# Reduction of Ultra-High-Frequency ECG Components Following Sodium Channel Blockade by Propafenone: Evidence for Their Electrophysiological Origin

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## Abstract

*Background: Ultra-high-frequency (UHF) ECG is a non-invasive method for assessing ventricular electrical dyssynchrony. The origin of UHF components in ECG remains uncertain. It has been hypothesized that UHF components arise from rapid changes in membrane voltage during sodium channel opening. This study aimed to evaluate changes in UHF components after the administration of propafenone, a sodium channel blocker.*

*Method: We analyzed data from 12 patients. For each patient, amplitude envelopes from 8 precordial leads (V1–V8) were analyzed across 76 frequency bands ranging from 150 to 1000 Hz. For each lead and frequency band, the ratio of the maximum and the area of envelopes before and after propafenone administration was calculated and subsequently averaged across frequency bands as well as leads.*

*Results: Our results show that 11 out of 12 patients exhibited a reduction in the UHF component following sodium channel blockade. The median ratios before versus after propafenone administration were 1.51 and 1.29 for amplitude envelope maximum and area, respectively ($p < 0.01$).*

*Conclusion: This study supports the hypothesis that the UHF components in the ECG are caused by the rapid opening of sodium channels.*

## 1. Introduction

Ultra-high-frequency ECG (UHF-ECG) is an advanced non-invasive technique for assessing ventricular electrical dyssynchrony [1]. UHF-ECG depolarization maps can display the temporal sequence of depolarization in different cardiac segments, which can be used to distinguish left from right bundle branch block, differentiate pacing modes, and evaluate the benefit of pacing for patients [2, 3, 4]. UHF-ECG has also been shown to predict response to cardiac resynchronization therapy (CRT) [5, 6]. This technology is already applied in clinical practice during pacemaker implantation [7].

The origin of UHF components in the ECG signal nevertheless remains uncertain. It is hypothesized that rapid changes in membrane voltage during Phase 0 of the action potential, associated with sodium channel opening, generate UHF components [1].

Propafenone is an antiarrhythmic drug that is highly effective in the treatment of both supraventricular and ventricular arrhythmias [8]. Propafenone belongs to class Ic, which is characterized by its strong ability to block fast sodium channels [9].

The objective of this study was to evaluate changes in the amount of UHF components following the administration of propafenone. The assumption was that sodium channel blockade slows Phase 0 of the action potential, resulting in a reduction of UHF components in the ECG.

## 2. Methods

### 2.1. Data

Supine resting 5 kHz ECG recordings with a bandwidth of 1.5 kHz were acquired from 12 subjects. An extended 12-lead ECG setup was used, with two

additional precordial leads, V7 and V8, placed as a continuation of the standard V1–V6 sequence.

Patients with diagnosed paroxysmal atrial fibrillation (AF) who were in sinus rhythm at the index visit were enrolled. Eligible patients were those who preferred pharmacological therapy over AF ablation.

Only patients without prior exposure to antiarrhythmic medication (propafenon, amiodarone), excluding beta-blockers (metoprolol, bisoprolol, nebivolol), were selected. Following the index recording, propafenone therapy was initiated, and patients were reassessed after 3 months.

Seven patients received 300 mg of propafenone three times daily, and five received 150mg three times daily. Follow-up blood tests were performed in each patient to confirm that propafenone was being taken as prescribed.

Eleven subjects had a narrow QRS complex (<120 ms) before propafenone administration, and one subject presented with left bundle branch block (LBBB).

## 2.2. Signal processing

The block diagram of the method used is shown in Figure 1. ECG recordings before and after propafenone therapy were processed in the same manner. QRS complexes were first detected using the algorithm described in [10] (block A). Amplitude envelopes were then computed in each precordial lead (V1–V8) across 76 frequency bands from 150 to 1000 Hz, with a bandwidth of 100 Hz and a frequency window shift of 10 Hz (block B). Median amplitude envelopes were constructed for QRS complexes of the same morphology (block C). A baseline, defined as the mean value in the interval 160–200 ms after the QRS center, was subtracted from each envelope (block D).

From these baseline-corrected envelopes, two parameters were calculated (block E): the maximum envelope amplitude (AEmax) and the area under the envelope from the beginning to the end of the QRS complex (AEarea). For each lead and frequency band, the ratios of AEmax and AEarea before versus after propafenone administration were calculated (block F) and subsequently averaged across leads and frequency bands (block G). The outputs of the method are AEmax_ratio and AEarea_ratio (block H).

Values greater than 1 indicate that the parameter was higher before treatment, reflecting the expected reduction after sodium channel blockade. Values less than 1 indicate an increase after treatment.

Normality of differences was tested using the Kolmogorov-Smirnov test, and statistical significance was assessed using a paired t-test.

## 2.3. Frequency band analysis

A secondary objective was to investigate how the reduction of UHF components varies with frequency. AEmax_ratio and AEarea_ratio (see Section 2.2) were computed within six aggregated frequency bands: 1–101 Hz, 11–101 Hz, 61–201 Hz, 101–401 Hz, 401–701 Hz, and 701–1001 Hz. Each aggregated band was obtained by averaging results from overlapping sub-bands (100 Hz bandwidth, 10 Hz shift).

