± 0.18
PrePwd (ms)	109.7 ± 18.4
PrePdis (ms)	55.4 ± 20.4
Beta blocker, n (%)	42(68.9%)
ACEIs, n (%)	5(8.2%)
ARBs, n (%)	12(19.7%)
CCB, n (%)	5(8.2%)
Amiodarone, n (%)	12(19.7%)
Propafenon, n (%)	19(31.1%)
OAD, n (%)	6(9.8%)
Warfarin, n (%)	7(11.5%)
Dabigatran, n (%)	10(16.4%)
Rivaroxaban, n (%)	0(%)

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CAD = coronary artery disease; CBA = cryoballoon ablation; CCB = calcium channel blockers; DM = diabetes mellitus; ESD = end systolic diameter; EDD = end diastolic diameter; HT = hypertension; LAD = left atrium diameter; LVEF = left ventricular ejection fraction; OAD = oral antidiabetic; PrePamp = preablation P wave amplitude; PrePwd = preablation P wave duration; PrePdis = preablation P wave dispersion.

RESULTS

Demographic baseline characteristics of patients are presented in Table 1. The study population consisted of 61 patients (31 males, 50.8%) and the mean age of the patients was 53 ± 11 years. The number of patients with HT was 26 (42.6%), mean left atrial diameter (LAD) was 3.3 ± 0.5, and mean left ventricular ejection fraction (EF) was 64.3 ± 2.6. The mean value of procedural time was 79.4 ± 18.8 minutes, fluoroscopic time was 22.3 ± 6.8 minutes, and energy delivery time was 43.8 ± 7.5 minutes. PrePwd was 109.7 ± 18.4 ms, PrePamp was 0.58 ± 0.18 ms, and PrePdis was 55.4 ± 20.4 ms.

All of the P wave parameters exhibited a significant decrease after CBA [PrePamp (0.58 ± 0.18) − PostPamp (0.48 ± 0.17), ($P < 0.001$), PrePwd (109.72 ± 18.43) − PostPwd (91.36 ± 22.53), ($P < 0.001$). PrePdis (55.44 ± 20.45) − PostPdis (45.30 ± 15.31), ($P < 0.001$)].

The demographics of patients with and without AF recurrence after CBA are detailed and compared in Table 2. Recurrence rate was 16% (n = 10). Both groups were similar in terms of age, gender, HT, DM, and CAD ($P > 0.005$ for all). There was no difference between groups regarding echocardiographic parameters ($P > 0.005$ for all). Procedural time, fluoroscopic time, and energy delivery time were similar between both groups ($P > 0.005$ for all). ΔPamp was significantly higher in the group without recurrence compared to the group with recurrence (0.10 ± 0.06 vs 0.04 ± 0.01, $P = 0.002$). ΔPwd and ΔPdis did not differ between groups ($P > 0.05$). The drugs used in the two groups were similar except warfarin ($P > 0.005$ for all). Warfarin use was significantly higher in the group with recurrence [n = 4 (7.8%) vs n = 3 (30%), $P = 0.044$].

Multivariate analysis revealed only ΔPamp as a predictor for AF recurrence among parameters of age, HT, LAD, fluoroscopic time, and ΔPamp ($P = 0.009$, OR: 2.83, 95% CI 12.25–1.18; Table 3).

ROC curve analysis was performed to detect the cutoff value of ΔPamp in prediction of postablation recurrence. Figure 1 illustrates the results of ROC curve analysis for ΔPamp in the detection of postablation recurrence. ΔPamp identified patients with postablation recurrence with a specificity of 100.0%, a sensitivity of 70.6%, and with a cutoff value of >0.06 mV (AUC: 0.836, 95% CI 0.742–0.934).

DISCUSSION

(1) This study investigated the changes in P wave parameters on surface ECG after CBA and also their relationship with AF recurrence after ablation. P wave parameters (Pamp, Pwd, Pdis) were significantly decreased after CBA compared to the preprocedural values.

(2) Decreased Pamp after CBA was associated with AF recurrence. Patients with higher ΔPamp had lower recurrence rates. Multivariate analysis revealed ΔPamp as the only independent predictor for AF recurrence among other factors including age, HT, LAD, and fluoroscopic time. Decreased Pamp with a cutoff value >0.06 mV was detected to predict procedural

Table 2. Clinical and Laboratory Characteristics and Comparison of Patients with and without Recurrence

