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Ibutilide Increases the Variability and Complexity of Atrial Fibrillation Electrograms: Antiarrhythmic Insights Using Signal Analyses

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Abstract

Introduction—Intravenous ibutilide is used to convert atrial fibrillation (AF) to sinus rhythm due to its Class III antiarrhythmic mechanisms. However, the effects of ibutilide on local electrograms during AF have not been elucidated.

Methods and Results—We used electrogram (EGM) analysis techniques to characterize how ibutilide administration changes the frequency, morphology, and repeatability of AF EGM signals, thereby providing insight into ibutilide's antiarrhythmic mechanism of action. AF recordings were collected from 21 patients with AF both before and after ibutilide administration. The effects of ibutilide on the following AF EGM parameters were assessed: 1) dominant frequency, 2) variations in EGM amplitude and overall morphology, 3) repetition of electrogram patterns, and 4) complexity of the AF frequency spectra.

When comparing pre- vs. post-ibutilide administration EGMs, DF decreased from 5.45 to 4.02 Hz ($p<0.0001$). There was an increase both in the variability of AF EGM amplitudes ($p=0.003$) and variability of overall AF EGM morphologies ($p=0.003$). AF EGM pattern repetitiveness decreased ($p=0.01$), and the AF frequency spectral profile manifested greater complexity ($p=0.02$).

Conclusions—Novel electrogram signal analysis techniques reveal that ibutilide administration causes increased complexity in the atrial electrical activation pattern while decreasing rate. These findings may be explained by the progressive destabilization of higher frequency, more homogeneous primary drivers of AF over the course of ibutilide administration and/or less uniform propagation of atrial activation, until AF maintenance becomes more difficult and either transforms to atrial tachycardia or terminates to sinus rhythm.

Keywords

Atrial Fibrillation; Ibutilide; Electrogram Analysis; Dominant Frequency; Linear Prediction

INTRODUCTION

Clinical studies suggest that local electrograms (EGMs) recorded during atral fibrillation (AF) reflect a variety of mechanisms, including driving sites of rapid atrial activation necessary for the maintenance of AF.[1–3] A careful study of how EGMs change in AF patients when they are treated with an antiarrhythmic medication can help elucidate how antiarrhythmic therapy affects the perpetuating mechanisms of AF. Past studies have shown

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that there are observable differences in the morphologies and repetitive patterns of complex fractionated atrial electrograms (CFAEs) between patients with paroxysmal AF and those with persistent AF.[4–6] We hypothesized that atrial EGMs in AF patients would manifest analogous morphological transformations over the brief time course of treatment with the antiarrhythmic medication ibutilide. The aim of this study was to compare several quantitative parameters of atrial EGMs in patients with AF before versus after intravenous ibutilide treatment in order to determine the effect of ibutilide on atrial electrical activation patterns and provide mechanistic insight into AF maintenance.

METHODS

Study population

Intracardiac atrial EGMs were collected from a consecutive series of 21 adult patients at Columbia University Medical Center who underwent electrophysiology study (EPS) ± catheter ablation and were in AF requiring treatment with ibutilide infusion. EGM data collection and analysis were approved by the Institutional Review Board of Columbia University Medical Center.

Electrophysiology Study

Patients underwent an initial evaluation that included history, physical examination, ECG, and echocardiogram. EPS was performed using either conscious sedation, or general anesthesia in those patients undergoing AF ablation. Membrane-active antiarrhythmic medications were held for at least 5 half-lives prior to electrophysiology study (no patients were taking amiodarone at the time of EP study). Both programmed burst and extra-stimulus testing were performed from atrial and ventricular sites as deemed necessary for the baseline diagnostic EPS. For those patients referred for AF radiofrequency ablation (RFA), atrial ablation consisted of pulmonary vein isolation + CFAE ablation (for persistent AF patients) ± linear ablations (cavotricuspid, left atrial roof, and/or mitral) for persistent AF patients as well as paroxysmal AF patients who manifested a corresponding AFL during their procedure or in the past.

A total of 7 patients had a history of paroxysmal AF (n=5) or atrial flutter (n=2), and all were in sinus rhythm at baseline. A second group of 7 patients had a history of persistent AF (4 in AF at baseline and 3 in sinus rhythm). The remaining 7 patients were undergoing study for other types of SVT (n=3 atrial tachycardia, n=1 atrioventricular nodal reentry tachycardia, and n=3 atrioventricular reentry tachycardia); 5 of those patients were in sinus rhythm (2 patients were in atrial tachycardia at baseline). Pulmonary vein isolation had been previously performed in 1 paroxysmal and 1 persistent AF patient. For all patients, AF persisted for at least 10 minutes prior to treatment with ibutilide 1 mg IV infusion. No other inotropic or chronotropic agent, magnesium infusion, beta blockers, or a second dose of ibutilide was administered during the data collection period.

Ibutilide Administration

Ibutilide was administered and EGM data were retrieved as per the protocol outlined in Figure 1. Briefly, patients received 1 mg of intravenous ibutilide over a 10-minute interval. All patients had a QTc interval < 500 msec prior to ibutilide administration. For each patient, EGMs were sampled at two time intervals: (1) immediately prior to the administration of ibutilide, and (2) 10 minutes after the start of the first 10-minute long intravenous dose of 1 mg ibutilide, or just prior to termination when AF terminated less than 10 minutes after the first ibutilide dose. In 12 patients for whom AF did not terminate (and the QTc interval was still < 500 msec), a second dose of ibutilide 1 mg was administered over 10 minutes. However, in order to eliminate the potential of a dose-response effect on

EGM measurements, data collection was not performed during or after the second ibutilide dose.

Atrial Fibrillation Electrogram Measurements

As a stable source of AF EGM data collection over the 10-minute infusion of ibutilide, a deflectable 6 F octapolar catheter (2 mm distal tip and 1 mm proximal tips with 5 mm spacing, Bard EP-XT, Lowell, MA, USA) was used to record bipolar atrial EGMs from the coronary sinus. Digitized EGM signals of bipolar AF CFAEs, defined as either continuous local electrograms or discrete electrogram deflections separated by less than 120 milliseconds as recorded over a 10-second interval[7] (from the most distal coronary sinus bipolar electrode not containing significant signal artifact) were collected in 8.4 second recording periods, filtered (30–500 Hz) to remove drift and high frequency noise, sampled at 977 Hz, and stored on a digital recording system (CardioLab, GE, WI, USA).

