Effect of the Selective Cardiac Myosin Activator, *Omecamtiv Mecarbil*, on Left Atrial Performance in Healthy Men

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Background

Omecamtiv mecarbil (formerly known as CK-1827452) is a small molecule designed to improve cardiac function by the novel mechanism of directly activating cardiac myosin.[1] In a dog model of heart failure, intravenous infusion of *omecamtiv mecarbil* increased left ventricular systolic function and cardiac output, with attendant decreases in filling pressures and heart rate.[2,3] Importantly, these effects on cardiac function did not result in an increase in coronary blood flow or myocardial oxygen demand. As opposed to ß-adrenergic receptor agonists and phosphodiesterase inhibitors, which have previously been shown to increase the rate of pressure development (dP/dt) and shorten left ventricular systolic ejection time, *omecamtiv mecarbil* increased systolic function by increasing systolic ejection time without changing dP/dt. Also, in distinction from currently available inodilators, *omecamtiv mecarbil* has no known direct vasoconstricting or vasodilating effects.

In this first-in-humans study, a 6-hour infusion of *omecamtiv mecarbil* was given to healthy men.[4] Consistent with the pre-clinical data, a dose-dependent lengthening of the left ventricular systolic ejection time (SET) was noted. In addition, *omecamtiv mecarbil* produced dose-dependent and statistically significant increases in stroke volume, ejection fraction and fractional shortening at 6 hours compared to placebo. Given these improvements in left ventricular systolic function and the similarity of atrial and ventricular cardiac myosin, we hypothesized that *omecamtiv mecarbil* could improve left atrial function. Therefore, we sought to quantify the effects of *omecamtiv mecarbil* on left atrial (LA) performance.

Methods

In this single center, double-blind study, healthy men (n=34 subjects) received a 6 hr double blind infusion each week x 4. Each subject received 3 ascending *omecamtiv mecarbil* doses with a placebo infusion randomized into the treatment sequence. *Omecamtiv mecarbil* was studied at 10 dose rates ranging from 0.005 to 1 mg/kg/hr. Echocardiograms were obtained at baseline, 1, 3, 6, 7, 8, 10, and 24 hrs. From this study, the protocol-specified maximum tolerated dose of *omecamtiv mecarbil* was determined to be 0.5 mg/kg/hr administered for 6 hours. We selected echocardiograms from patients who received both placebo and *omecamtiv mecarbil* at 0.5 mg/kg/hr (n=14-16 for the selected variables) and measured left atrial (LA) and ventricular (LV) volumes as well as Doppler flows blinded to treatment. Left atrial reservoir function was defined as [(left atrial end-systolic volume – left atrial end-diastolic volume)/left atrial end-systolic volume] * 100%. The least squares mean difference for the change from baseline as compared to placebo was computed and compared between placebo and maximum tolerated dose of OM (0.5 mg/kg/hr) using an ANCOVA analysis based on the following model:

Change from baseline = Treatment Groups + Baseline + Error, treating patients as random effect.

Results

Analogous to the increase in LV systolic ejection time (SET), omecamtiv mecarbil increased the duration of LA contraction (mitral A wave duration). In addition, omecamtiv mecarbil increased LA performance as indicated by improvements in LA reservoir function, A velocity, and A' velocity. No change in HR or E velocity was noted. These improvements in LA performance were associated with increased LV stroke volume as assessed by LVOT velocity time integral (VTI).

	N		Least Square Mean change from baseline			95% CI		
Echo Parameter	0.5 mg/kg/hr	Placebo	0.5 mg/kg/hr	Placebo	Difference (SE)	Lower	Upper	p-value
MV A wave duration (msec)	16	28	14.8	-1.94	16.73	8.13	25.33	0.0002
					-4.31			
Doppler MV Peak A Velocity (m/sec)	16	19	0.069	-0.021	0.089	0.054	0.12	<0.0001
					-0.017			
A' velocity from Doppler tissue imaging (cm/sec)	16	19	0.006	-0.004	0.01	0.001	0.02	0.03
					-0.005			
Left atrial end-diastolic volume index (LAEDVI)(ml/m²)	14	16	-4.85	-5.9	1.05	-1.51	3.6	NS
					-1.25			
Left atrial end-systolic volume index (LAESVI)(ml/m²)	14	16	-1.02	-5.5	4.48	1.32	7.63	0.007
					-1.53			
Left atrial reservoir function %	14	16	8.04	3.9	4.14	-0.25	8.53	0.06
					-2.14			
Doppler LVOT VTI (cm)	15	19	3.2	-0.33	3.53	2.27	4.79	<0.0001
					-0.62			

Table. Summary of Results from the Statistical Analysis of Change from Baseline Echo Parameters Taken at 6 Hours between Treatment Group and Placebo

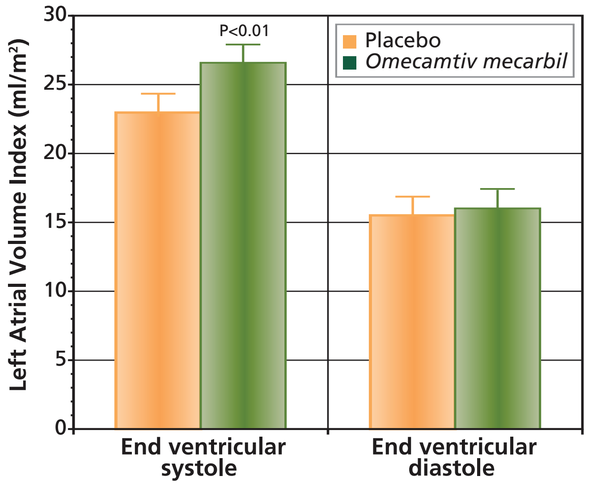

Figure 1: Left atrial volume index at ventricular end-systole and end-diastole by treatment group (mean ± SEM)

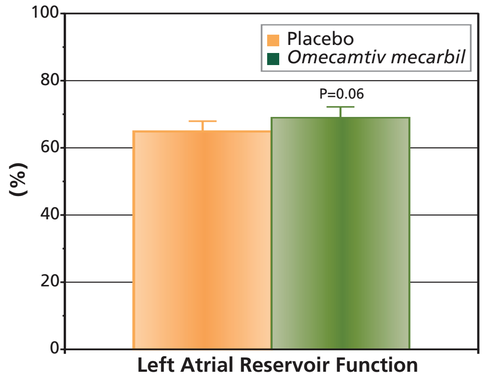

Figure 2: Left atrial reservoir function by treatment group (mean ± SEM)

Conclusions

This study is the initial report of improved left atrial performance with *omecamtiv mecarbil* in humans. In previous pre-clinical studies as well as the human studies with *omecamtiv mecarbil*, the most direct evidence of its pharmacologic effect was an increase in LV systolic ejection time. In a similar fashion, the duration of atrial systole (A wave duration) was increased with *omecamtiv mecarbil*. This increase in atrial systole was associated with measures of increased left atrial performance. Although the effect on left atrial performance could be due to improved left ventricular diastolic function, the improvement in A and A' Doppler velocities support intrinsic improvement in LA contractility. Future clinical studies will measure its effects on left atrial function in heart failure.

References

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