

Structural analysis of the corpora cavernosa in patients with ischaemic priapism

Waldemar S. Costa, Bruno Felix, Andre G. Cavalcanti, Jorge Medeiros Jr and Francisco J. Sampaio

Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, Brazil

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OBJECTIVE

To evaluate, using quantitative and qualitative methods, the changes in the corpora cavernosa of patients with ischaemic priapism.

PATIENTS AND METHODS

We obtained samples of corpora cavernosa from seven patients with ischaemic priapism (mean age 38 years, range 28–44) who had a cavernous-glandular shunt. The control tissues were fragments of corpora cavernosa obtained from autopsies of seven age-matched men who died from causes

unrelated to the urogenital tract. Histochemical and immunohistochemical techniques were used to assess and quantify the extracellular matrix and smooth muscle fibres. The volumetric density of smooth muscle, elastic fibres and collagen were determined in corpora cavernosa.

RESULTS

From the stereological analysis the mean (SD) values of volumetric density were: for collagen, control 34.76 (4.64), priapism 39.64 (2.91) ($P=0.002$); elastic system fibres, controls 28.10 (2.85), priapism 36.10 (3.06) ($P=0.001$); smooth muscle fibres, controls 43.37 (4.96), priapism 26.48 (5.00) ($P<0.001$). There were significantly more fibrous elements of the connective tissue and significantly fewer smooth muscle fibres

in the corpora cavernosa of patients with ischaemic priapism than in controls.

CONCLUSION

Ischaemic priapism is associated with early and significant changes in the components of the extracellular matrix and smooth muscle fibres of the corpora cavernosa. This could explain the frequent occurrence of erectile dysfunction found in patients with ischaemic priapism.

KEYWORDS

penis, priapism, erectile dysfunction, smooth muscle, extracellular matrix, stereology/quantification

INTRODUCTION

Priapism is defined as a pathological condition of prolonged and persistent painful erection of the penis not associated with sexual stimulation and desire [1–3]. Persistent erection is caused by blood congestion in the corpora cavernosa sinusoids, which usually are bilaterally involved, with no involvement of the corpus spongiosum [3]. Priapism is a urological emergency and can develop into erectile dysfunction (ED), even after effective treatment [1–7].

Priapism is classified as ischaemic, low-flow or veno-occlusive, and as high-flow, non-ischaemic or arterial. The first type is the most common, accounting for 80–90% of cases. Ischaemic priapism is related to intracavernous congestion by high-viscosity blood, due to low levels of O_2 and high levels of CO_2 , which leads to a significant effect on

tissue oxygenation [4,6]. By contrast, high-flow priapism is usually associated with arteriovenous fistula (traumatic or iatrogenic) and with normal levels of O_2 , and therefore does not lead to an important effect on tissue oxygenation [8].

Ischaemic priapism is often idiopathic, being the secondary effect often associated with different causes. In a study involving a review of 230 cases of priapism, 35% corresponded to idiopathic cases, distributed as follows; 21% associated with alcohol or drug abuse, 12% with perineal trauma, 11% with sickle-cell anaemia and 8% with inflammatory disease of the genital tract [9]. The use of intracavernous vasoactive drugs is also linked to the risk of prolonged erections. It is estimated that the risk is 0.4–1.7% for the use of prostaglandins, and can reach 15% with the use of papaverine [10]. In prolonged and recurrent cases, the rate

of subsequent ED can be as high as 56% [11].

Most cases of ischaemic priapism occur in patients aged 16–45 years, being idiopathic in the majority. In young patients, with haematological diseases like sickle-cell anaemia, the first episode of priapism can occur at 15–20 years old, and in 75% of cases the first episode occurs before 20 years old [12]. Priapism is among the most frequent manifestation of sickle-cell disease, affecting 42–87% of patients [11–13].

Several studies have shown that ED is the most serious complication of ischaemic (low-flow) priapism [1–4,14,15]. A literature review showed that most studies of the changes in low-flow priapism focused only on smooth muscle as the pathological substrate for ED, and did not examine other important elements that could also contribute to ED.