# 3. Results

Figure 2 shows AEmax_ratio and AEarea_ratio across all 12 patients. The median ratios of UHF components before versus after propafenone were 1.51 [1.34; 1.78] and 1.29 [1.19; 1.53] for AEmax and AEarea, respectively (values given as median [Q1; Q3]). Both parameters decreased significantly after propafenone treatment ($p < 0.01$).

Differences between frequency bands are illustrated in Figure 3. Median AEarea_ratio values increased with frequency: 0.97, 1.22, 1.24, 1.29, 1.40, and 1.43 for the six bands. This suggests stronger attenuation of UHF components in higher frequency bands. However, inter-individual variability was large, and this trend did not hold consistently for all patients.

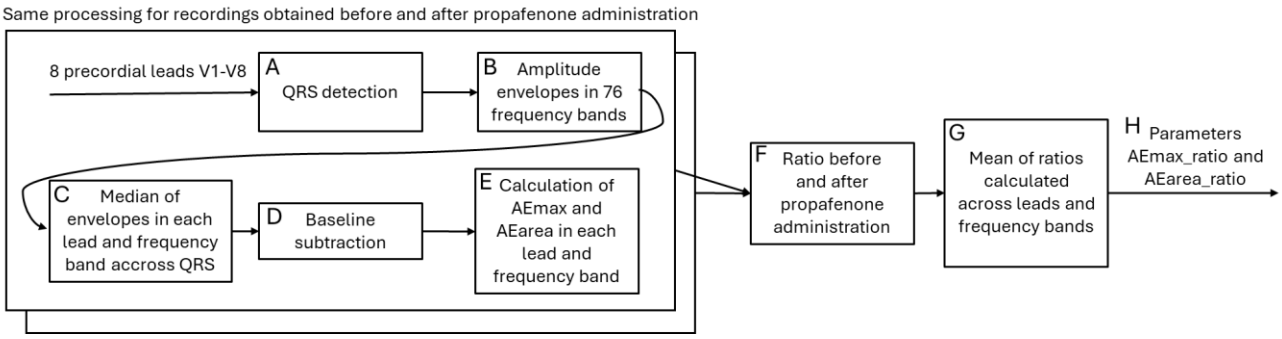


Figure 1. Block diagram of the method used

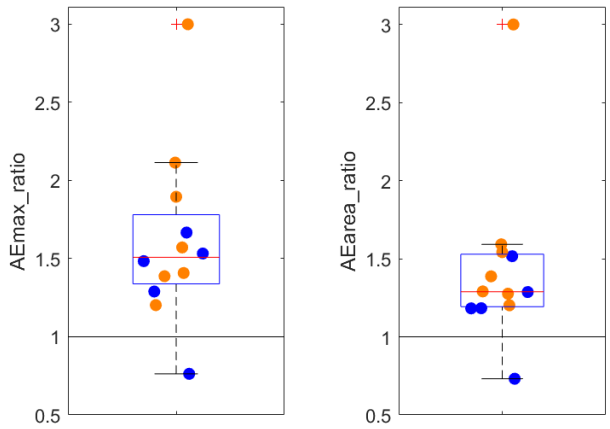


Figure 2. The ratio of UHF amplitudes before/after propafenone. 150 mg dose in blue, 300 mg dose in orange. The maximum ratio value is limited to 3 for both parameters to improve figure readability (the original values were 4.28 for AEmax_ratio and 104.90 for AEarea_ratio.

## 4. Discussion

Two parameters were used to quantify UHF components in QRS: AEmax and AEarea. AEmax represents the peak amplitude of the envelope, but does not account for temporal distribution differences, making it less robust. AEarea integrates the envelope across the entire width of the QRS complex and is therefore more representative. However, AEarea is affected by QRS widening, a known effect of propafenone [11]. In our dataset, all patients exhibited QRS widening (Figure 4), with a median increase of 10.5 ms (Q1 = 2 ms; Q3 = 11.5 ms). The AEarea parameter is therefore slightly artificially elevated after propafenone administration. Nevertheless, even for this parameter, a statistically significant reduction was observed following propafenone treatment.

