INTRODUCTION

Mavacamten (mava) is a first-in-class, small-molecule inhibitor of cardiac myosin that can offer sustained symptomatic relief to patients with obstructive hypertrophic cardiomyopathy (HCM), normalizing contractility and improving exercise capacity. Mava can improve LV compliance by limiting residual cross-bridges during diastole. Given the frequent use of β-adrenergic receptor (AR) blockers in HCM, these experiments evaluated the diastolic effects of mavacamten in the setting of metoprolol administration.

METHODS

In vivo: Beagle dogs were chronically instrumented for simultaneous arterial pressure and LV pressure-volume (LVPV) recordings. Mavacamten (1.5 mg/kg PO) was evaluated under concomitant β-AR blockade for 7 days (+BB, metoprolol 0.5 ± 0.1 mg/kg PO tid; n = 4). Systemic/LV hemodynamics, geometry, and cardiac function were examined.

Ex vivo: Isolated Sprague Dawley rat hearts were perfused via a modified Langendorff method to assess LV function at (isometric/isovolumic) steady-state as well as during rapid (30 μL) stretch challenges (see Fig. 1). Mavacamten (0.3 μM) was studied under control conditions (n = 6) and after β-AR blockade (metoprolol 0.1 μM + 10nM of isoproterenol; n = 7).

Mavacamten: pro-compliance

Mavacamten decreased load-dependent (dP/dtmax: -24 ± 5%, EF: -28 ± 5%) and independent inotropic indices (PRSW: -31 ± 2%), while preserving systemic pressure. Mavacamten increased LV EDV (+14 ± 2%), but preserved both EDP (6 ± 1 to 7 ± 1 mmHg) and estimated stiffness (2.0 ± 0.2 to 2.2 ± 0.3 mmHg/mL). Metoprolol at matched negative inotropy (PRSW: -31 ± 4%), increased both EDP (6 ± 0 to 10 ± 1 mmHg) and stiffness (1.8 ± 0.1 ± 2.5 ± 0.1 mmHg/mL) with only modest changes in EDV (+3 ± 1%). #: P<0.05 vs. PRE

RESULTS

In vivo β-AR blockade decreased (P<0.05) heart rate (108 ± 7 vs. 123 ± 7 bpm) as well as contractility (EF: -20 ± 3%, PRSW: -20 ± 5%). While maintaining end-diastolic volumes (EDV: 0 ± 1%), in this setting, mavacamten increased EDV (+17 ± 2%, P<0.05) while preserving both EDP (4 ± 1 to 5 ± 2 mmHg) and end-diastolic stiffness (1.4 ± 0.2 to 1.9 ± 0.5 mmHg/mL), indicating improved compliance/distensibility despite additive negative inotropy (PRSW: -30 ± 6% vs. +BB). (see Fig. 3, right)

Similar results were obtained ex vivo, where mavacamten decreased dP/dtmax and developed pressures (DP) (see Fig. 4A). Moreover, mava reduced diastolic pressures (EDP) both at steady-state (1 ± 1 vs. 3 ± 1 mmHg) and in response to a preload increase (Eed: ΔP/L: -7 ± 1%, 3.2 ± 0.1 vs. 3.5 ± 0.1 mmHg/μL); β-AR blockade did not alter these responses (Eed: ΔP/L: -5 ± 2%). (see Fig. 4, below).

CONCLUSIONS

Direct myosin modulation with mavacamten has a unique cardiac profile characterized by systolic functional attenuation with improved LV compliance. This novel profile appears to be independent of β-AR responsiveness, and could have salutary effects in patients with HCM and/or impaired ventricular filling.

Figure 2. In healthy conscious dogs, mava (1.5 mg/kg PO) led to parallel rightward shift of the LV pressure-volume relationships (right), decreasing contractility (inset), recruiting EVD, and preserving both end-diastolic pressures (EDP) as well as elastance (EDPVR)

Figure 3. Single-dose mavacamten (mava, 1.5 mg/kg PO) given to dogs in the setting of mild cardiac-dysfunction induced via selective β-AR blockade for seven days (metoprolol, +BB in gray) decreased indices of contractility while preserving systemic hemodynamics. Mava further blunted dP/dtmax increases under dobutamine (+DOB, 10 μg/kg/min IV) it enhanced the ability of this β-AR agonist to hasten relaxation (tau and dP/dtmax) preserving cardiac output recruitment (insets). Average data for Mava (red) were taken 3 hours (3HR) post-dosing.

Figure 4. Changes in dP/dtmax developed pressure (DP), heart rate (HR), as well as end-diastolic pressures (EDP) (A) and elastance (Eed, via a 30 μL stretch challenge; B) due to mavacamten (0.3 μM) in isolated rat hearts. C: Representative balloon pressure (out of the heart) and resulting LVPV (absolute and adjusted) as well as dLVP/dt during stretch.

In vitro: Representative ECG and functional changes at both isovolumic steady-state (SS) and during rapid (30 μL) stretch challenges. A: Representative ECG, left-ventricular pressure (LVPV) and its first time derivative (dLVP/dt) at SS; B: Cardiac ultrasound showing the intra-cardiac balloon, and LV M-mode (isovolumic); C: Representative balloon pressure (out of the heart) and resulting LVPV (absolute and adjusted) as well as dLVP/dt during stretch.