

CASE REPORT

BEGINNER

CLINICAL CASE

# Ginkgo Biloba

## Plant-Based Proarrhythmic Potential?



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### ABSTRACT

Ginkgo biloba is a commonly used herbal supplement in the United States. We describe a 63-year-old man with a significant ventricular ectopic burden (32.7%) that was refractory to metoprolol tartrate (41.7%) and resolved (<1%) when Ginkgo was discontinued. This case supports a potential proarrhythmic side-effect of over-the-counter Ginkgo leaf extract. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:968-72) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

A 63-year-old man with no known cardiac history presented for routine pre-operative evaluation for a right hemicolectomy after being found to have an unresectable cecal polyp. Pre-operative electrocardiogram (ECG) demonstrated unifocal ventricular bigeminy, at which time the patient reported no symptoms. The patient underwent uncomplicated laparoscopic-assisted right hemicolectomy and was subsequently admitted for post-operative recovery. Approximately 30 h after the patient was made NPO (including medications), a repeat ECG in the hospital demonstrated normal si-

nus rhythm with no premature ventricular contractions (PVCs). The patient was discharged home in stable condition, and at primary care follow-up, an ECG re-demonstrated ventricular bigeminy (Figure 1).

### PAST MEDICAL HISTORY

The patient's past medical history was remarkable for hyperlipidemia and former tobacco use of 45 pack-years. The patient had also been previously diagnosed with a 2-cm cecal tubulovillous adenoma with features that were not amenable to endoscopic removal, prompting his right hemicolectomy. The patient's medications included aspirin 81 mg daily, atorvastatin 40 mg nightly, and several supplements (manufactured by Nature's Bounty): ginkgo biloba leaf extract 120 mg twice daily, coenzyme Q10 300 mg daily, fish oil 1,400 mg daily, and vitamin E 1,000 IU daily.

### LEARNING OBJECTIVES

- To appreciate the widespread use of dietary supplements such as Ginkgo biloba leaf extract in the United States.
- To recognize ventricular arrhythmias as a potential side effect of Ginkgo biloba.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* [author instructions page](#).

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## DIFFERENTIAL DIAGNOSIS

Differential diagnosis for this patient's unifocal ventricular ectopy was guided by several features in the patient's history. In the absence of known cardiac disease, we considered toxic-metabolic causes of both abnormal ventricular automaticity and late afterdepolarizations (e.g., hypokalemia, hypomagnesemia), medications affecting the myocardial membrane potential, as well as idiopathic PVCs. Furthermore, although the patient reported no symptoms concerning for underlying heart disease, he did have 2 cardiovascular risk factors that warranted further evaluation for myocardial ischemia and structural heart disease.

## INVESTIGATIONS

At the patient's post-hospital follow-up primary care visit, a 14-day ECG patch (Zio, iRhythm Technologies, San Francisco, California) was ordered and showed a large burden of isolated PVCs (32.7%) and 3 episodes of nonsustained ventricular tachycardia (NSVT) (longest 14 s). The patient was referred to outpatient cardiology, where myocardial perfusion imaging showed no perfusion defects and transthoracic echocardiography revealed a left ventricular ejection fraction of 55% to 60% with normal cardiac structure and function.

## MANAGEMENT

The patient was started on metoprolol tartrate (25 mg twice daily). Repeat 14-day ECG patch while on metoprolol redemonstrated significant ventricular bigeminy with 41.7% PVC burden and 3 episodes of NSVT (Figure 2A). Electrolytes were within normal limits. He was referred to the electrophysiology service for possible PVC ablation. During this visit, review of the patient's ECGs showed unifocal PVCs with a morphology consistent with an origin from the area of the right ventricular moderator band. Further history revealed that the patient was taking Ginkgo biloba leaf extract to help increase energy and that Ginkgo had been stopped during the perioperative period that had coincided with a diminution of PVCs. A link between Ginkgo and its possible contribution to his ventricular ectopy was made, and the patient was asked to discontinue all over-the-counter supplements including Ginkgo. One week following discontinuation, a 24-h Holter monitor showed a total of 20 isolated PVCs in 24 h. Repeat 14-day ECG patch 1 month later showed almost complete resolution of his ventricular ectopic burden (<1%) with no NSVT episodes (Figure 2B). Of note, this 14-day ECG patch

was performed after the patient had also discontinued metoprolol tartrate due to side effects of fatigue.

