

Penile Histomorphometrical Evaluation in Hypertensive Rats Treated with Sildenafil or Enalapril Alone or in Combination: A Comparison with Normotensive and Untreated Hypertensive Rats

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DOI: 10.1111/jsm.12750

ABSTRACT

Introduction. Erectile dysfunction (ED) is frequently associated to hypertension and antihypertensive drugs; however, the penile morphological aspects on these situations are poorly known.

Aim. Evaluate the penile morphology of untreated hypertensive rats and rats treated with enalapril or sildenafil alone or in combination to verify the hypothesis that morphological alterations promoted by hypertension on corpus cavernosum could be ameliorated by the use of angiotensin-converting enzyme inhibitors and/or phosphodiesterase type 5 inhibitors.

Methods. Fifty male rats were assigned into five groups: normotensive rats, untreated spontaneously hypertensive rats (SHRs), and SHR treated with enalapril or sildenafil alone or in combination. Blood pressure was measured weekly. At the conclusion of the study, the rats were euthanized, and their penises were collected for histomorphometrical analysis.

Main Outcome Measures. The cross-sectional areas of the penis, tunica albuginea, and corpus cavernosum were measured. The density of the corpus cavernosum structures was quantified.

Results. Both groups of SHR rats treated with enalapril became normotensive. Untreated SHR showed no difference in penile and cavernosal cross-sectional area compared with normotensive rats; however, those rats treated with enalapril or sildenafil alone demonstrated an increase in these parameters. Rats receiving combination therapy showed no cross-sectional area differences compared with normotensive rats. Cavernosal connective tissue density was increased, while the sinusoidal spaces were diminished in untreated SHR. All treatments were effective in maintaining connective tissue density in comparison with normotensive animals. Cavernosal smooth muscle density was similar in all groups, with the exception of the combination therapy group, which demonstrated a reduction in smooth muscle.

Conclusions. Hypertension promoted structural alterations in the corpus cavernosum that may be related to ED. Enalapril- and sildenafil-treated animals had preservation of normal corpus cavernosum structure and an increase in penile and cavernosal cross-sectional area. The combination of these drugs showed less benefit than individual use. **Felix-Patricio B, Medeiros JL, Jr, De Souza DB, Costa WS, and Sampaio FJB. Penile histomorphometrical evaluation in hypertensive rats treated with sildenafil or enalapril alone or in combination: A comparison with normotensive and untreated hypertensive rats. J Sex Med 2015;12:39–47.**

Key Words. Erectile Dysfunction; Hypertension; Morphology; Penis

This work was conducted at the Urogenital Research Unit, State University of Rio de Janeiro. All authors read and approved the final manuscript.

Introduction

The persistent inability to reach or maintain penile rigidity enough for sexual intercourse, known as erectile dysfunction (ED), is the most common sexual complaint of men presenting to their physicians, with a worldwide prevalence of 10–20% [1,2]. Systemic hypertension and ED are closely intertwined diseases. Hypertension is the most commonly reported comorbidity in patients with ED. Also, ED affects as many as 68% of hypertensive men [3]. In both diseases, endothelial factors are involved, resulting in an increased smooth muscle contraction, which leads to increased vascular pressure, poor cavernosal perfusion, and inadequate intumescence [4].

In addition to this similar pathophysiology, the use of antihypertensive agents has been thought to impair normal penile erection [5]. However, evidence suggests that only certain diuretics and beta-blockers may adversely influence erectile function. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers have been reported to have no negative effects and, on the contrary, may possibly have positive effects on erectile function [6]. ACE inhibitors have been shown to not impair erectile function in rats [7] and may improve sexual function in humans [8].

Phosphodiesterase type 5 (PDE5) inhibitors are widely used as first-line therapy for ED in normotensive and hypertensive men. As PDE5 inhibitors act by promoting smooth muscle relaxation, it has been suggested that they could ameliorate elevated arterial blood pressure by relaxing vascular smooth muscle in a manner similar to their action on corpus cavernosum smooth muscle. Some authors have shown that daily usage of PDE5 inhibitors may be beneficial in antihypertensive therapy [9,10].

Although ED may be of multiple causes [11], the structure of the corpus cavernosum is thought to play a key role in the mechanism of erection [12]. The parenchyma of the corpus cavernosum is mainly composed by collagen fibers supporting smooth muscle cells that surround the sinusoidal spaces. These spaces are filled by blood leading to penile elongation and rigidity during erection [13]. Normal proportions of these structures are required for developing and maintaining erection, and altered proportions may be related to ED [12].

The spontaneously hypertensive rat (SHR) strain was obtained by inbreeding of Wistar Kyoto rats with elevated blood pressure [14]. In these

rats, blood pressure continuously increases from the fifth to the fifteenth week of life when it stabilizes in values higher than 200 mm Hg. SHR animals presents vascular alterations and thus have been the main animal model used to study hypertension and other cardiovascular-associated diseases, including ED [15]. The penis of these animals showed structural and ultrastructural alterations, with sinusoidal collagen increase and vascular wall modifications [16].

Although the morphology of the corpus cavernosum was shown to be altered by hypertension in the SHR model, with impairment of erectile function in these animals [16–18], it is not known if these morphological alterations can be prevented or reversed with the use of enalapril (an ACE inhibitor), sildenafil (a PDE5 inhibitor), or a combination of both medications. The hypothesis of this study was that morphological alterations on corpus cavernosum, promoted by hypertension, could be ameliorated by the use of ACE inhibitors and/or PDE5 inhibitors. Thus, the objective of this study was to compare, in an animal model, the penile morphology of normotensive rats, untreated SHR, SHR treated with enalapril or sildenafil alone, and SHR treated with these two drugs in combination.

Material and Methods

Experimental Design

Fifty 120-day-old male rats ($n = 40$ SHR and $n = 10$ Wistar Kyoto) were used in this experiment. The rats were maintained in an animal facility room at a temperature of $21 \pm 1^\circ\text{C}$, with a controlled 12-hour light/dark cycle (artificial light, 7:00 AM to 7:00 PM). The rats received commercial food and water ad libitum. All procedures were carried out in conformity with the conventional guidelines on animal experimentation. The experimental protocols were approved by the Institutional animal experimentation ethics committee (protocol no. CEUA/051/2012).

The rats were divided into five groups of 10 animals each: (i) WKY group, composed of normotensive Wistar Kyoto rats; (ii) H group, composed of SHR; (iii) HE group, composed of SHR treated with enalapril; (iv) HS group, composed of SHR animals treated with sildenafil; and (v) HES group, composed of SHR treated with enalapril and sildenafil.

All drugs were administered orally for 40 days. Groups HE and HES received 30 mg/kg/day of enalapril (Primordium, Rio de Janeiro, Brazil)

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