**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 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.

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%).

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*103), *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.