CFAE Characteristics

AF EGMs were analyzed for frequency and morphologic characteristics. The methods of EGM signal data analysis have been validated previously. First, four spectral characteristics were measured.[8] The dominant frequency (DF) is defined as the largest fundamental periodic component in the frequency range of interest (3–12 Hz). The amplitude of this dominant peak is the dominant amplitude (DA). The magnitude (ordinate) axis of the power spectrum is then normalized to a range of 0–1. The mean spectral profile (MP) is defined as the average level of the normalized spectrum. Second, morphologic (electrogram shape) characteristics were also measured.[4] The amplitude of each electrogram deflection was measured and expressed as mean ± standard deviation for all deflections and the coefficient of variation or COV (= standard deviation/mean), while the uniformity of amplitude peaks was expressed as the mean sum of absolute values of EGM morphologies. Third, the degree of repetitiveness of any patterns present in CFAE, whether periodic or not, was estimated using linear prediction and signal reconstruction methodology.[5]

In short, these three types of measurements describe the complexity of CFAE in three different ways. Greater complexity in CFAE patterns is indicative of a greater degree of randomness in the atrial electrical activation pattern. Greater complexity is expressed as a lower value of DA and higher values of MP and spectral profile for spectral characteristics, greater value of amplitude COV and lower sum of absolute EGM amplitude values for morphological characteristics, and greater error for repetitiveness characteristics. In previous work, greater complexity has been associated with paroxysmal AF recordings, as compared with longstanding persistent AF recordings which were found to have significantly less complexity.[4, 9]

Statistical Analysis

Demographic characteristics were reported as mean ± standard deviation. Comparisons of continuous variables, including pre-ibutilide vs. post-ibutilide measurements, were analyzed by the Student paired *t*-test. Analysis of variance was used to assess group differences in the measured variables and post-hoc group comparisons were performed using Tukey's procedure. In a secondary analysis, patients with baseline sinus rhythm were combined and compared to patients with baseline AF by unpaired t-test. A p value of <0.05 was considered to be statistically significant. Statistical analysis was performed using SAS 8.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Summary characteristics of the patients' demographics are listed in Table 1. The study population included 21 patients (14 male/7 female; mean age 57 ± 10 years) who underwent EPS. AF terminated with ibutilide 1 mg intravenous administration in 8 patients.

Atrial Fibrillation Electrogram Measurements

For the following parameters, there were no significant differences in EGM analyses between the subgroup of patients who presented to EPS with baseline AF vs. those in sinus rhythm.

Dominant Frequency and Spectral Profile Changes—DF of AF EGMs decreased from a pre-ibutilide level of 5.45 ± 0.83 Hz to 4.02 ± 0.73 Hz ($p<0.0001$). There was no difference in the degree of DF change when comparing patients whose AF terminated (n=8; 5.71 ± 0.87 Hz pre-ibutilide vs. 4.14 ± 0.82 Hz post-ibutilide) versus those whose AF did not terminate with 1 mg of ibutilide (n=13; 5.30 ± 0.80 Hz pre-ibutilide vs. 3.96 ± 0.70 Hz post-ibutilide) (p=0.29).

Figure 2 is a representative example of the observed changes that occurred in the power spectra over the course of ibutilide administration. Overall, Figure 3A shows that the peak amplitude of the dominant frequency (DA) decreased from 1.57 to 1.43, p=0.02) while Figure 3B shows that the mean of the normalized power spectra (MP) increased from 0.39 to 0.43 (p=0.01).

Morphological Characteristics

Variation of EGM Amplitude: CFAE amplitude variation increased with ibutilide administration. Figure 4 is a representative example of the AF EGMs and their respective phase plots in a sample collected from the CS both pre-ibutilide and post-ibutilide administration. The phase plot (Figure 4B) of the pre-ibutilide EGMs (Figure 4A) have more overlapping points and more repetitive amplitudes when compared to the phase plot (Figure 4D) of the post-ibutilide EGMs (Figure 4C). As a whole, the amplitudes of the AF EGM deflections became more variable after ibutilide administration, reflected by an increase in the coefficient of variation of EGM amplitudes (1.62 ± .47 mV vs. 1.89 ± .53 mV, p=0.003) (Figure 5).

Variation of Overall EGM Morphologies: Figure 6 notes that post-ibutilide AF EGM signals possessed more morphologic variation than pre-ibutilide EGMs, as measured by mean sum of absolute values of EGM amplitudes (0.57 pre- vs. 0.53 post-ibutilide, p=0.003). This result indicates that there was significantly more variation of EGM morphologies after administration of ibutilide. Morphological changes in EGMs were not significantly different between the subgroups of patients whose AF terminated with ibutilide compared to those whose AF did not terminate.

EGM Pattern Repetitiveness: Figure 7 is a representative example of the changes that occurred in repetitiveness of EGMs when comparing pre-ibutilide vs. post-ibutilide EGMs. In total, there was a significant increase in the linear prediction error of EGMs (0.34 ± .05 Hz pre-ibutilide to 0.40 ± .14 Hz post-ibutilide, p= 0.01). Therefore, there was significantly more error evident in EGMs when attempting to estimate reproducible CFAE patterns after ibutilide was administered, signaling an increased overall complexity of EGMs.

DISCUSSION

We used recently developed and novel electrogram signal analysis techniques to show that EGMs recorded during persistent, as well as newer-onset AF, manifest significant, quantitative changes when treated with the intravenous antiarrhythmic medication ibutilide.[4, 5] The main findings of this investigation are that AF EGMs manifest the following changes over the time course of intravenous ibutilide administration: 1) a decrease in dominant frequency; 2) more complexity of the frequency power spectra; 3) an increase in EGM morphologic heterogeneity; and 4) less repeatability of EGM patterns. These findings provide insights into how ibutilide manifests antiarrhythmic effects on an electrogram level.

