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HEART FAILURE AND CARDIOMYOPATHIES

THE FOUR CORNERS: CLINICAL VIGNETTE CORNER

Riding the Waves of Novel Therapies in Hypertrophic Cardiomyopathy

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ABSTRACT

We discuss a case of a 60-year-old man with hypertrophic cardiomyopathy treated with the novel cardiac myosin inhibitor, mavacamten. Dynamic electrocardiogram patterns of left ventricular hypertrophy and left ventricular strain coincided with the patient starting mavacamten, discontinuing the drug, and then restarting mavacamten, highlighting electrocardiograms as accessible and inexpensive potential tools to monitor drug efficacy. This case also shows the ability of myosin inhibition to positively alter the adverse electrical changes associated with hypertrophic cardiomyopathy. (JACC Case Rep. 2024;29:102585) © 2024 The Authors. 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 60-year-old man with obstructive hypertrophic cardiomyopathy (HCM) showed dynamic electrocardiogram (ECG) changes after starting, discontinuing, and restarting the novel cardiac myosin inhibitor mavacamten. ECG abnormalities commonly observed in HCM include patterns of left ventricular hypertrophy (LVH) with left ventricular (LV) strain. These findings are present in the patient's baseline ECG (**Figure 1A**), which met voltage criteria for LVH per Cornell, Sokolow-Lyon, and Peguero-Lo Presti criteria and showed repolarization abnormalities signifying LV strain. ECG approximately 2 years following initiation of mavacamten (**Figure 1B**) showed improvement in LVH and LV strain patterns. The drug was temporarily discontinued due to an asymptomatic drop in LV ejection fraction. ECG 2 months later (**Figure 1C**) noted recurrence of LV strain patterns and again met LVH voltage criteria. Transthoracic echocardiography at that time (Video 1) showed asymmetric septal hypertrophy consistent with HCM. The patient ultimately restarted mavacamten after normalization of LV systolic function. ECG 3 months later (**Figure 1D**) again showed marked improvement in the LVH and LV strain patterns. Transthoracic echocardiography at that time (Video 2) showed persistent asymmetric septal hypertrophy despite improvement in electrical changes on ECG.

Mavacamten selectively targets the myosin motor of the sarcomere and promotes a super relaxed state of myosin. This leads to reduced adenosine triphosphatase consumption and myocardial contractility, which are the primary derangements in HCM. Moreover, animal studies have shown that mavacamten partially normalizes the $Ca2+$ sensitivity of thin filaments and improves myocardial relaxation.[1] Imaging subanalyses of the pivotal mavacamten clinical trials have shown reductions in LVH and plasma biomarkers of myocardial stress and injury along with improvements in diastolic function.[2] However, the ECG

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

HCM = hypertrophic cardiomyopathy

LVH = left ventricular hypertrophy

correlates of these structural changes have not been well described.

This case highlights several learning points. First, it emphasizes some of the typical ECG findings associated with HCM, including LVH with LV strain patterns. It also highlights that the ECG can be considered a biomarker of treatment with the novel cardiac myosin inhibitor, mavacamten. As ECG is accessible, inexpensive, and noninvasive, it may emerge as a convenient patient-level tool for monitoring response to cardiac myosin inhibitor therapy. Although a few limited case series have shown normalization of LVH and LV strain pattern in a subset of patients after starting mavacamten,[3] no data currently exist describing the dynamic changes of ECG patterns in patients who stop and restart this medication. This case shows the ability of myosin inhibition to positively alter the adverse electrical changes associated with LVH in the setting of HCM.

