

# Carboxytherapy for Conservative Treatment of Peyronie's Disease

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**Abstract:** PD (Peyronie's disease) is an acquired disorder of tunica albuginea characterized by the formation of plaques of fibrous tissue often associated to symptoms like ED (erectile dysfunction) and coital pain. The inflammatory process is unknown, even if it is known that Activated inflammatory cells produce many ROS (radical oxygen species), leading to fibroblast proliferation and collagen synthesis. Endothelial dysfunction is the responsible of inflammatory chain reaction in which an inflammatory protein, NF-kB seems involved in ROS synthesis. Conservative treatments (laser, ultrasound, iono/iontophoresis) seem to have poor therapeutic effects in PD. Clinical studies have indicated that altered CO<sub>2</sub> (carbon dioxide) levels can impact upon disease progression. CO<sub>2</sub> levels can be sensed by cells resulting in the initiation of pathophysiologic responses with a sensible reduction of oxydative phenomena (Bohr/Haldane effects). We have tried carboxytherapy, by using sovrapubic subcutaneous injection of sterile CO<sub>2</sub> gas in 20 patients aged from 40 to 65, affected by PD. After the cycle of treatment of 10 weekly applications. We have observed in all patients a subjective reduction of penile deviation, an improvement of quality of erections and a sensible reduction of plaque's dimensions, documented by ultrasound controls and IIEF questionnaire before and after the end of cycle. We should consider co<sub>2</sub> as a powerful antioxidant against endothelial dysfunction and oxydative stress. NF-kB is a target of CO<sub>2</sub> antioxidant power. Preliminary qualitative results could encourage an extended use of carboxytherapy in PD treatment.

**Key words:** Carboxytherapy, Peyronie's disease, induratio penis plastica, conservative treatment.

## 1. Introduction

PD (Peyronie's disease) is an acquired disorder of tunica albuginea characterized by penis plaques of fibrous tissue often associated with ED (erectile dysfunction).

PD (Peyronie's disease) affects 1-3% of the male population. Greater than 75% of patients with PD are between 45 and 65 y of age. In this aging population the modulus of elasticity of tunical and septal tissues is diminished [1, 2].

Peyronie's disease has been linked to systemic conditions such as hypertension and diabetes.

PD is associated with Dupuytren's disease (palmar aponeurosis), Ledderhose's disease (plantar aponeurosis), Psoriasis.

An immunologic component to Peyronie's disease has been proposed. Activated inflammatory cells produce oxygen radicals (ROS) initiating a chain of biochemical events leading to fibroblast proliferation and collagen apposition. The principal protein involved is NF-kB [1].

Carboxytherapy refers to the administration of CO<sub>2</sub> for therapeutic purposes. It has been shown that CO<sub>2</sub> has cell interaction in regulating factors of tissue perfusion. Nowadays CO<sub>2</sub> is used as anti-aging treatment, for cellulite of all grades, for wrinkles reduction and for stretch marks [3].

Clinical studies have indicated that altered tissue CO<sub>2</sub> levels can impact upon inflammation progression [4].

The objective of the study is to demonstrate that CO<sub>2</sub> subcutaneous subministration, carboxytherapy, could obtain a sensible reduction of fibrosis and oxydative phenomena of ROS in PD, reducing sexual

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discomfort of patients. Carboxytherapy could be employed as new easy method and free risk conservative treatment for PD.

## 2. Material and Methods

We have recruited 20 patients, aged from 40 to 60 years old, affected by PD until 1 year. Ten patients tried normal conservative therapy with ionophoresis and laser-ultrasound therapy without any results.

We have used IIEF questionnaire and we have studied ultrasound plaque's morphology before and after treatments to assess patients. We have injected by specific medical device 500 cc of sterile Medical CO<sub>2</sub> for 10-15 weekly applications in sovrapubic subcutaneous tissue. CO<sub>2</sub> subcutaneous flux provokes a sort of subcutaneous emphysema along crural region, penis and scrotum. The controller regulates flux intensity and total volume of injection and is managed according to the sensibility of patients.

The medical device is externally connected to a CO<sub>2</sub> sterile tank and provide to administrate the flux, heating the CO<sub>2</sub> volume injected till human body temperature. The site of injection is the sovrapubic region, far from the plaque. We have used a 30 Gauge needle and a mean of 3 injections per application. CO<sub>2</sub> has a subcutaneous diffusion along crural region, penis and using scrotus as reservoir. CO<sub>2</sub> quantity could have a variation according to patient size. The subcutaneous emphysema is painless and disappears after 2-3 hours. The same method of CO<sub>2</sub> subcutaneous sovrapubic application is already currently used in esthetic medicine, because CO<sub>2</sub> has also special lipolitic properties.

## 3. Results

We have observed in all patients a subjective reduction of penile deviation, a reduction of penetration discomfort and an improvement of quality of erections. In four patients we have obtained the reduction of dimensions of plaques.