Antiarrhythmic medications such as sodium channel blockers are known to cause increased destabilization and meandering of primary AF rotors and decreased wavebreak and secondary AF rotor formation, which have been correlated with AF termination.[10, 11] Increased rotor meandering has in turn been correlated with reduced AF EGM periodicity and increased EGM fractionation.[12] Fewer data exist regarding the effect of these and other antiarrhythmic agents, including the Class III agent ibutilide, on AF EGM changes (as well as their electrophysiologic basis) prior to AF conversion to atrial flutter/tachycardia or termination to sinus rhythm, particularly when used in the setting of AF ablation.[2, 13] Because various AF ablation strategies target CFAEs, attempts to understand more clearly the electrophysiologic bases for the changes that occur in AF EGMs over the course of antiarrhythmic treatment, either medical or catheter-based, are of increasing importance.[1, 12, 14–19]

By analyzing the effect of antiarrhythmic medication on multi-component atrial EGMs, we have gained insight into how ibutilide may be exerting its clinical effect at the electrophysiological level. The observed changes in EGMs due to ibutilide administration likely reflect electrophysiologic changes inherent in the underlying mechanisms maintaining atrial fibrillation. AF EGMs become more variable and heterogeneous in morphology, less repetitive in pattern, and more complex in the frequency spectrum over time, a result of ibutilide-induced modification of atrial electrical substrate. Several factors may explain these observations, including destabilization of primary drivers and/or less uniform propagation of activation. First, by increasing the refractory periods of more dominant, higher-frequency, and stable drivers of atrial fibrillation, ibutilide may be destabilizing such drivers, leading to increased variability and randomness in the morphologies of remaining EGMs. In addition, changes in refractory periods of atrial tissue may result in less uniform atrial activation in general. These factors may result in a decreased ability to maintain less uniform and stable AF activation pattern(s), leading either to transformation to atrial tachycardia or termination to sinus rhythm.

The EGM changes in pre- vs. post-ibutilide patients may be similar to those previously noted when comparing patients with paroxysmal vs. persistent AF.[4, 5] That is, the EGMs in both persistent and pre-ibutilide AF patients have less EGM variability and more repeatability, which is in contrast to the EGMs in paroxysmal and post-ibutilide AF patients, who have more EGM variability and less repeatability. These findings appear to reflect the common theme of AF possessing faster, more stable, and homogeneous drivers in both the persistent and pre-ibutilide AF patients, as compared to slower, less stable, and more heterogeneous drivers of AF in the paroxysmal and post-ibutilide AF patients. Such observations may be due to the fact that most patients with paroxysmal AF are thought to manifest drivers of AF that originate in and around the pulmonary veins, as well as relatively more normal atrial substrate that manifests more heterogeneous EGM characteristics. However, as AF progresses from a paroxysmal to a persistent state,

concomitant atrial remodeling results in a more homogeneous atrial substrate with less variability in electrophysiological properties, resulting, for example, from AF drivers possessing relatively more similar characteristics due to sources of focally localized microreentry.[20] Pre-. vs. post-ibutilide patients manifest EGM differences analogous to those of paroxysmal vs. persistent AF patients. Like the paroxysmal AF patients, ibutilide-treated patients are less likely to maintain sustained arrhythmogenic potential after ibutilide administration, leading either to AF transformation or termination. Prior analyses have revealed that the morphological parameters used in this study do not correlate well with atrial frequency alone, lending support to the notion that the observed morphological changes in EGMs are not caused solely by a decrease in frequency/activation rates over the course of ibutilide administration.[4]

The results of the study are in agreement with prior findings related to the use of ibutilide during AF ablation, which have noted that ibutilide administration leads to decreased left atrial rate and CFAE substrate area, with conversion to sinus rhythm or transformation to atrial tachycardia after additional ablation in a vast majority of patients.[13] Further analyses of whether the administration of ibutilide during CFAE-based AF ablation can improve clinical outcomes is an intriguing avenue for further study.[21]

Study Limitations

This study was limited by its relatively small number of patients collected in a retrospective fashion. Electrograms were recorded from the coronary sinus, which may possess electrophysiological characteristics different from other endocardial left and right atrial areas. The investigation was also performed in a heterogeneous group of AF patients, some of whom had undergone left atrial ablation, which may itself affect the EGM characteristics of patients. Thus, comparisons between patients who responded to ibutilide by converting to sinus rhythm versus patients who did not convert were not possible. Nevertheless, the study was performed in a relatively common clinical setting, characterizes a large percentage of patients presenting for EPS who manifest AF, and possessed results that did not differ significantly for those patients manifesting baseline AF vs. baseline SR. Therefore, these observations provide real-world insights into antiarrhythmic mechanisms of ibutilide. Finally, further comparisons using larger numbers of patients are required for more insight into the degree to which baseline EGM differences exist in AF patients, as well as whether the use of EGM characteristics can help guide and predict clinical outcome not only of AF medical treatments (such as ibutilide), but also of percutaneous catheter ablation treatment for AF.

Conclusion

Intracardiac signal electrogram analyses can be used to show that ibutilide administration leads to greater complexity of atrial electrical activity with decreased rate. These findings may be explained by the progressive destabilization of higher frequency, more homogeneous primary drivers of AF over the course of ibutilide administration and/or less uniform propagation of atrial activation, until AF maintenance becomes more difficult and either transforms to atrial tachycardia or terminates to sinus rhythm. Further research using AF electrogram signal analysis techniques to help guide medical as well as ablative therapies in AF patients is warranted to validate this hypothesis.

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Abbreviations

AF	atrial fibrillation
AFL	atrial flutter
AT	atrial tachycardia
AVNRT	atrioventricular nodal reentry tachycardia
AVRT	atrioventricular reentry tachycardia
CFAE	complex fractionated atrial electrogram
COV	coefficient of variation
DA	amplitude of dominant peak
ECG	electrocardiogram
EGM	electrogram
EPS	electrophysiology study
RFA	radiofrequency ablation
SP	mean spectral profile