## DISCUSSION

Dietary supplements comprise a multibillion-dollar industry, with more than one-half of American adults reporting the use of 1 or more supplements. Among herbals, Ginkgo biloba is one of the most commonly used supplements in the United States (1). Ginkgo biloba, or the maidenhair tree, has been used as an herbal remedy for several millennia in traditional Chinese medicine. Today, Ginkgo has become a popular supplement for its purported benefits for memory, cognition, and cerebrovascular and peripheral vascular diseases, and is widely available in American grocery stores and online (2). The primary bioactive isolates in the Ginkgo leaf consist of terpene lactones (e.g., bilobalide, ginkgolides A, B, and C) and flavanol glycosides (e.g., quercetin, kaempferol, isorhamnetin). These constituents operate through incompletely understood mechanisms that include antioxidant, free-radical scavenging, and antiplatelet effects, although contemporary systematic reviews remain inconclusive in supporting their clinical benefits (2-4).

Common side effects of Ginkgo are nonspecific and include headache, nausea, diarrhea, and rash, the most severe of which appears to be an increased bleeding risk likely relating to its antiplatelet effects (5). To date, descriptions of proarrhythmic effects of Ginkgo are limited. In vitro studies in guinea pig cardiomyocytes have suggested both flavonoids and terpenoids may prolong the ventricular action potential, theoretically predisposing to ventricular arrhythmias. Of note, this effect was inconsistent across different isolate concentrations, suggesting possible heterogeneity in the clinical effects seen in Ginkgo supplements not standardized for their constituents (6). Translated clinically, Ginkgo has been implicated in only a small number of case reports. In 1 case of a 49-year-old man with a structurally normal heart, Ginkgo was suggested to have caused frequent, isolated ventricular ectopic beats that resolved after discontinuation (7). In another case, Ginkgo use was implicated in causing ventricular tachycardia storm in a patient with ischemic cardiomyopathy, again resolving after Ginkgo discontinuation (8). Ginkgo has also been linked with atrial tachyarrhythmia, suggesting activity at atrial ion channels as well (9).

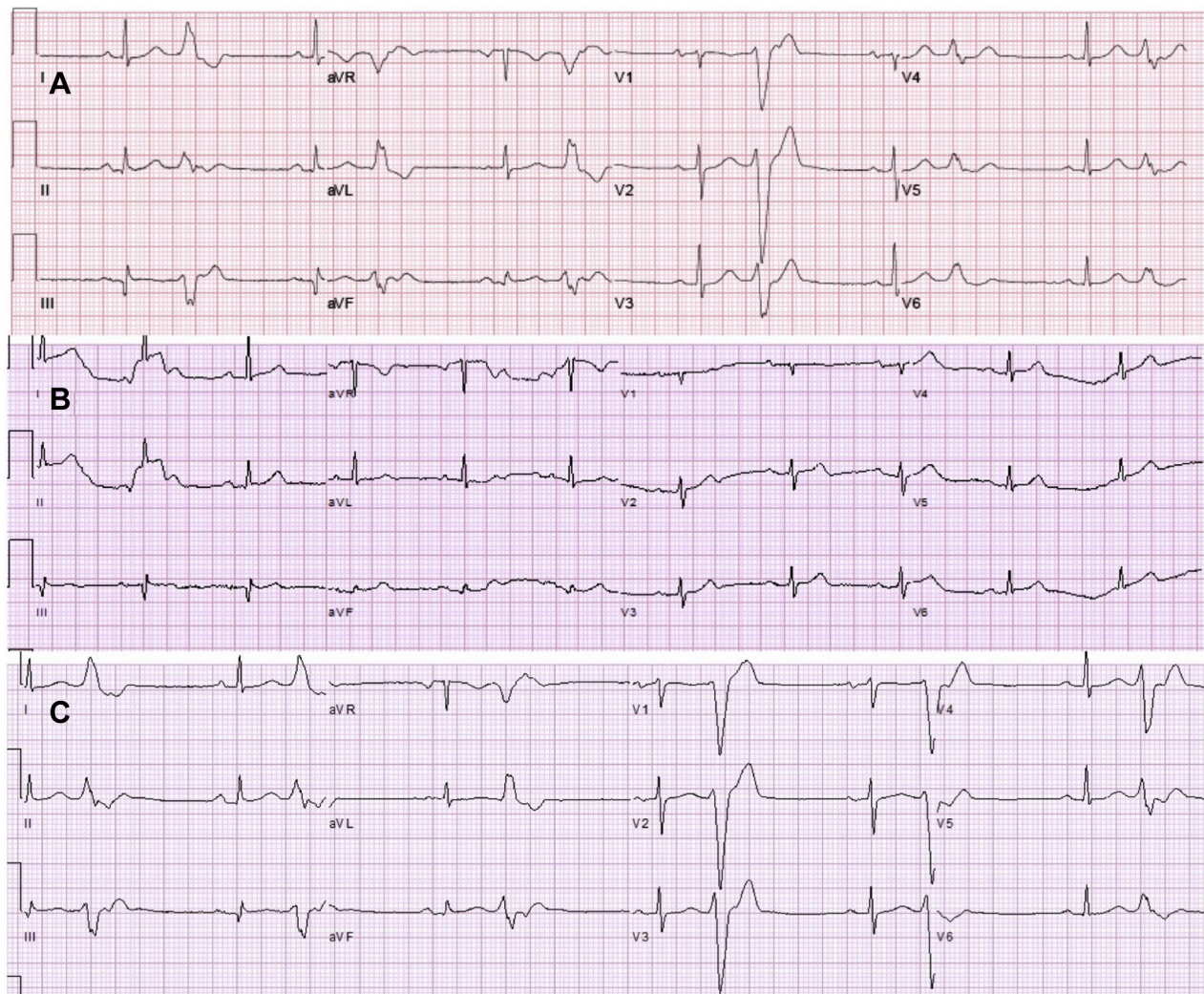
With the passing of the Dietary Supplement and Health Education Act of 1994, dietary supplement manufacturers are no longer required to demonstrate

## ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

NSVT = nonsustained ventricular tachycardia

PVC = premature ventricular contraction

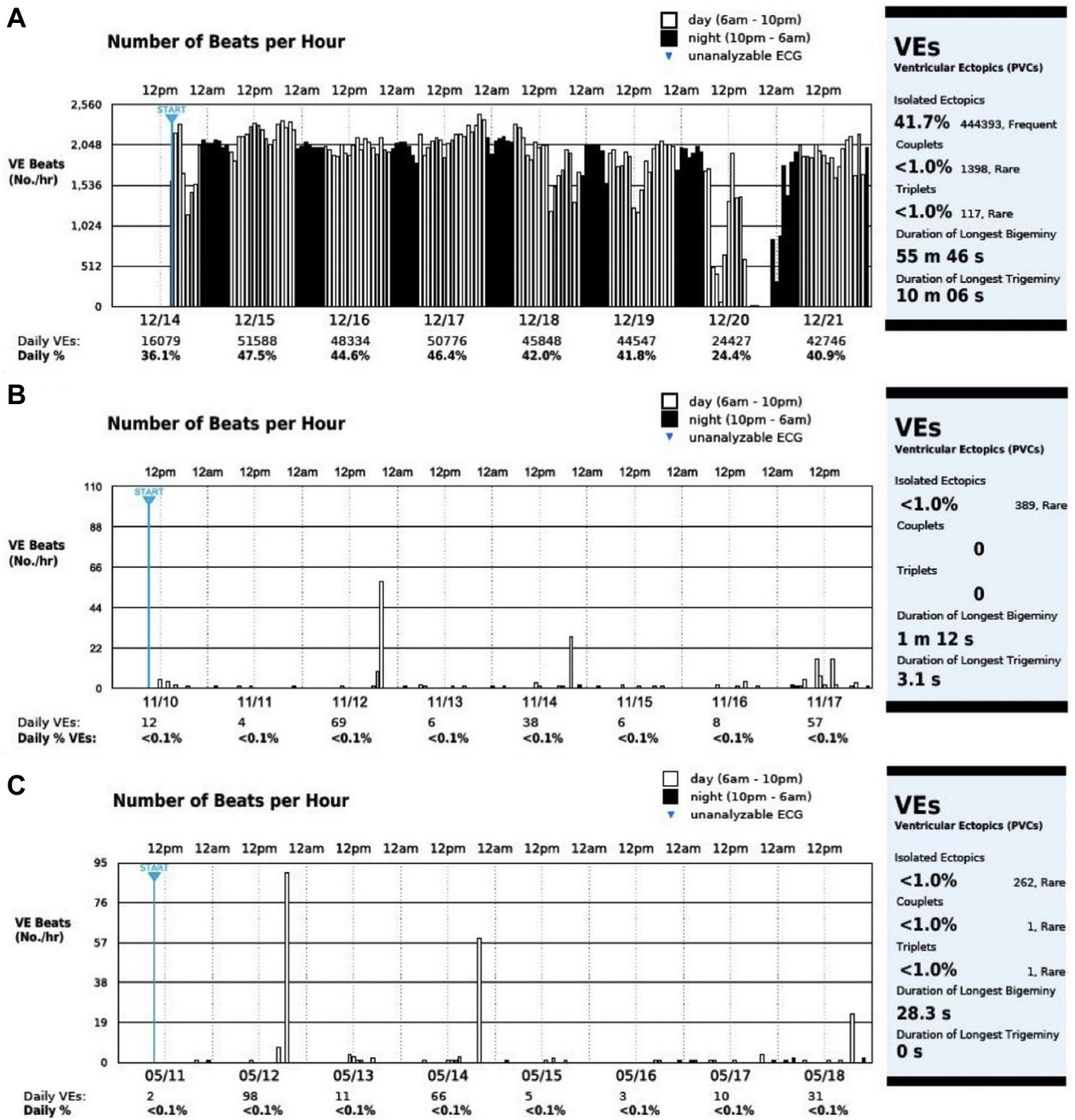
**FIGURE 1** Initial ECGs

**(A)** Electrocardiogram (ECG) showing frequent, unifocal ventricular ectopic beats in a bigeminy pattern while the patient was taking Ginkgo biloba leaf extract. **(B)** Diminution of premature ventricular contractions after Ginkgo discontinuation in the immediate post-operative period. **(C)** Return of premature ventricular contractions after resuming Ginkgo post-operatively.

product safety or purity. As a result, much of our understanding of the adverse effects of dietary supplements is limited to post-marketing surveillance data. For this reason, the true incidence of Ginkgo-associated arrhythmia may be under-reported. In the absence of purity testing for the patient's Ginkgo supplement, it is also possible that an inactive or unlisted ingredient was contributory to his arrhythmia. Furthermore, in this case we note that the patient was also taking vitamin E, coenzyme Q10, and fish oil (omega-3 fatty acid) supplements. Upon review, current published data does not link vitamin E or coenzyme Q10 with proarrhythmia (10,11). Although there

had been some question of proarrhythmia with omega-3 fatty acid supplementation in the past from limited evidence in animal studies, available human trials support an antiarrhythmic effect, summarized in a 2017 Science Advisory from the American Heart Association, concluding that "omega-3 polyunsaturated fatty acid supplements may reduce coronary heart disease death, possibly through a reduction in ischemia-induced sudden cardiac death, among patients with prior coronary heart disease" (12). Similar to Ginkgo, however, each of these supplements remain subject to containing proarrhythmic impurities that could have contributed to his ectopic