In most cases, ED, which occurs frequently in patients with priapism lasting for >48 h, can have a morphological basis, with conspicuous changes in the different elements of the penile corpora cavernosa. A detailed study of these elements could contribute to a better understanding of the effects of priapism in the corpora cavernosa.

The aim of the present study was to evaluate, based on quantitative and qualitative methods, the structural changes in the penile corpora cavernosa of patients with ischaemic priapism, and compare these results with those found in penile samples from age-matched controls.

PATIENTS AND METHODS

The present study was approved by the institutional review committee and was carried out in accordance with the ethical standards of the responsible institutional committee on human experimentation. Samples were obtained from seven patients with ischaemic priapism (mean age 38 years, range 28–44) who had surgery to place a cavernosal-glandular shunt (Al-Ghorab technique) [16]. The priapism in these patients lasted a mean (range) of 56 (48–72) h and was the first episode in all. Minimally invasive techniques like puncture and cavernosal irrigation or injection of vasoconstrictor agents had been used without success before surgery. None of the patients had a history of diabetes or hypertension that could have led to alterations in the normal penile structure. Two patients had idiopathic priapism and in five it was related to sickle-cell disease.

The control group comprised samples from the corpora cavernosa obtained from autopsies, up to 6 h after death, of seven age-matched men who died from causes unrelated to the urogenital tract.

The tissue samples of corpora cavernosa were immersed in PBS-formalin fixative (pH 7.2) for 24 h and then routinely processed for paraffin embedding. Sections of 5- μ m thick were obtained and all samples were initially stained with haematoxylin-eosin and analysed by a pathologist to confirm tissue integrity. The samples were then processed using histochemical and immunohistochemical techniques, as follows: Masson's trichrome and Picrosirius red to detect and quantify the collagen, and Weigert resorcin-fuchsin with previous oxidation to detect elastic

TABLE 1 The stereological analysis of smooth muscle cells, elastic system fibres and collagen fibres in corpora cavernosa of patients with ischaemic priapism and controls

Mean (SD) % of	Priapism	Control	P
Smooth muscle fibres	26.48 (5.00)	43.37 (4.96)	<0.001
Elastic system fibres	36.10 (3.06)	28.10 (2.85)	0.001
Collagen	39.64 (2.91)	34.76 (4.64)	0.002

FIG. 1. Smooth muscle cells in the corpora cavernosa. The brown stain represents the smooth muscle cells immunolabelled with anti- α -actin: (a) priapism; (b) control. These views show the difference in smooth muscle content between priapism and controls, with fewer smooth muscle cells in patients with priapism than controls. Immunohistochemistry with human anti- α -actin, $\times 200$.

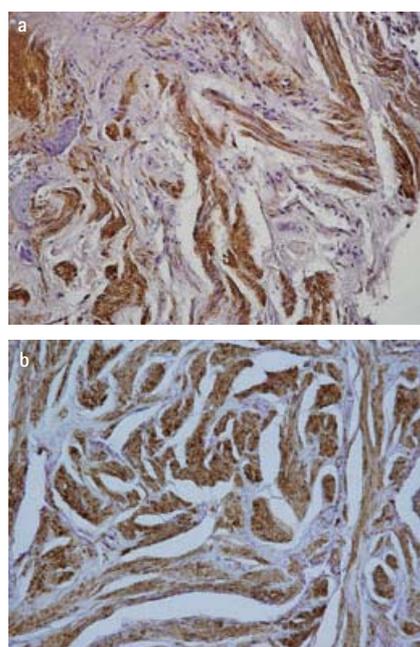
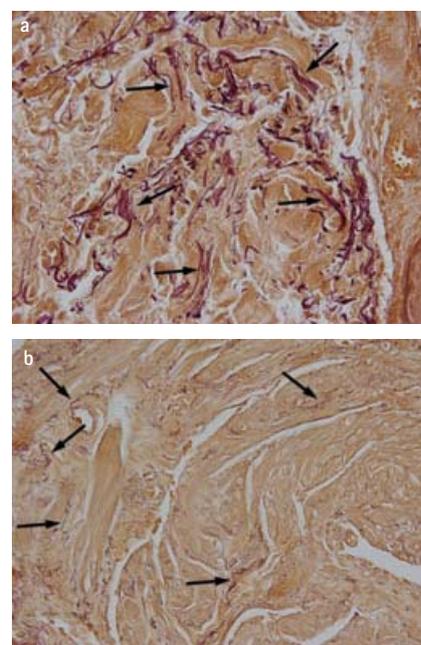