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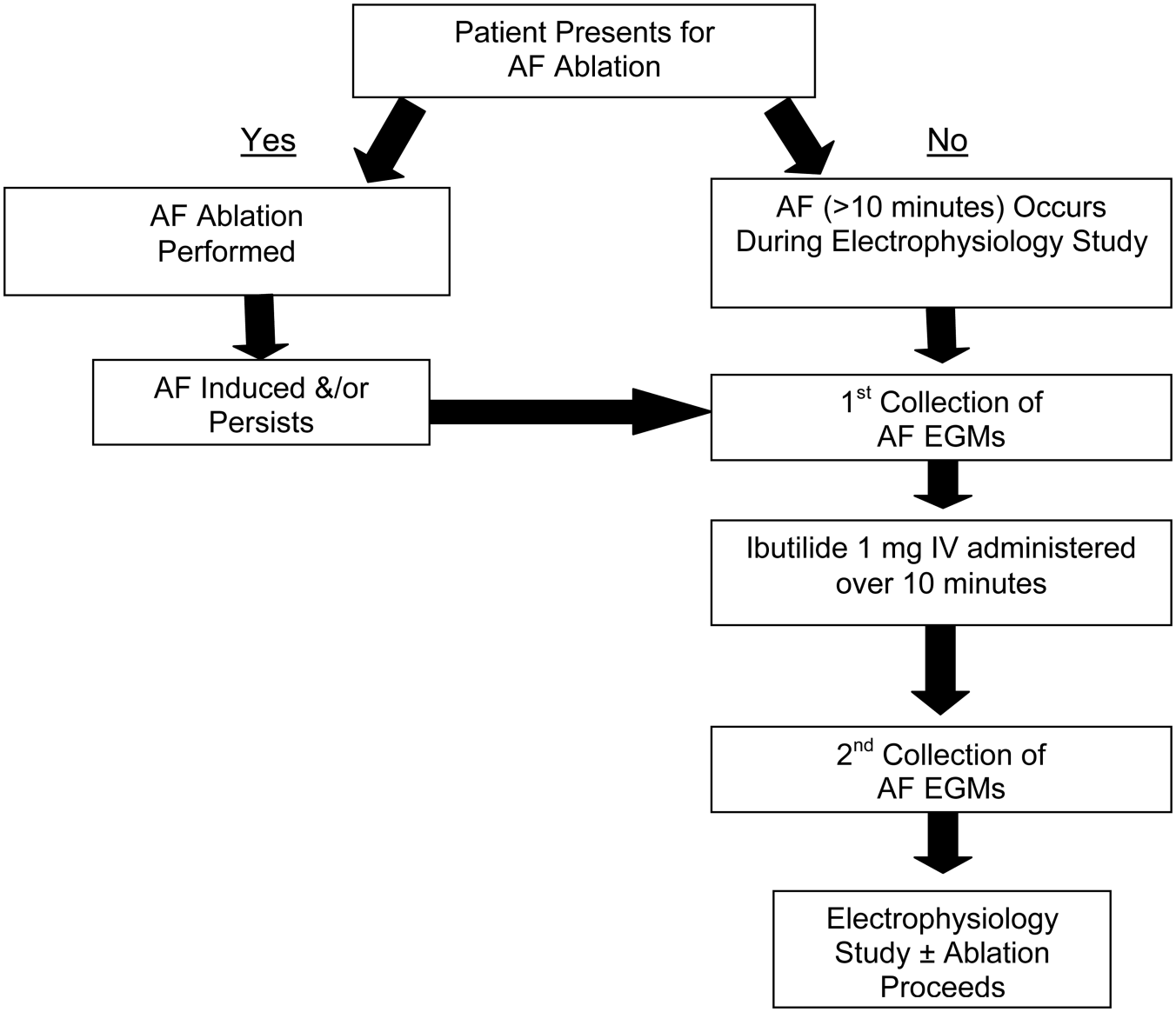


Figure 1.
Protocol for EGM sampling in AF patients before and after ibutilide administration.

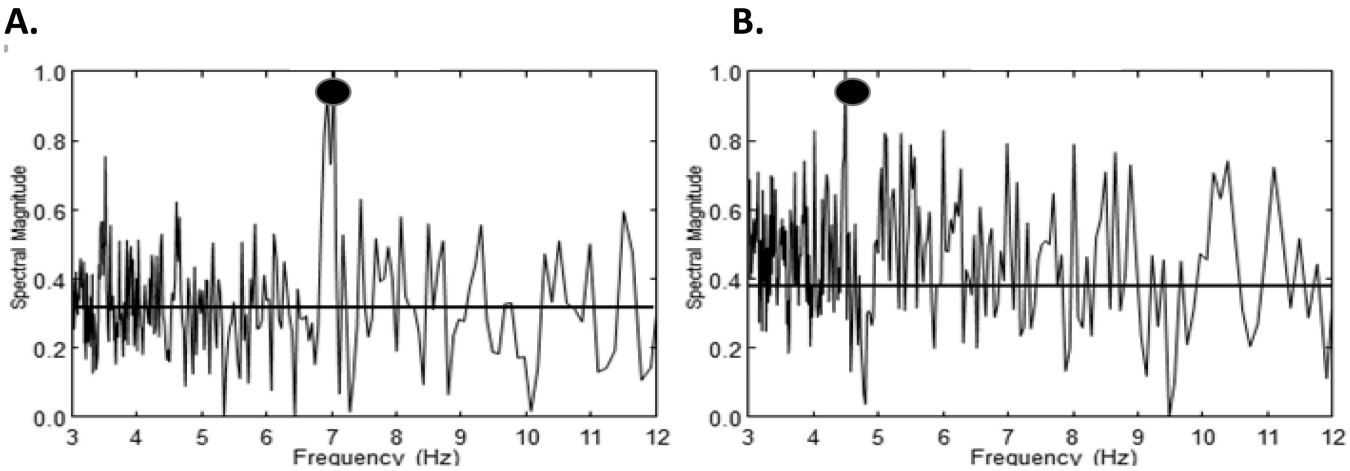
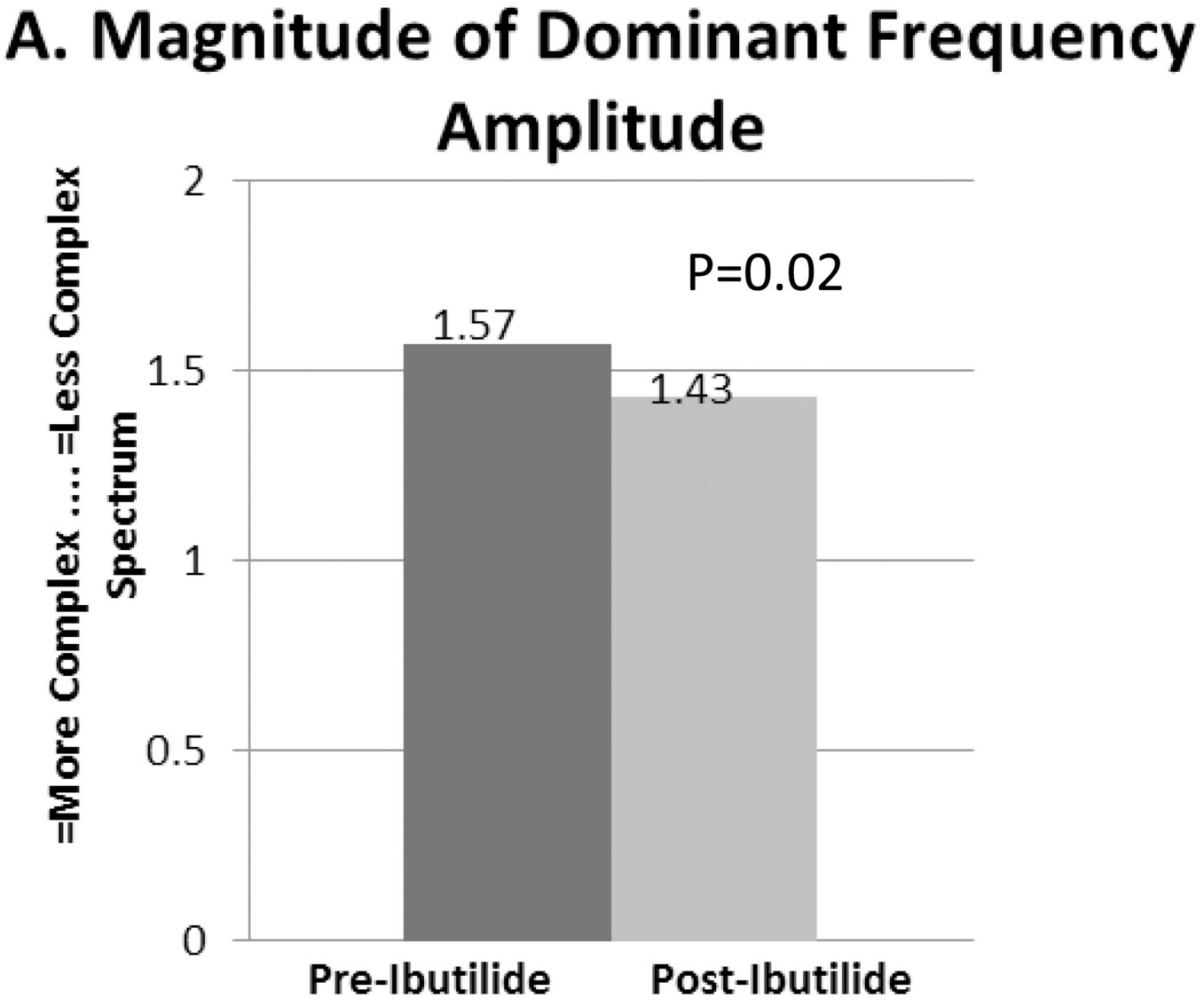