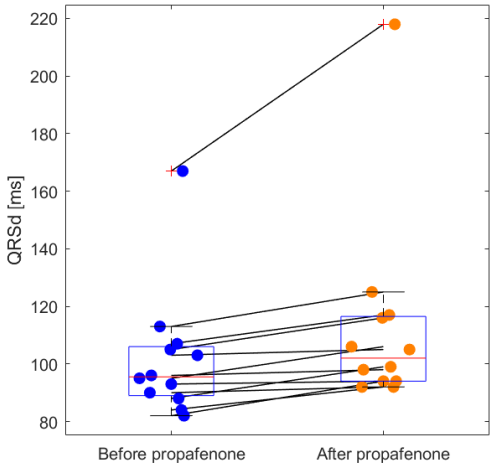


Figure 4. Increase in QRSd after propafenone treatment

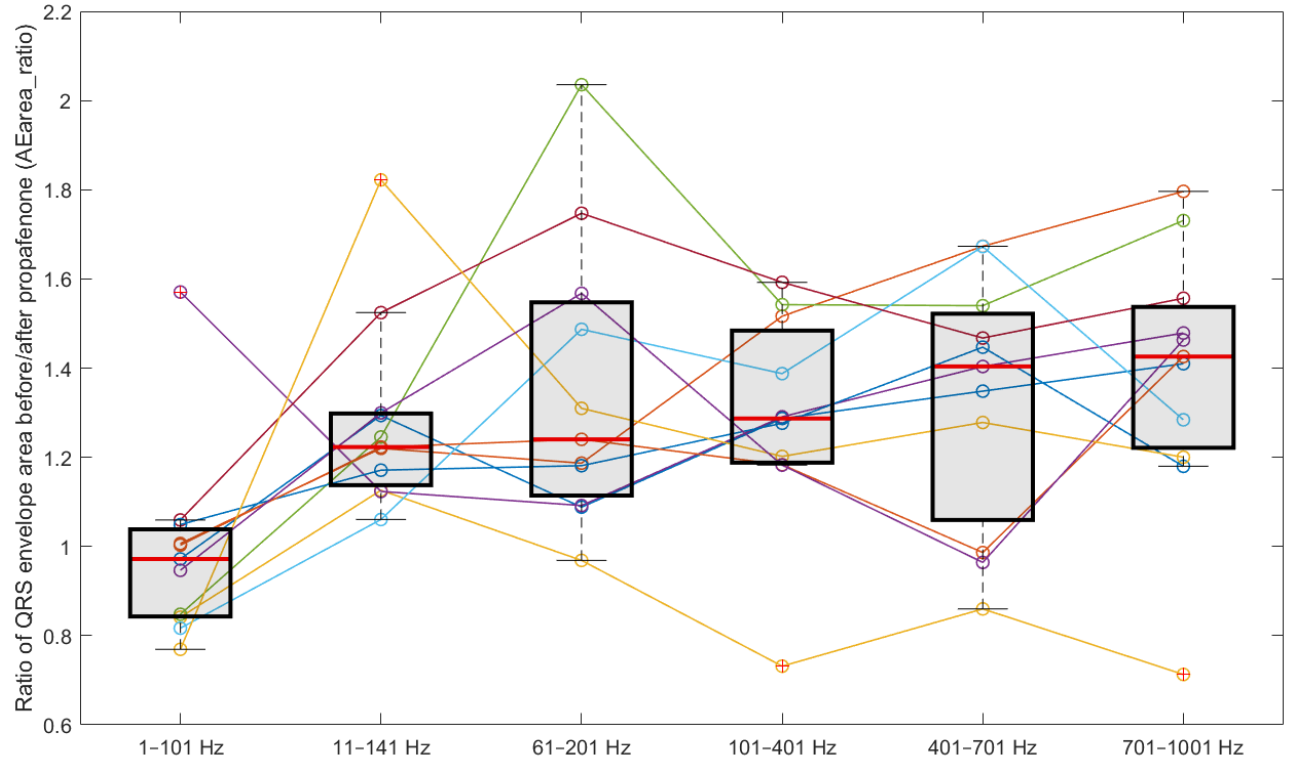


Figure 3. AEarea_ratio in different frequency bands. The patient with LBBB is not shown in this figure.

Our results (Figure 2) demonstrate that propafenone consistently reduced UHF components, except for one patient. This outlier may reflect inter-individual variability in propafenone metabolism. This may be explained by two genetically determined patterns of propafenone metabolism. In more than 90% of patients, the drug is rapidly and extensively metabolized, with an elimination half-life of 2–10 h, primarily via CYP2D6, CYP3A4, and CYP1A2 [12]. In about 10% of patients, metabolism is markedly slower, with an elimination half-life of 10–32 h, due to CYP2D6 deficiency [13]. This slower metabolism results in higher plasma concentrations of propafenone and potentially greater pharmacodynamic effects [14].

One patient had an extremely high ratio of both parameters before and after propafenone use compared to the others (Figure 2). This is a patient with LBBB who experienced a large increase in QRS duration (QRSd) due to propafenone use (from 167 ms to 218 ms). This patient had extremely low UHF components after propafenone use, resulting in an extremely high ratio.

The main limitation of this study is the relatively small sample size (12 patients), which restricts the generalizability of the findings. In addition, only one sodium channel blocker (propafenone) was evaluated, and the effects of other class I antiarrhythmic drugs on UHF ECG components remain to be investigated.

## 5. Conclusion

This study demonstrates that the blockade of sodium channels reduces the amplitude of the UHF components in the ECG signal. This finding supports the hypothesis that the UHF components in the ECG are caused by the rapid opening of sodium channels.

## Acknowledgments

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