	Recurrence - n = 51	Recurrence + n = 10	P Value
Age (years)	52.6 ± 11.3	55.5 ± 13.7	0.487
Gender, n (male %)	27(52.9%)	4(40%)	0.454
HT, n (%)	23(45.1%)	3(30%)	0.377
DM, n (%)	7(13.7%)	2(20%)	0.609
CAD, n (%)	8(15.7%)	0(0%)	0.179
LAD (cm)	3.3 ± 0.5	3.4 ± 0.5	0.665
LVEF (%)	64.4 ± 2.5	64 ± 3.1	0.658
ESD (cm)	2.8 ± 0.4	2.6 ± 0.5	0.111
EDD (cm)	4.1 ± 0.4	4.3 ± 0.4	0.471
Procedure time (mins)	77.7 ± 17.2	87.9 ± 24.8	0.121
Fluoroscopic time (mins)	22.1 ± 6.7	23.3 ± 7.5	0.637
Energy delivery time (mins)	43.1 ± 7.1	47.4 ± 8.5	0.098
Preheart rate (bpm)	65 ± 8	65 ± 10	0.987
Postheart rate (bpm)	68 ± 9	69 ± 11	0.789
ΔPamp	0.10 ± 0.06	0.04 ± 0.01	0.002
ΔPwd	18.82 ± 24.36	16.00 ± 22.71	0.736
ΔPdis	11.35 ± 17.40	4.00 ± 15.77	0.220
Beta-blocker, n (%)	36(70.6%)	6(60%)	0.509
ACEIs, n (%)	5(9.8%)	0(0%)	0.301
ARBs, n (%)	10(19.6%)	2(20%)	0.977
CCB, n (%)	5(9.8%)	0(0%)	0.301
Amiodarone, n (%)	8(15.7%)	4(40%)	0.077
Propafenon, n (%)	17(33.3%)	2(20%)	0.405
OAD, n (%)	5(9.8%)	1(10%)	0.985
Warfarin, n (%)	4(7.8%)	3(30%)	0.044
Dabigatran, n (%)	8(15.7%)	2(20%)	0.736
Rivaroxaban, n (%)	0(0%)	0(0%)	0

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CAD = coronary artery disease; CBA = cryoballoon ablation; CCB = calcium channel blockers; ΔPamp = preablation P wave amplitude – postablation P amplitude; ΔPwd = preablation P wave duration – postablation P wave duration; ΔPdis = preablation P wave dispersion – postablation P wave dispersion; DM = diabetes mellitus; ESD = end systolic diameter; EDD = end diastolic diameter; HT = hypertension; LAD = left atrium diameter; LVEF = left ventricular ejection fraction; OAD = oral antidiabetic; PrePamp = preablation P wave amplitude; PrePwd = preablation P wave duration; PrePdis = preablation P wave dispersion.

Table 3. Multivariate Analysis of Independent Predictors of AF Recurrence

	Univariate P Value	Univariate OR and 95% CI	Multivariate P Value	Multivariate OR and 95% CI
Age (years)	0.481	1.02 (1.09–0.96)	0.639	1.02 (1.10–0.95)
HT, n (%)	0.603	1.44 (0.36–5.73)	0.802	1.25 (7.20–0.28)
LAD (cm)	0.767	1.30 (4.26–0.40)	0.791	1.22 (5.21–0.28)
Fluoroscopic time (mins)	0.631	1.02 (1.13–0.93)	0.664	1.03 (1.16–0.91)
ΔPamp	0.007	3.01 (4.92–1.99)	0.009	2.83 (12.25–1.18)

HT = hypertension; LAD = left atrium diameter; ΔPamp = preablation P wave amplitude – postablation P amplitude.

success with 100.0% specificity and 70.6% sensitivity.

(3) AF recurrence after CBA was not associated with ΔPwd or ΔPdis.

P Wave Amplitude after Cryoballoon Ablation

Previous studies investigated the changes in Pamp after CPVI; however, no study to date has investigated the changes in Pamp after CBA. Van Beeumen et al. evaluated the changes in P wave after CPVI in 39 patients, and found a significant decrease in Pamp (from 0.15–0.2 to 0.1) and P wave area; but none of these decreases was associated with AF recurrence.[12] In another study by Zhao et al. consisting of 50 patients with PAF who underwent CPVI, Pamp on surface ECG was decreased significantly after ablation, but it was not associated with

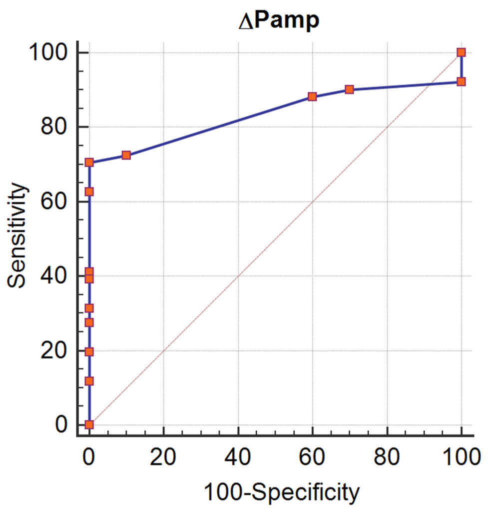

Figure 1. ROC curve analysis for ΔPamp in the detection of postablation recurrence.