FIG. 2. Elastic system fibres in corpora cavernosa. The resorcin-fuchsin stain is bright violet in the presence of elastic system fibres: (a) priapism and (b) control group. There are more elastic fibres (arrows) in patients with priapism than in controls. Weigert's resorcin-fuchsin, $\times 400$.



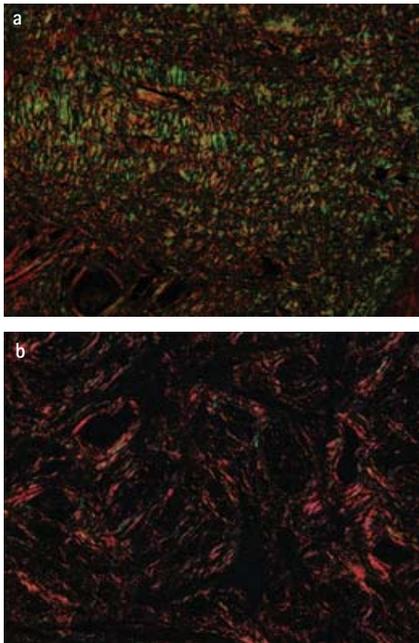
system fibres. Smooth muscle fibres were detected by Masson's trichrome and immunohistochemical analysis, using anti- α -actin antibody. All elements evaluated were quantified by stereological methods, as described previously [17]. Briefly, for each patient and each histological staining technique, 10 sections of corpus cavernosum were obtained, and for each section, 10 fields were analysed. All images were photographed with a digital camera directly coupled to a microscope, at $\times 200$. The volumetric density (Vv) of histological structures was then evaluated while unaware of the source of the

tissue samples, by superimposing an M-42 test system on the digital images, following techniques described in detail elsewhere [17]. The unpaired Student's *t*-test was used to determine the differences between the groups.

RESULTS

Table 1 shows the results of the different elements analysed. The stereological quantification in the corpora cavernosa showed that the Vv of smooth muscle fibres was significantly lower in patients with priapism (Fig. 1). By contrast, there was a significant parallel increase in the Vv of elastic system fibres in patients (Fig. 2). Also, there

FIG. 3. Collagen in corpora cavernosa under polarized light, for a (a) priapism and (b) the control group. There is predominant red staining in the control group, while in the priapism group there is predominant green staining, showing the two types of collagen fibres, type III (green) and type I (red or orange). Picrosirius red, $\times 200$.



was a significantly greater Vv of collagen in patients with priapism than in the controls. The qualitative analysis of Picrosirius red staining, observed under polarized light, showed that there were diverse collagen types in the corpora cavernosa trabeculae, with a predominance of green-stained collagen (increased collagen turnover) in patients with priapism, and a predominance of red-stained collagen (stable collagen state) in the control group (Fig. 3).

DISCUSSION

In priapism there is a sustained erection not followed by penile detumescence, corresponding to a breakdown in the physiology of erection [4,18]. Corpora cavernous smooth muscle fibres are of utmost importance for normal erection and detumescence. Smooth muscle relaxation is necessary to achieve erection, whereas corpora cavernosa smooth muscle contraction is necessary to obtain detumescence [4]. Muneer *et al.* [18] reported that in priapism the cavernous tissue becomes

hypoxic, and there is acidosis and glycopenia. Subsequently, there is an infiltration of inflammatory cells and proliferation of fibroblasts, resulting in necrosis of smooth muscle cells in the corpora cavernosa, with the development of different grades of fibrosis [7,18]. The replacement of normal smooth muscle by fibrosis is in most cases directly involved in the ED that often occurs in patients with priapism [6,16]. According to Spycher *et al.* [19] and Muneer *et al.* [18], it is possible to detect a focal necrosis of smooth muscle cells and their transformation into fibroblast-like cells 24 h after the development of priapism. These observations could explain the marked decrease in the muscular component that we found in the present study, when the patients were analysed at >48 h after the start of priapism.