CO<sub>2</sub> could be considered a powerful antioxidant

against endothelial dysfunction and oxydative stress with easy management and poor toxicity.

In conclusion, CO<sub>2</sub>, as natural antioxidant could reduce the activity of inflammatory agents as NF-κB protein, involved in the evolution of PD.

## 4. Discussion

The tunica albuginea is a thick fibroelastic sheath composed predominantly of thick collagenous bundles and elastic fibers surrounding the trabecular smooth muscle of the corpora cavernosa. Any defect in tunica albuginea can deform penile fibroelastic framework, resulting in curvature or bend, shortness, progressive lack of elasticity, and also occasionally affecting hemodynamic function of the penis [1, 2].

The inflammatory process origin is unknown. it is postulated the occurrence of penile trauma.

Injury causes delamination of the tunica albuginea predominantly at the dorsal, midline septum resulting in small hematoma [4, 5].

Inflammation, induration, and accumulation of leukocytes increase ROS activities with a chain of biochemical events leading to fibroblast proliferation and resulting in collagen and fibrin biosynthesis-deposition between the layers of the tunica albuginea [6].

It seems to be involved some specific inflammatory proteins that provoke the rising of radicals of oxygen and Nitric oxide. The principal protein involved in the genesis of ROS is NF-κB.

The nuclear transcription factor NF-κB is a heterodimeric, sequence-specific transcription factor found in many cells. In unstimulated cells, NF-κB is found in the cytoplasm and is bound to its inhibitor IκB, which prevents it from entering nuclei. A number of stimuli have been shown to activate NF-κB, including cytokines, activators of protein kinase C, viruses and oxidants [7].

The family of NF-κappaB (nuclear factor kappaB) transcription factors is a topic of intense interest in the biomedical community stemming from the role

NF- $\kappa$ B plays in almost every aspect of cell regulation: stress responses, immune cell activation, apoptosis, proliferation, differentiation and oncogenic transformation.

NF- $\kappa$ B has long been considered a prototypical proinflammatory signaling pathway, largely based on the activation of NF- $\kappa$ B by proinflammatory cytokines such as IL-1 (interleukin 1) and TNF $\alpha$  (tumor necrosis factor  $\alpha$ ), and the role of NF- $\kappa$ B in the expression of other proinflammatory genes including cytokines, chemokines, and adhesion molecules, which has been extensively reviewed elsewhere.

In PD altered CO<sub>2</sub> levels could impact upon disease progression. CO<sub>2</sub> levels can be sensed by cells resulting in the initiation of physiologic and pathophysiologic responses. A role for CO<sub>2</sub> in the regulation of gene transcription has recently been identified with exposure of cells and model organisms to high CO<sub>2</sub> leading to suppression of genes involved in the regulation of innate immunity and inflammation.

Recent evidence suggests that CO<sub>2</sub> may also directly regulate gene expression through the NF- $\kappa$ B pathway. The suppression of NF- $\kappa$ B activity by hypercapnia was recently provided by the demonstration of CO<sub>2</sub>-induced nuclear localization of the IKK $\alpha$  subunit [7].

Molecular O<sub>2</sub> (oxygen) is sensed by prolyl and asparaginyl hydroxylases, which confer oxygen-dependent instability upon transcription factor. Activation of this pathway in hypoxia leads to the expression of adaptive genes. The sensor for regulation of NF- $\kappa$ B-dependent gene expression in response to changes in CO<sub>2</sub> has yet to be defined. However, elevated CO<sub>2</sub> leads to repression of the NF- $\kappa$ B pathway and decreased levels of genes which promote innate immunity and inflammation.

Therapeutic hypercapnia seems to have a suppressive effect on NF- $\kappa$ B signaling [7].

Carboxytherapy leads to blood vessels dilatation in the area where the gas is injected. This reaction to

carbon dioxide injection gives a better oxygenation of skin layers with increased lipolysis capabilities. Carboxytherapy has been used for over 70 years in Europe where it was discovered (France, Royat). The procedure was widely used to treat ischemic vascular diseases because of the vasodilation properties of CO<sub>2</sub>. The most common CO<sub>2</sub> treatments are: cellulite reduction, liposuction complementary solution, arterial diseases associated with diabetes and skin ulcers [3].

Carboxytherapy stimulates microcirculation at the level of metarterioles, arterioles and precapillary sphincteres by increasing tissue flow velocity and consequently, by improving lymphatic drainage [3, 8].

## 5. Conclusion

In PD the use of carboxytherapy shows in all patients subjective improvement of erection and in 15 cases the reduction of plaque dimensions.

Carboxytherapy shows very easy management and free risk subadministration. Side effects are minimal and resolve quickly, and include mild pain at the injection site and possible self limiting bruising of the tissues.

Preliminary qualitative and quantitative results could encourage an extended experimentation of carboxytherapy in PD conservative treatment.

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