Circulation: Heart Failure

RESEARCH LETTER

Long-Term Effects of Mavacamten on Electromechanical Dispersion and Deformation in Obstructive Hypertrophic Cardiomyopathy

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Regional electromechanical abnormalities have long been known to characterize hypertrophic cardiomyopathy (HCM), particularly in the presence of left ventricular outflow tract obstruction, contributing considerably to left ventricular (LV) diastolic dysfunction and—potentially—arrhythmic propensity.[1,2] Mavacamten—a first-in-class allosteric cardiac myosin inhibitor—has recently shown substantial symptomatic benefit in patients with obstructive HCM, associated with marked and sustained decrease in LV outflow tract gradients, improved diastolic function,[3] and normalization of electrocardiographic abnormalities.[4] Data from the EXPLORER-HCM trial has shown initial evidence of favorable cardiac remodeling including reduced LV mass, consistent with the disease-modifying effects observed in transgenic mice. Based on these pleiomorphic effects, we postulated that improved electromechanical dispersion might contribute to the long-term benefits of mavacamten. To date, the effects of mavacamten on LV regional deformation have not been assessed, as speckle tracking imaging was not routinely included in trials. We performed echocardiographic LV global longitudinal strain (GLS) analysis at baseline and after 3-year mavacamten therapy, as well as an assessment of regional electromechanical dispersion using speckle tracking imaging and QT dispersion analysis.

We evaluated 6 patients with obstructive HCM, representing the whole Florence cohort in EXPLORER-HCM (Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy; URL: https://www.clinicaltrials.gov; unique identifier: NCT03470545), at the time of enrollment in the open-label extension MAVA-LTE study (A Long-Term Safety Extension Study of Mavacamten in Adults With Hypertrophic Cardiomyopathy; URL: https://www.clinicaltrials.gov; unique identifier: NCT03723655) and at 3 years. Patients underwent dose-blinded titration of mavacamten starting with 5 mg daily, with dose increase permitted at weeks 4, 8, 12, and 24 based on resting or postexercise LV outflow tract gradients and LV ejection fraction. Echocardiographic GLS studies were performed on Vivid E9 with postprocessing (EchoPac version 206, GE Healthcare). The time-to-peak longitudinal strain SD for each LV segment over the whole cardiac cycle was used to compute peak systolic dispersion, as an indicator of LV mechanical dispersion. QT dispersion was calculated as the difference between the longest and shortest QT values for each patient. Nonparametric Wilcoxon paired signed-rank test was used to assess the difference between baseline and year 3; statistical significance was set at $P<0.05$, and results were expressed as median+IQR (R version 4.2.2). The subjects provided their informed consent for these post hoc analyses of data acquired as part of the study.

At baseline, the median age was 57 (52–61) years, and 83% were males. One patient had arterial hypertension, 3 had dyslipidemia, and none had diabetes. Only 1 patient had a family history of sudden cardiac death. Genetic testing was carried out in 5 patients: 3 patients had a single pathogenic sarcomeric variant (MYH7, TNNI3, and MYBPC3), 1 patient had a variant of unknown significance (MYBPC3) and 1 had negative genetic testing.

Key Words: left vetricular dispersion ■ myosin inhibitor ■ obstructive HCM

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For Sources of Funding and Disclosures, see page 283.

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Nonstandard Abbreviations and Acronyms

GLS	global longitudinal strain
HCM	hypertrophic cardiomyopathy
LV	left ventricular

At 3-year follow-up, mavacamten achieved a marked reduction in resting left ventricular outflow tract gradient (5 [3–7] versus 90 [75–106] mm Hg at baseline, median individual difference −83 mm Hg; *P*=0.031) and increase in absolute LV cavity volume (128 [125–131] versus 108 [86–116] mL, median individual difference +14 Ml; *P*=0.031), with mild reduction in LV ejection fraction (64 [64–65] versus 68 [66–70]%, median individual difference, −3.5%; *P*=0.036), in line with previous results.[3] There was marked reduction in N-terminal pro-B-type natriuretic peptide (97 [86–114] versus 1818 [1576–2313] pg/mL, median individual difference, −1717 pg/mL; *P*=0.031), while a trend toward improvement in E/e′ ratio (13.1 [10.3–14.7]