**FIGURE 2** PVC Burden On and Off Ginkgo



(A) A 14-day electrocardiogram (ECG) patch showing a significant ventricular ectopic (VE) burden without diurnal variation while taking Ginkgo biloba leaf extract. (B) Premature ventricular contraction (PVC) resolution after Ginkgo discontinuation. (C) Sustained resolution of PVCs off of Ginkgo 8 months later.

burden. Last, in this case we report an arrhythmia that lacked diurnal variation, a notable finding given that many of Ginkgo's isolates appear to have shorter half-lives of 3 to 6 h (13). However, we felt

that the patient's twice-daily dosing of Ginkgo could have created a steady plasma concentration sufficient to account for the incessant nature of his arrhythmia.

## FOLLOW-UP

Eight months after the discontinuation of Ginkgo, the patient was seen in follow-up and reported feeling well. A 14-day ECG patch performed at this juncture demonstrated sustained resolution of his arrhythmia with <1% ventricular ectopic burden (Figure 2C).

## CONCLUSIONS

Ginkgo biloba leaf extract is among the most commonly used herbal supplements in the United

States. Consideration for Ginkgo as well as other herbal supplements should be a part of every arrhythmia evaluation given our limited understanding of the side effects of these compounds. This case joins a small body of evidence demonstrating a potential proarrhythmic side effect of Ginkgo biloba.

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