Figure 2.

Example of the use of linear spectral analysis to calculate the normalized magnitude of the dominant frequency and the mean of the power spectrum in a representative patient comparing pre-ibutilide (A) vs. post-ibutilide (B) infusion patients. After ibutilide (B), the dominant frequency (black dots) decreases from 7.0 to 4.5 Herz, while the mean of the normalized power spectrum (solid lines) rises from 0.33 to 0.38, indicating more disparate, lower frequency sources contributing to the frequency power spectrum.



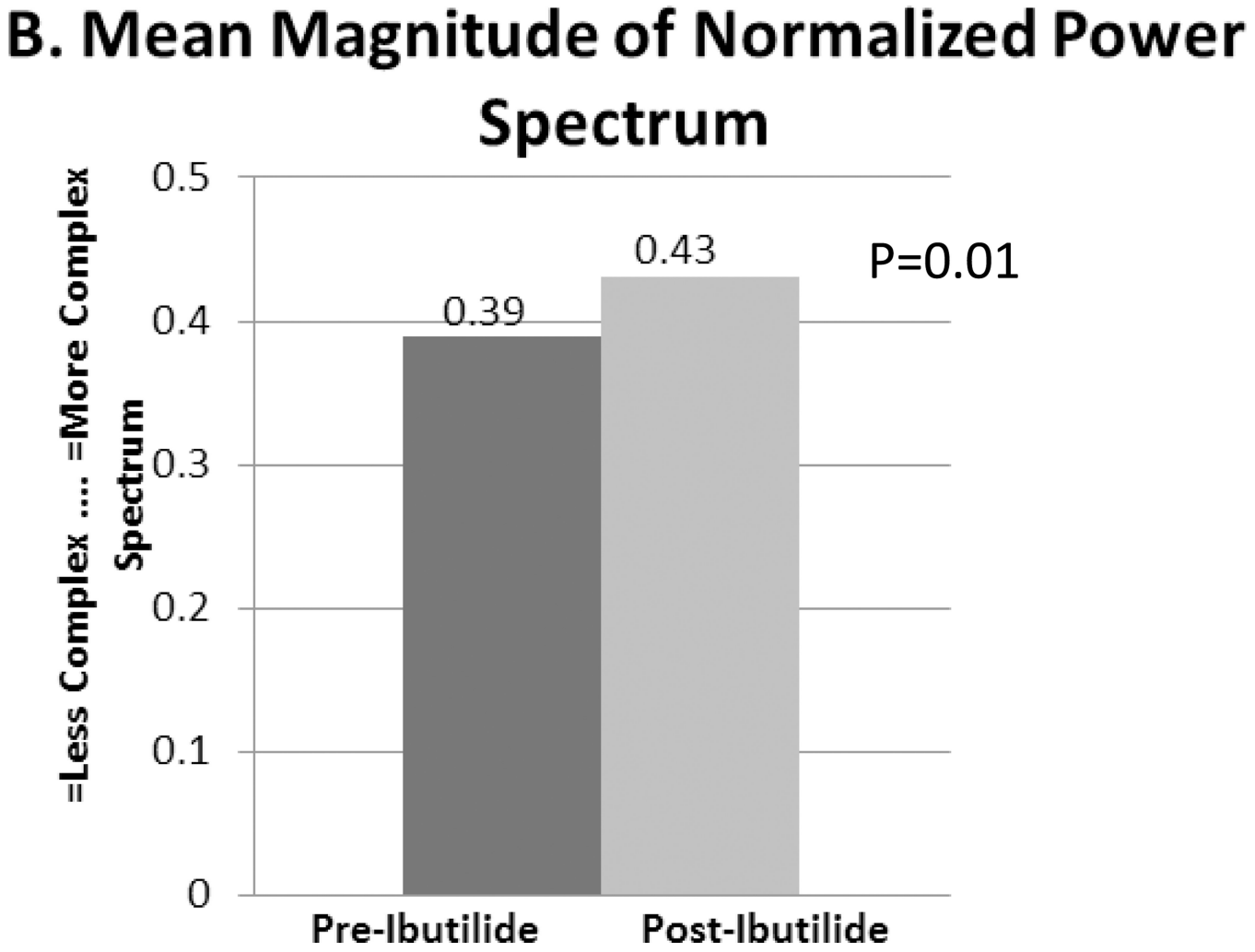


Figure 3.

