Abstract # 1117. Additive pro-erectile effect of Low intensity-Shockwave Therapy (Li-ESWT) delivered by Aries® combined with sildenafil in spontaneously hypertensive rats (SHR)

R. Assaly-Kaddoum [1], F. Giuliano [2], S. Compagnie [1], J. Bernabé [1], D. Behr-Roussel [1]

(1) Université De Versailles Saint-Quentin-En-Yvelines, Pelvipharm, Montigny-Le-Bretonneux, France, (2) Université De Versailles Saint-Quentin-En-Yvelines, AP-HP Raymond Poincaré Hospital-Dept. of Neurological Rehabilitation, Garches, France

PELVI PHARM

OBJECTIVES

- Hypertension is a risk factor for erectile function in humans.
- Low intensity extracorporeal shock waves therapy (Li-ESWT) has been reported to improve erectile function in patients with moderate or severe ED or even convert phosphodiesterase type 5 inhibitors (PDE5is) non-responders to responders
- Indeed, we and others have reported on the efficacy of Li-ESWT in diabetic rat models of ED [1], but studies of Li-ESWT on hypertension associated ED models have not been described.

Aim of the study:

To investigate whether Li-ESWT could further enhance in vivo erectile responses following acute sildenafil administration in the spontaneously hypertensive rats (SHR), a validated model for hypertension-associated ED [2-3].

Summary of research design

Group #	Groups	Rat strain	LI-ESWT treatment	Acute treatment during erectile function testing	N
I	SHR	SHR	Sham	Saline	12
III	SIL		Sham	Sildenafil 0.3mg/kg	12
III	ESWT+SIL		ESWT	Sildenafil 0.3mg/kg	12

- Male SHR (n=12/group) were used at 11 weeks of age.
- ED function and ex-vivo experiments were performed at 22 weeks of age.

All procedures are performed in compliance with the legislation on the use of laboratory animals (NIH publication N°85-23, revised 1996) and Animal Care Regulations in force in France as of 1988 (authorization from competent French Ministry of Agriculture - Agreement No. A78-423-01, 2013).

MATERIALS & METHODS

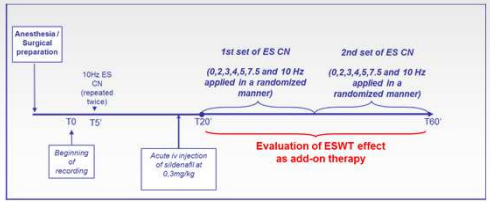
LI-ESWT Treatment protocol

Male SHR rats received 1 session of Li-ESWT per week for 6 weeks. Shockwaves were delivered by a calibrated probe yielding a controlled energy flux density of 0.051mJ/mm2 attached to a compact electrohydraulic unit with a focused shockwave source (Aries®, Dornier Medtech, Germany).
To facilitate coverage and transmission of the shockwaves, the penis of each anesthetized rat was manually stretched and dipped into a specifically designed water-filled tank. Following a 4-week wash-out period, erectile function was assessed by electrical stimulation of the cavernous nerve in rats under anesthesia.

Erectile function evaluation: electrical stimulation of the cavernous nerve (ES CN) [4]

After 5 minutes of baseline recording of simultaneous computerized measure of mean arterial pressure (MAP) and intracavernous pressure (ICP), the CN was stimulated (6 V, 1 ms for 45 s) at different frequencies (0, 2, 3, 4, 5, 7.5 and 10Hz) at 3-minute intervals in a randomized manner in order to assess the erectile responses. Erectile responses to ES CN were expressed as a ratio of ICP (mmHg) / MAP (mmHg) x 100, ICP being the difference between ICP in the flaccid state, i.e. before stimulation and ICP during the plateau phase of the erectile response, and MAP, the mean arterial pressure during the plateau phase, and as the ratio of AUCtot / MAP and AUC45 / MAP, AUCtot and AUC45 being the area under the curve during the whole erectile response or the first 45 s during ES CN

LI-ESWT treatments delivered using a special probe attached to a compact electrohydraulic unit with a focused shockwave source to the penis of anesthetized rat dipped into a water-filled tank

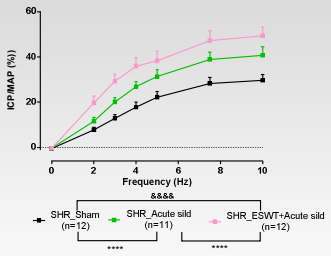


Experimental design of ES CN investigation

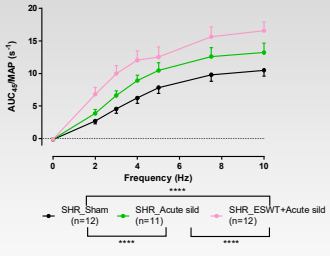
RESULTS

Effect of Li-ESWT on erectile function in SHR

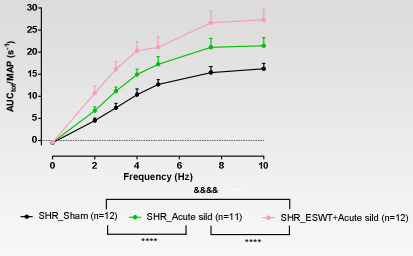
Erectile responses elicited by cavernous nerve stimulation at increasing stimulation frequencies in anaesthetized SHR.



**** p<0.001, 2-way ANOVA
&&&& p<0.001, 2-way ANOVA with interaction



**** p<0.001, 2-way ANOVA



**** p<0.001, 2-way ANOVA
&&&& p<0.001, 2-way ANOVA with interaction

➡ **The erectile responses elicited by electrical stimulation of the cavernous nerve (6V, 1 ms for 45s) were significantly increased in SHR treated with acute sildenafil at 0.3mg/kg**

➡ **ESWT delivered by Aries® significantly increased erectile responses of SHRs treated with acute sildenafil alone.**

CONCLUSIONS

- ✓ This study shows that acute sildenafil significantly improved erectile responses elicited by ES CN in SHR, in line with clinical findings reporting a response to PDE5is in hypertension associated ED.
- ✓ Interestingly, this study reports that Li-ESWT delivered by Aries® was able to potentiate the pro-erectile effect of acute sildenafil in an experimental model of ED associated to hypertension, the SHR.
- ✓ This experimental study confirms the therapeutic benefit of Li-ESWT in ED of vascular origin.
- ✓ Furthermore, it may indicate that combining PDE5i with Li-ESWT delivered by Aries® could salvage PDE5is non responders.
- ✓ To our knowledge, this is the first study to investigate the effect of Li-ESWT for ED using an SHR model.

REFERENCES

1.**Assaly-Kaddoum R, Giuliano F, Laurin M, Gorny D, Kergoat M, Bernabe J, Vardi Y, Alexandre L, Behr-Roussel D.** Low Intensity Extracorporeal Shock Wave Therapy Improves Erectile Function in a Model of Type II Diabetes Independently of NO/cGMP Pathway. J Urol 2016; 196:950-956
2.**Oudot A, Oger S, Behr-Roussel D, Caisey S, Bernabe J, Alexandre L, Giuliano F.** A new experimental rat model of erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: the testosterone-supplemented spontaneously hypertensive rat. BJU Int 2012; 110:1352-1358.
3.**Behr-Roussel D, Gorny D, Mevel K, Compagnie S, Kern P, Sivan V, Bernabe J, Bedigian MP, Alexandre L, Giuliano F.** Erectile dysfunction: an early marker for hypertension? A longitudinal study in spontaneously hypertensive rats. Am J Physiol Regul Integr Comp Physiol 2005; 288:R276-R283.