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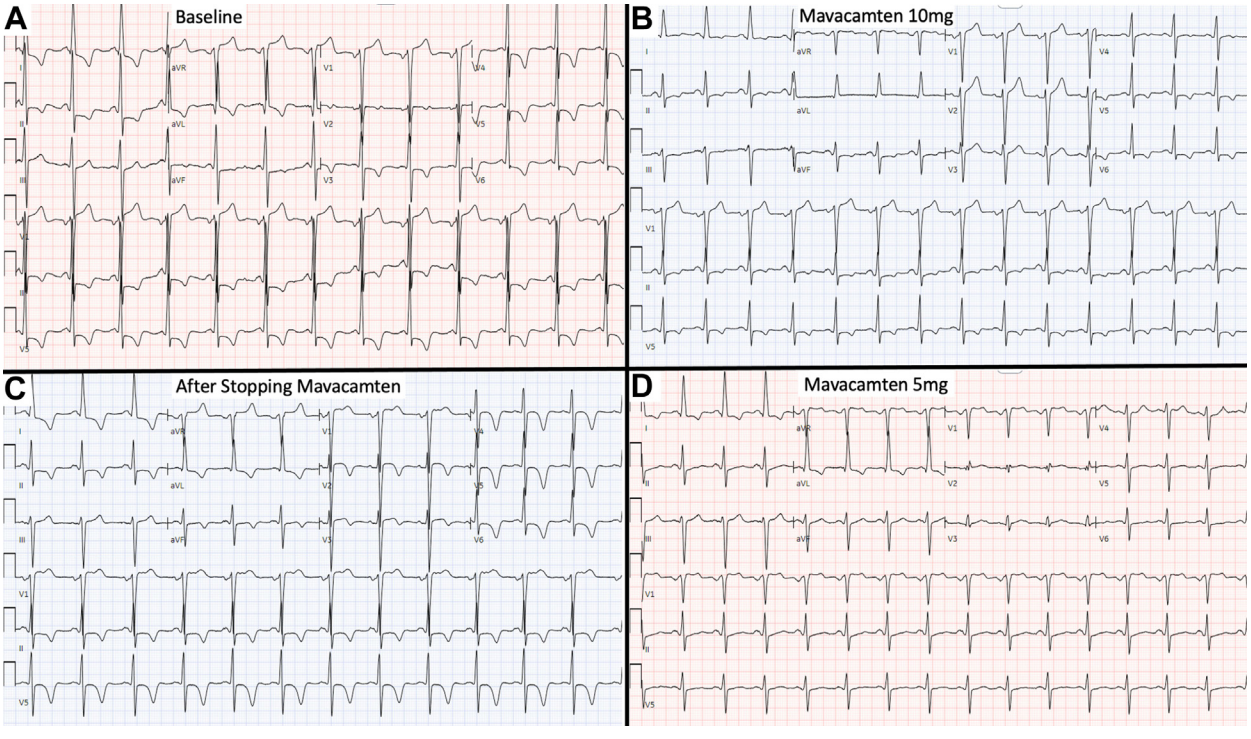
FIGURE 1 Dynamic ECG Changes Associated With Mavacamten



(A) Baseline electrocardiogram (ECG) shows deep S-waves in V_1-V_2 and large R waves in V_4-V_6, and aVL meeting voltage criteria for left ventricular hypertrophy (LVH) per Cornell, Sokolow-Lyon, and Peguero-Lo Presti criteria. Repolarization abnormalities signifying left ventricular (LV) strain were also present, including ST-segment depressions and T-wave inversion in I, aVL, and V_3-V_6. (B) ECG after initiation of mavacamten and uptitration to 10 mg daily shows improvement in LVH (only meets Peguero-Lo Presti criteria) and LV strain patterns. (C) ECG after discontinuation of mavacamten noted recurrence of LV strain pattern (marked T-wave inversions in I, aVL, and V_2-V_6), and deep S-waves in V_1-V_3 with large R waves in V_5-V_6 and aVL, once again meeting LVH voltage criteria per Cornell, Sokolow-Lyon, and Peguero-Lo Presti criteria. (D) ECG after restarting mavacamten again shows marked improvement in the LV strain pattern (resolution of T-wave inversions in precordial leads) and decreased S- and R-wave amplitudes (LVH only per Peguero-Lo Presti criteria).

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APPENDIX For supplemental videos, please see the online version of this paper.