Comparison of the change in the magnitude of the dominant frequency amplitude of the power spectrum in pre-ibutilide (A) vs. post-ibutilide (B) AF patients. EGMs manifest lower dominant frequency amplitudes post-ibutilide, consistent with less contribution to the power spectrum by a more stable, dominant source, as well as more complexity in their frequency spectra post-ibutilide, manifested by higher means of the normalized power spectrum, consistent with AF frequencies due to more disparate sources of activation.

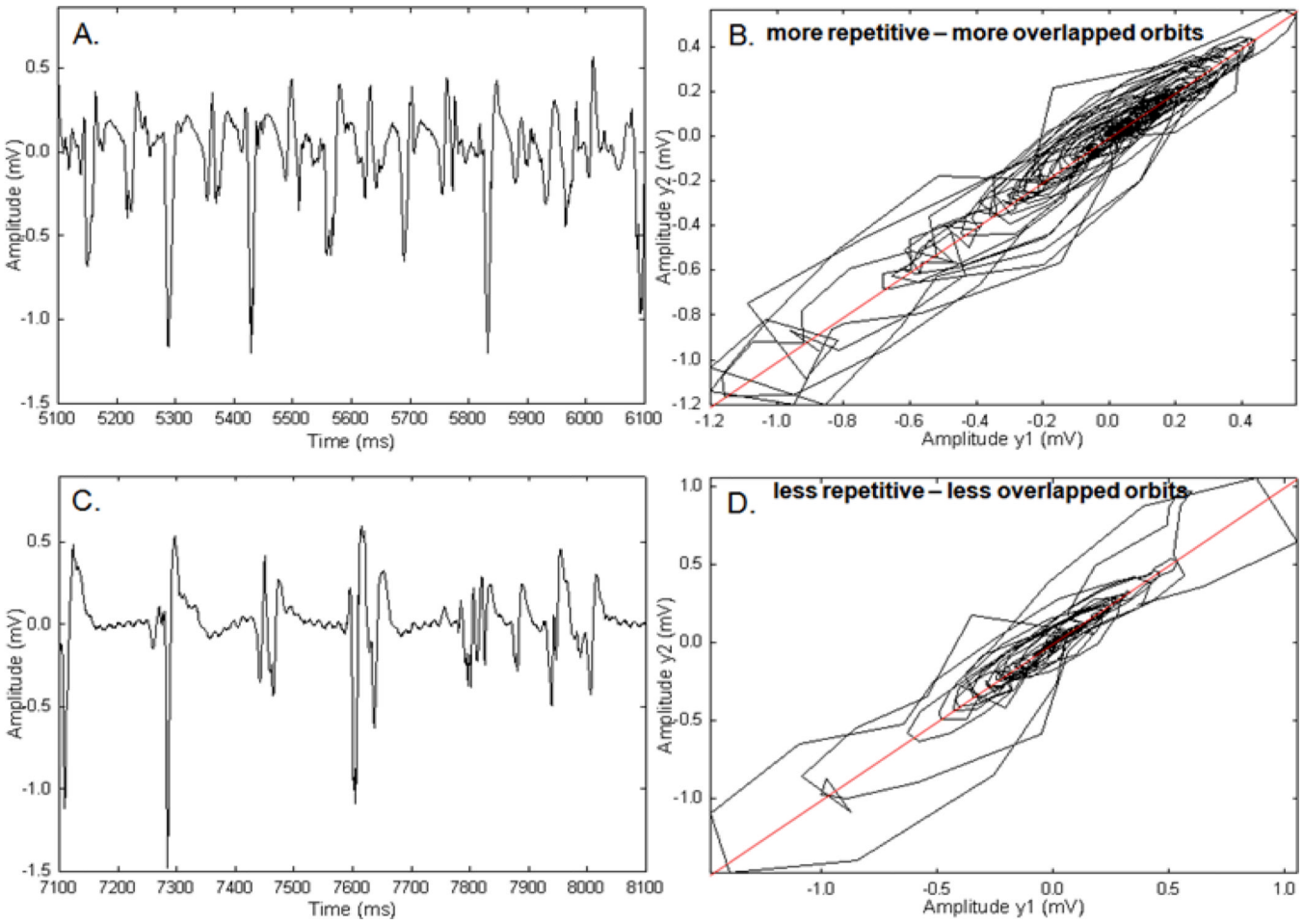


Figure 4.

Example of phase plot method used to measure the variation of amplitudes in an AF EGM signal. Pre-ibutilide EGMs (A) possess phase plots with more overlapped amplitude points (B) than the phase plots (D) of post-ibutilide EGMs (C), indicating more variation in AF EGM amplitudes post-ibutilide infusion.