recurrence.[13] Consistent to the previous studies, our study demonstrated that Pamp on surface ECG after CBA was decreased significantly, but unlike other studies, it was associated with AF recurrence after ablation. Changes in P wave after CBA are thought to be associated with reduced electrical burden of LA after PVI. Conflicting results were obtained in studies evaluating the relationship between decreased electrical burden and procedural success. We found that decreased Pamp, which is considered to be an indicator of reduced voltage after ablation, is a predictor for procedural success Diverse results obtained in studies evaluating the relationship between Pamp and AF recurrence after CPVI may be related to ablation technique. Acute thermal injury applied by radiofrequency during CPVI causes coagulation necrosis and extensive inflammation in the tissue while CBA causes better-defined homogenous lesions and less intensive inflammatory reactions.[17–22] This technical difference might lead distinct electrical activity recorded after the procedure. Besides, difference of the P wave parameters after ablation in the studies may be related to the amount of antral tissue that is ablated. Moreover, selected patient population and operator-dependent technical differences might have contributed in different outcomes. Changings of Pamp due to decreased electrical activity after CBA may indicate more effective ablation due to the aforementioned technical difference; however, further studies are required to better clarify the relationship between changes in P wave parameters and AF recurrence.

P Wave Duration after Cryoballoon Ablation

Studies evaluating the changes in P wave after ablation and their association with AF recurrence have provided distinct results. Ogawa et al. examined 27 patients with PAF or persistent AF, and found significantly decreased Pwd in the group without recurrence after CPVI (161 + 7 to 151 + 8 ms, ΔPwd 10 ± 7 ms, $P < 0.0001$) and insignificant change of Pwd in the group with recurrence (ΔPwd 2 ± 9 ms, P = NS).[23] Zhao et al. evaluated 50 patients with PAF who underwent CPVI and found decreased Pwd on surface ECG after ablation; however, it was not a predictor for AF recurrence.[13] Another study which included 45 patients with PAF found significantly decreased Pwd after both CBA (n = 15) and radiofrequency ablation (n = 30); however, the relationship with recurrence was not investigated.[24] The mechanism underlying decreased Pwd after ablation remains unclear. One of the suggested mechanisms is the interruption of electrical connection between PVs and LA, resulting in shortened terminal portion of P wave, which indicates late activation of PVs-LA region.[12,23] Inadequate isolation or reconnection of electrical activity between PVs and LA give rise to AF recurrence.[25] On the other hand, Date et al. demonstrated that excitation of myocardial tissue within the PVs was mainly responsible for the formation of the middle part of the P wave, and PVI did not affect Pwd in their study population including 21 patients with drug-refractory PAF.[26] Therefore, PVs-LA isolation may not be the sole reason for the shortening of Pwd after ablation. Decreased number of depolarizing cells after ablation may contribute to decreased Pwd by causing electrical blockade through the ablation line.[13] We detected decreased Pwd after CBA in consistence with previous studies; however, the changes in Pwd were not associated with AF recurrence. Changes in P wave configuration after CPVI and their relationship with recurrence have been thoroughly investigated in previous studies; however, no study to date has investigated the changes in Pwd and their relationship with recurrence after CBA. Our study population included only patients with PAF, and excluded patients with persistent AF. This difference may have played a role in obtaining dissimilar results compared to other studies.

P Wave Dispersion after Cryoballoon Ablation

Association between increased Pdis and prediction of AF has been previously demonstrated.[27] Pdis measures the difference between distinct vectors within atrial conduction. Thus, it may reflect variability and heterogeneity of atrial conduction.[28] Zhao et al. found decreased Pdis after CPVI in patients with PAF, and showed that this decrease was associated with AF recurrence after ablation.[13] Similarly, we found significantly decreased Pdis after ablation; however, there was no association between decreased Pdis and AF recurrence. In contrast with the aforementioned study, we utilized CBA as the ablation method. Decreased Pdis after ablation may refer to the projection of decreased conductive heterogeneity within the atrium to surface ECG; however, further research is required for better comprehension of decreased Pdis and AF recurrence association.

Study Limitations

A major limitation is the use of 24-hour Holter recordings for AF detection. Seven-day ambulatory ECG monitoring or implantable loop recorders could have better detected AF episodes by longer monitoring periods. We used 12-lead standard ECG, an easily accessible noninvasive technique for P wave measurements. No intracardiac ECGs were examined. Intracardiac ECGs could have shown the effects of changes in atrial conduction on P wave in an improved better and more effective fashion. Measurements of Pamp and Pwd were performed on aVF lead, and not all leads were used. Postprocedural 12-lead ECG recordings were obtained 12 hours after the procedure, and longer follow-up could have provided distinct P wave measurements. A small sample size of the patient population was another limitation of our study.

CONCLUSION

Pamp, Pwd, and Pdis parameters on surface ECG were decreased after CBA. Decreased Pamp was shown to be a predictor of good clinical outcomes after CBA. Changes in Pamp after ablation may be beneficial for the prediction of AF recurrence in long-term follow-up.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of article.

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