Interestingly, the elastic system fibres were also affected, showing a significant increase. We speculate that the ischaemia that causes the transformation of smooth muscle cells into fibroblast-like cells could also be the cause of the increase in corpora cavernous elastic fibres. This phenomenon could help to promote detumescence, which occurs in the penile tunica albuginea, where the fibres of the elastic system are also responsible for promoting detumescence [20]. The response of elastic system fibres to different stimuli could be manifested in different ways. Costa *et al.* [21], analysing the elastic system fibres in a study of severe ED, from which patients with priapism were excluded, showed that the elastic fibres were significantly decreased. This suggests that the reaction mechanism of elastic system fibres is a particular characteristic of ischaemic priapism. The increase in the collagen content of the corpora cavernosa was statistically significant in these patients; nevertheless, it was proportionally lower when compared to the other histological features assessed (elastic system and smooth muscle fibres). The collagen content increased by 4.8%, with concomitant occurrence of fibrosis, which seems to occur in a relatively short period. Costa *et al.* [21] and Luanghot *et al.* [22], reported that there was no significant increase in collagen content in corpora cavernosa of patients with ED. However, these studies did not focus on ischaemic priapism as the causal factor of ED. Tissue ischaemia is a well known factor for stimulating collagen production. The transformation of smooth muscle cells into fibroblast-like cells, as described previously [19], could also be

significant in this process, justifying the increase in collagen content in the patients studied.

The qualitative analysis of Picrosirius-stained sections observed under polarized light showed different collagen types in the trabeculae of the corpora cavernosa, in both patients and controls. The predominance of green-stained collagen in patients with priapism signified an increase in collagen turnover, with an active process of collagen formation. However, there was a predominance of red-stained collagen in controls, which implies a stable collagen state.

Our results showed that ischaemic priapism is associated with significant changes in corpora cavernosal components, mainly the occurrence of tissue fibrosis and a decrease in smooth muscle cells. The changes seem to appear at a very early stage, in the present study after the first 48 h of the development of priapism.

The duration of ischaemic priapism is the main risk factor for the development of ED [5,14]. The analysis of our morphological results corroborate the view that the treatment of ischaemic priapism should be administered at a very early stage, to restore penile tissue oxygenation and possibly avoid the structural alterations observed.

In conclusion, the significant changes in the corpora cavernosal extracellular matrix and smooth muscle cells, mainly a decrease in smooth muscle and increase in elastic system fibres, as well as changes in collagen, could explain the frequent occurrence of ED found in patients with ischaemic priapism.

CONFLICT OF INTEREST

None declared.

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Correspondence: Francisco Sampaio, Urogenital Research Unit, State University of Rio de Janeiro, Avenue. 28 de Setembro, 87 – fundos – FCM – térreo Rio de Janeiro, Rio de Janeiro 20551-030, Brazil.
e-mail: sampaio@urogenitalresearch.org

Abbreviations: ED, erectile dysfunction; Vv, volumetric density.

EDITORIAL COMMENT

This study showed a significant increase in the fibrous elements of the connective tissue and a decrease in smooth muscle fibres in the corpora cavernosa of patients with ischaemic priapism. There were only seven patients but the results complement those in other studies that also showed that smooth muscle death is a feature of refractory priapism [7,18]. All of the patients had priapism for only 48–72 h and therefore it is not possible to assess the degree of smooth muscle loss in relation to the duration of priapism. These patients needed shunt operations, and given the histological findings are likely to develop ED. The authors should be congratulated in furthering our understanding of the pathological processes in ischaemic priapism.

David Ralph

Institute of Urology, London, UK