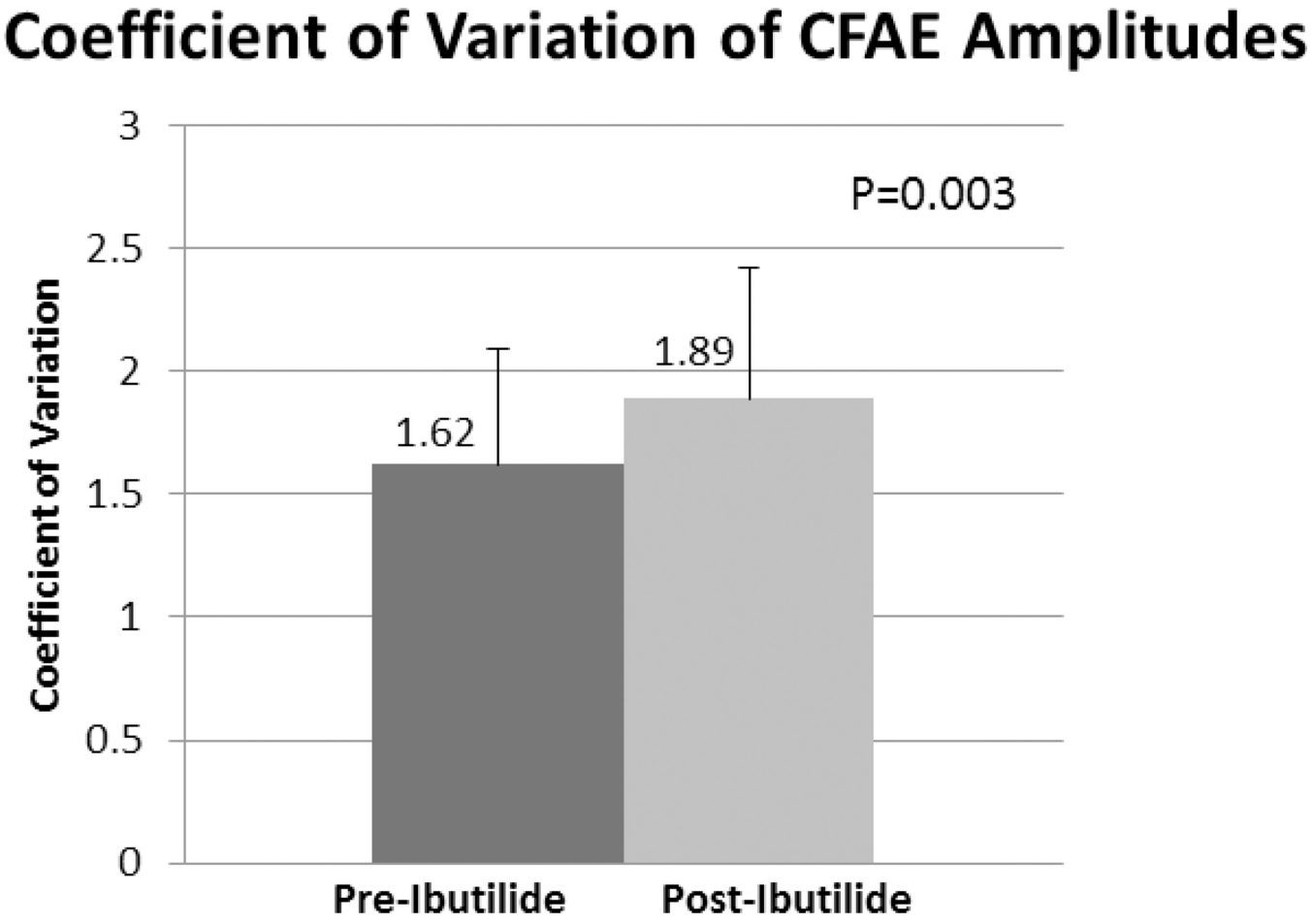


Figure 5.
Comparison of coefficient of variation for EGM amplitudes collected pre-ibutilide vs. post-ibutilide. EGM amplitudes become more variable post-ibutilide.