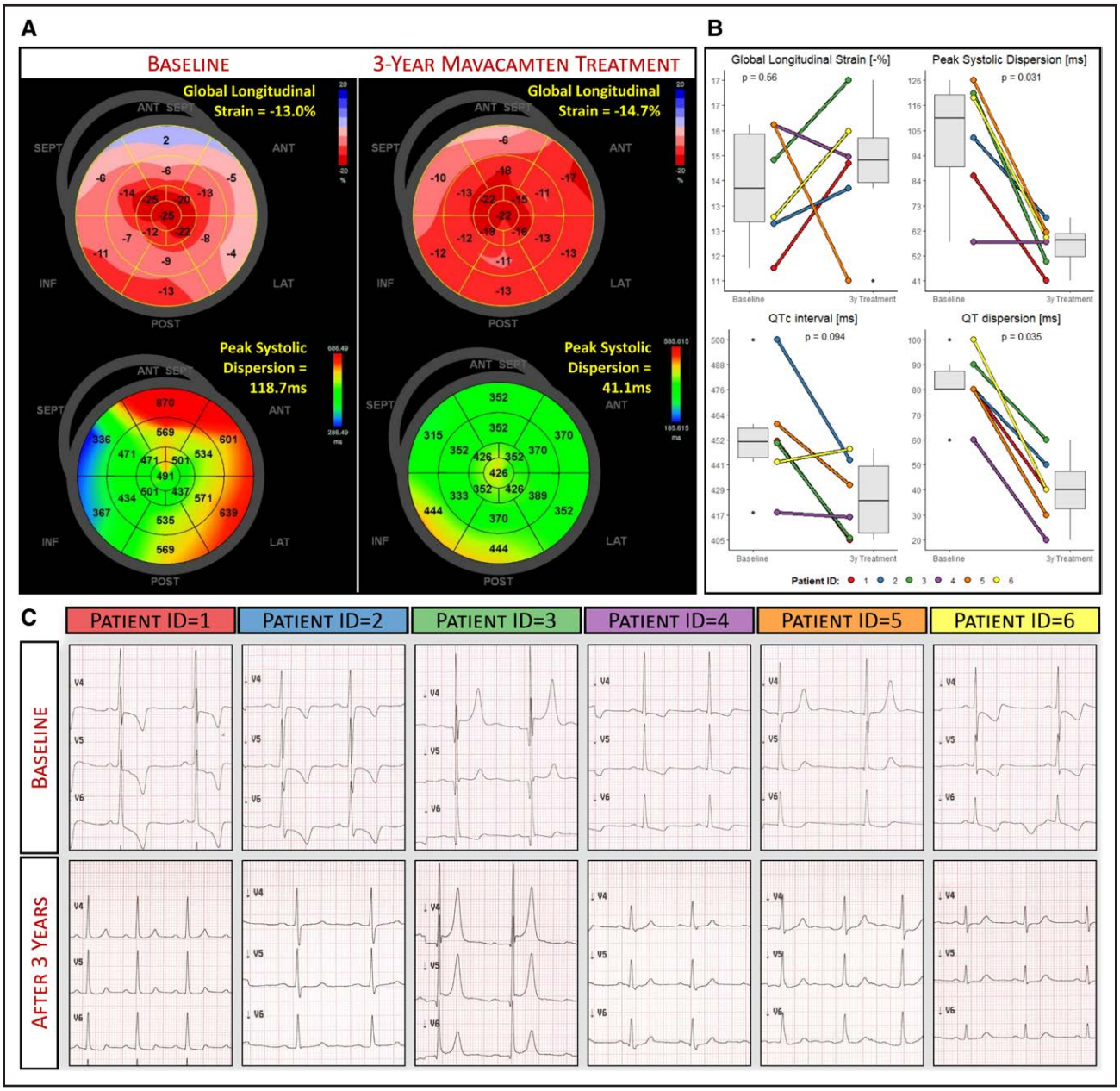

Figure. Long-term effects of mavacamten on electromechanical dispersion, systo-diastolic function, and outflow gradients. **A**, An example of a 46-year-old man with sarcomeric hypertrophic cardiomyopathy shows no significant change in global longitudinal strain and a decrease in peak systolic dispersion. **B**, Changes in global longitudinal strain and peak systolic dispersion, QTc interval, QT dispersion before and after 3-year mavacamten therapy. Individual variation for each parameter is shown using different colors. **C**, Changes in the ECG could be seen with the normalization of repolarization abnormalities in each subject, who are denoted by distinct colors (only leads V4–V6 were shown at baseline and after 3 years of treatment). ANT indicates anterior; INF, inferior; LAT, lateral; POST, posterior; and SEPT, septum.

versus 17.1 [13.5–18.3]; *P*=0.220) was not significant due to worsening in 1 patient who developed atrial fibrillation (which also resulted in a loss of ≈5% points in GLS and LV ejection fraction). At speckle tracking analysis, there was a consistent improvement in peak systolic dispersion (58.6 [51.4–61.2] versus 110.2 [89.7–120.3] ms, median individual difference −51.9 ms; *P*=0.031) with no change in GLS (−14.8 [14.1–15.5] versus −13.9 [12.9–15.6]%; *P*=0.560; Figure). electrocardiographic analysis showed marked attenuation of baseline repolarization abnormalities in all patients (Figure), with marked improvement in QT dispersion (40 [32–47] versus 80 [80–88] ms at baseline, median individual difference, −40 ms; *P*=0.035) and a trend toward decreased QTc duration (423 [409–440] versus 452 [444–458] ms; *P*=0.094). No differences were observed for QRS complex duration (108 [97–123] versus 103 [101–112] ms at baseline; *P*=0.999). No severe adverse drug-related events were recorded.

Overall, mavacamten treatment is associated with marked improvement in LV electromechanical dispersion at 3 years in our obstructive HCM cohort. Electromechanical isotropy is an important determinant of myocardial efficiency and an independent predictor of ventricular arrhythmias in HCM.[5] The observed reduction in QTc dispersion, combined with the improvement in ventricular repolarization, suggests a modulatory effect of mavacamten on the profound electrophysiological abnormalities described in HCM cardiomyocytes, which are thought to represent a direct consequence of sarcomere gene mutations.[2] Furthermore, the stability of GLS findings over 3 years is reassuring with regard to the preservation of global and regional systolic performance in the presence of sustained cardiac myosin inhibition. As a study limitation, no evaluation was performed throughout the timeframe or after the wash-out phase.

Such effects of mavacamten suggest a disease-modifying action, with the potential to improve long-term energetic sustainability and electrical stability of the HCM myocardium; warranting further investigation.

ARTICLE INFORMATION

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Source of Funding

Dr Palinkas received a scholarship supported by the New National Excellence Program-23-4 of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Fund of Hungary.

Disclosures

Dr Olivotto has served as Principal Investigator in the Explorer Trial program and has received research funds and had served in advisory boards for Bristol Myers Squibb. The other authors report no conflicts.

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