Vasomera™, a Novel VPAC2-Selective Vasoactive Intestinal Peptide Agonist, Improves Arterial Elastance and Ventriculo-Arterial Coupling:

Effects in Rats with Induced Diastolic Dysfunction via Renoprival Hypertension

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Introduction

Vasomera™ is a first-in-class stable long-acting vasoactive intestinal peptide (VIP) agonist, with preferential actions on the G-protein-coupled VPAC2-receptors; VIP mediates cardiopulmonary regulation and has been proposed as a therapeutic target for both hypertension and systolic dysfunction.

In this set of studies, the acute effects of Vasomera in load-independent function and ventriculo-arterial coupling were in evaluated in a rats with induced (renoprival hypertension) chronic diastolic dysfunction, mimicking heart failure with preserved ejection fraction (HFpEF).

Materials and Methods

HFpEF, as demonstrated via serial echocardiography (e.g., altered E/A ratios, see table), was induced by bilateral renal wrapping (RW), leading to renoprival hypertension.

	EF (%)	E/A (n/u)	IVRT (ms)	LVPWd (mm)
CTRL	81 ± 1	1.5 ± 0.1	25 ± 1	1.47 ± 0.03
HFpEF	81 ± 1	2.1 ± 0.1	29 ± 1	1.70 ± 0.03
P-value†	*N.S.*	*↓<0.005*	*↑<0.05*	*↑<0.005*

Values are mean ± SEM (n = 7). †: P-value vs. CTRL.

Conditioned rats (n = 7, 368 ± 14g) were instrumented (under anesthesia) for the determination of left-ventricular (LV) hemodynamics as well as load-independent function and ventriculo-arterial coupling (via pressure-volume relationships); data were evaluated before/after a continuous IV infusion of Vasomera (PB1046, 7.5 µg/kg/min).

In addition, the hemodynamic effects of one of Vasomera (PB1046, 1-9 mg/kg SQ) were evaluated in conscious telemetered SHR rats (351±4 g, n=8) during the normal/untreated state, β-AR blockade (+BB, atenolol 20 mg/kg), calcium-channel blockade (+CCB, amlodipine 5 mg/kg), and ACE-inhibition (+ACE, ramipril 1 mg/kg).

Results

Vasomera decreased the estimated arterial elastance (Ea: -19 ± 3*%) with negligible changes in heart rate (-2 ± 2%). Improved inotropy (Ees: +24 ± 7*% and PRSW: +27 ± 4*%) was observed post-treatment, suggesting improved ventriculo-arterial coupling (Ea/Ees: -34 ± 3*%). Vasomera also reduced filling pressures (EDP: -30 ± 8*%), accelerated the time-constant of relaxation (tau: -22 ± 2*%) and improved compliance (EDPVR: -24 ± 4*%).

Fig 1. Mechano-Energetic effects (Table, right) and representative LV pressure-volume curves/relationships (ESPVR, EDPVR; left) in rats with induced HFpEF via bilateral renal (silk) wrapping (RW).

	HR (bpm)	LV-EDP (mmHg)	LV-ESP (mmHg)	LV-Tau (ms)	EDPVR (mmHg/V)	PRSW (mmHg)	Ea/Ees (n/u)
PRE	383 ± 11	11.4 ± 0.9	155 ± 7	11 ± 1	2.0 ± 0.2	38 ± 5	2.1 ± 0.3
POST	376 ± 13	8.6 ± 1.1	126 ± 5	9 ± 1	1.5 ± 0.1	49 ± 6	1.3 ± 0.1
P-value†	*N.S.*	*↓0.004*	*↓<0.001*	*↓<0.001*	*↓0.002*	*↑<0.001*	*↓0.003*

Values are mean ± SEM (n = 7). †: P-value vs. PRE (repeated measures Student's t-test). V: RVU.

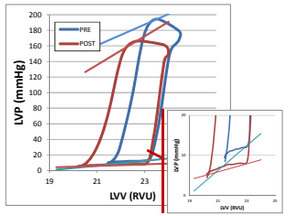
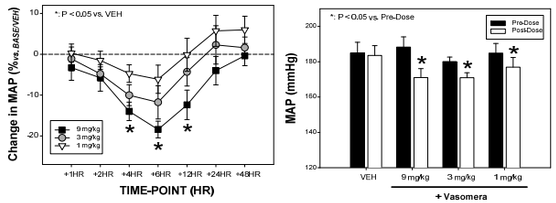


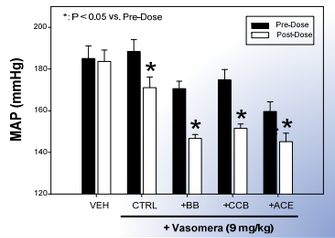
Fig-2. Pressure effects of Vasomera (1, 3, and 9 mg/kg SQ, single-dose) in SHR.



When given as a single SQ dose in SHR rats, Vasomera induced dose-dependent blood pressure decreases that were sustained for up to 12 hours post-dosing (see 2A-B). At 9 mg/kg, Vasomera lowered MAP by 9 ± 1% (188 ± 6 to 171 ± 5* mmHg), with a peak reduction of 16 ± 3% (154 ± 5 mmHg vs. 184 ± 6 in VEH*) observed ~6hr post-dosing (see 2A).

Moderate (dose-dependent) cardio-acceleration was also noted; for example, heart rate increased +8 ± 1% at 9 mg/kg (355 ± 6 to 384 ± 8* bpm); no significant cardio-acceleration was observed at the lowest dose-level.

Fig 3. Effects in SHR treated w/ antihypertensives.



Moreover, despite the mildly increased HR, the rate-pressure product was unaffected (e.g., at 9 mg/kg, -2 ± 1%, from 67 ± 2 to 66 ± 2 mmHg*bpm x10^3). *: P< 0.05 vs. pre-treatment (i.e., baseline) values.

Vasomera's vaso-relaxation was preserved in rats pre-treated with either atenolol (+BB: -14 ± 1%, P<0.05), amlodipine (+CCB: -13 ± 2%, P<0.05) and/or ramipril (+ACE: -9 ± 2%, P<0.05) (see Fig. 3); similar results were observed in animals pretreated with a diuretic (-8 ± 0%, P<0.05). On the other hand, chronotropy seemed to be blunted under β-AR blockade (+6 ± 1%, 278 ± 2 to 294 ± 2 bpm), but was unaffected by amlodipine, ramipril, or hydrochlorizide. In all cases, no adverse clinical effects and/or drug-to-drug interactions were noted.

Conclusion

Vasomera, a novel VPAC2 agonist, improved arterial elastance and ventriculo-arterial coupling, while favorably affecting indices of diastolic function (i.e., lusitropy) in animals with chronic renoprival hypertension mimicking HFpEF.

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