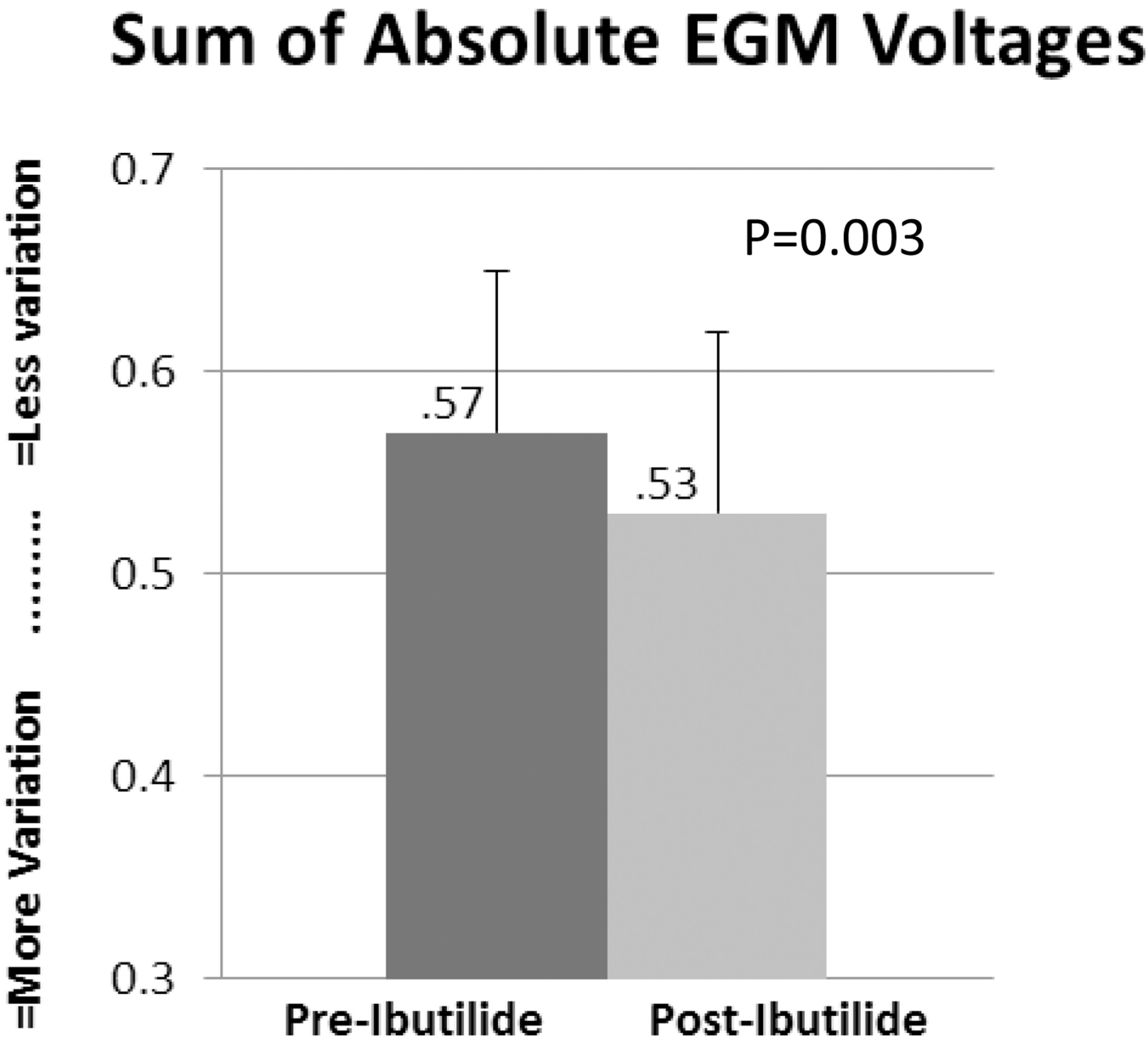


Figure 6.
Graph of mean sum of absolute values of EGM morphologies in pre- vs. post-ibutilide EGM collections. A lower magnitude implies more variation of overall EGM morphologies.

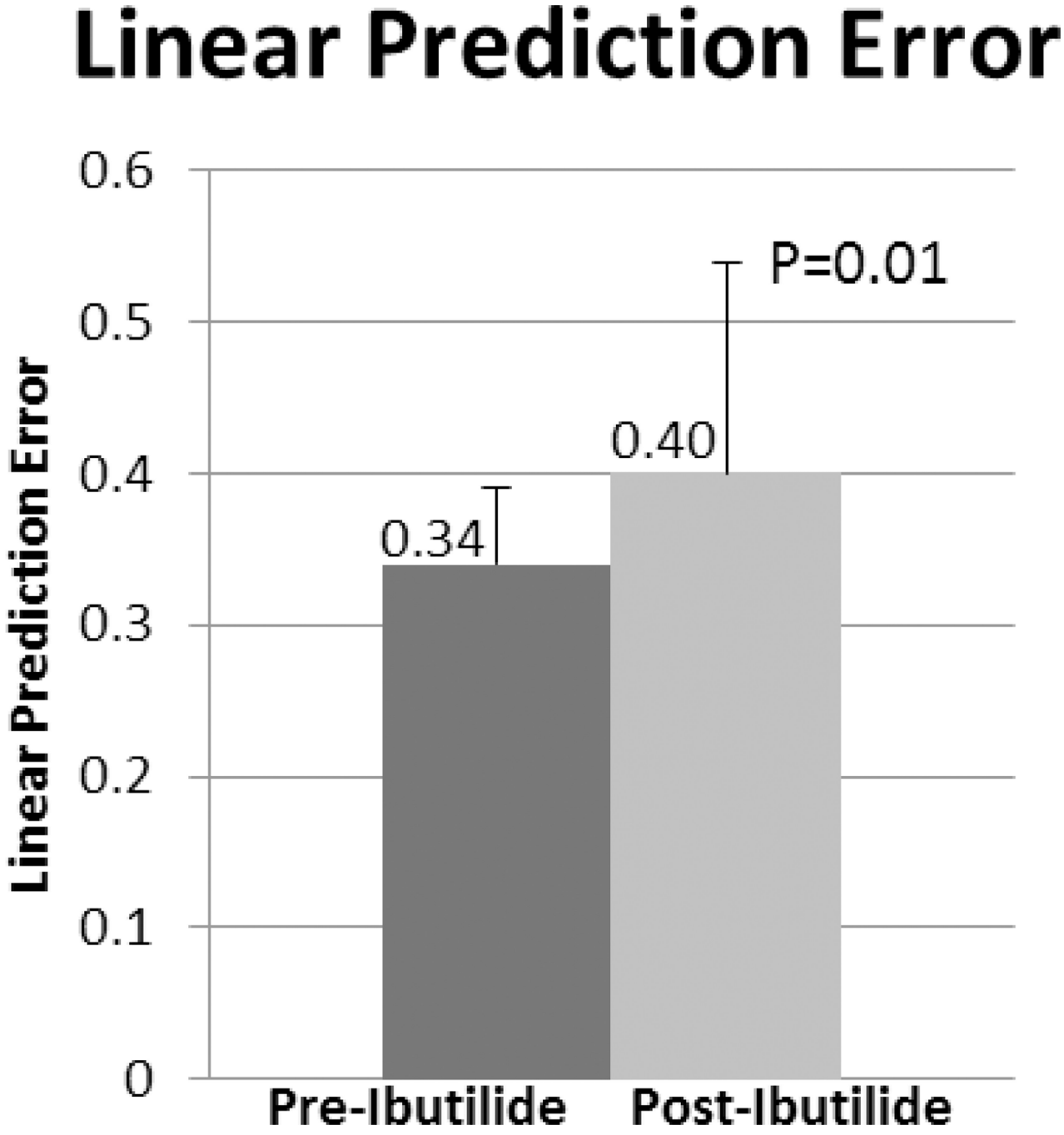


Figure 7.
Graph of linear prediction error of EGMs collected pre-ibutilide vs. post-ibutilide. More reproducible EGM patterns, consistent with less complex EGMS, were present in patients before ibutilide was given.

Table 1

Patient Characteristics

Characteristic	Number (%)
Number of Patients	21
Male/Female Gender	14 (67)/7 (33)
Age (years)	57 ± 14 [Range 20–77]
Clinical SVTs under study	
- Atrial Fibrillation	12 [7 persistent/5 paroxysmal]
- Atrial Flutter	2 [cavotricuspid-isthmus dependent]
- Atrial Tachycardia	3
- AVNRT	1
- AVRT	3 [1 manifest/2 concealed]
Ibutilide Success Terminating AF (yes/no)	8 (38)/13 (62)
Left Atrial Size (cm)	
- Normal (≤ 4.0)	13 (62)
- Mild-Moderately Enlarged (4.1–4.9)	5 (24)
- Severely Enlarged (≥ 5.0)	3 (14)
Left Ventricular Ejection Fraction (%)	
- Normal (≥ 55)	16 (76)
- Mildly Decreased (45–54)	2(10)
- Moderately Decreased (35–44)	3 (14)

Data are presented as mean ± SD, ranges, and percentages. AVNRT=atrioventricular nodal reentry tachycardia, AVRT=atrioventricular reentry tachycardia.