Nonrevascularizable buttock claudication improved with Sildenafil

A case report

Loukman Omarjee, MSc, MD<sup>a,b</sup>*, Audrey Camarzana, MD<sup>a</sup>, Samir Henni, MSc, MD<sup>a,b</sup>, Pierre Abraham, MD, PhD<sup>a,b</sup>

Abstract

Rationale: Sildenafil, a phosphodiesterase-5-inhibitor (PDE5i), could represent a new treatment in addition to the medical treatment and advice to walk in peripheral arterial disease (PAD).

Patient concerns and Diagnoses: We report a case of a 62-year-old heavy smoker man who developed a buttock claudication and a severe walking limitation following an aorto-bi-femoral bypass in 1992. Since 2003, each year, he has been referred for investigation of bilateral buttock claudication on treadmill using transcutaneous oxygen pressure (tcpO<sub>2</sub>) measurement during exercise to argue for the vascular origin of the walking impairment. He had a severe bilateral buttock ischemia and the maximum walking distance (MWD) he reached was 258 m in 2011 despite the medical optimal treatment and walking rehabilitation. Ethical approval is not necessary for this case report according to the French legislation and written consent to publication was obtained from the patient.

Interventions: Sildenafil, 100 mg/d, was introduced in February 2015 and the MWD increased to 310 m only after 2 h after the first oral intake, then to 713 m after 3 weeks, and finally to 1313 m in January 2017.

Outcomes: Recently, the patient is treated with Sildenafil 100 mg/d. He has no more pain during walking and his quality of life has improved.

Main lessons to learn: Sildenafil, a PDE5i, may represent a new therapeutic option in addition to the conventional optimal medical therapy in patients with arterial claudication. tcpO<sub>2</sub> measurement during exercise is a promising technique for the diagnosis and monitoring of patients with PAD. A crossover, double-blind, prospective randomized monocenter study (ARTERIOFIL-NCT02832570) and a double-blind prospective randomized multicenter study (VALSTAR-NCT02930811) are ongoing to confirm our original observation.

Abbreviations: ABI = ankle brachial index, ACE = angiotensin converting enzyme, DROP = decrease from rest of oxygen pressure, DROP<sub>min</sub> = minimal DROP value, MWD = maximum walking distance, PAD = peripheral arterial disease, PDE5i = phosphodiesterase-5-inhibitor, QoL = quality of life, tcpO<sub>2</sub> = transcutaneous oxygen pressure, VEGF = vascular endothelial growth factor.

Keywords: angiogenesis, buttock claudication, exercise-tcpO<sub>2</sub>, pain, peripheral arterial disease, Sildenafil, treadmill walking test
1. Introduction
A heavy smoker, complained in 1987 of severe walking impairment and calf claudication. He was 33. The neurological and rheumatological examinations were normal, the angiography found aorto-iliac lesions. Rehabilitation and medical treatment led to a transient improvement of symptoms and walking limitation followed by clinical deterioration 1 year later. He had an aorto-bi-femoral bypass in 1992. He stopped smoking in 2001 while developing buttock claudication with severe walking limitation.

2. Presenting concerns of the patient
In March 2003, at 49, he was referred for investigation of bilateral buttock claudication. Transcutaneous oxygen pressure (tcpO2) measurement during exercise was performed to argue for the vascular origin of the walking impairment. During exercise-tcpO2, chest tcpO2-change is subtracted from limb tcpO2-changes and expressed as “Decrease from Rest of Oxygen Pressure” (DROP; mm Hg). DROP is 0 at rest and returns to 0 after recovery. The minimal DROP value (DROPmin) is the lowest observed DROP. During this first test, DROPmin was 24/32 mm Hg on the left/right buttocks, respectively (close to zero on both calves). The MWD was 163 m, and walking was stopped because of buttocks pain corresponding to the usual symptoms. Then, tcpO2 confirmed exercise-induced proximal-without-distal bilateral ischemia. Angiography found a bilateral nonrevascularizable hypogastric occlusion and a patent bypass. In 2004, in addition to the medical treatment (statin, antplatelet, angiotensin converting enzyme [ACE] inhibitor) and advice to walk, a 5-week supervised rehabilitation did not significantly increase the walking capacity. Exercise-tcpO2 after the training was not improved, and MWD was 223 m (the test was stopped because of buttocks pain), and values of the DROP were always above +15 mm Hg on both buttocks. Then tcpO2 was repeated with the following results: MWD was 91 m and walking was stopped at 1313 m. Interestingly, during exercise phase, there was no pain, and values of the DROP were always above +15 mm Hg on the left buttock, which could suggest a recruitment of collateral vessels newly formed from an active angiogenesis.

3. Interventions
Mid February 2015, a new tcpO2 test showed an MWD of 167 m. DROPmin were 31 mm Hg on both buttocks (Fig. 1, panel 1). Since the patient, now aged 61, was complaining impotence, we tested Sildenafil, a phosphodiesterase-5-inhibitor (PDE5i) at a single dose of 50 mg. A test was done 2h after the first oral intake and stopped at 310 m for thigh fatigability but without the usual buttocks pain. No side effects were observed. DROPmin was 39/43 mm Hg on the left/right buttocks, respectively. We decided to treat the patient with a once-a-day morning oral dose of 100 mg.

Two weeks later, the MWD was 378 m and treadmill stopped due to thigh fatigability but not buttock pain despite persistent severe proximal ischemia. DROPmin were 51/53 mm Hg on the left/right buttocks, respectively. At 1 month of Sildenafil treatment, the patient described an improvement of his sexual ability and QoL and the almost complete absence of buttock pain daily. The MWD was 713 m. DROPmin was 35/50 mm Hg on the left/right buttocks, respectively (Fig. 1, panel 2).

To date the patient is treated with 100 mg/d Sildenafil without deterioration of his walking capacity and symptoms.

4. Outcomes

5. Discussion
Claudication is the most common clinical expression of peripheral arterial disease (PAD). Buttock claudication is an unusual presentation of PAD except in patients who have had an aorto-bi-femoral revascularization and is frequently under-reported by the patients. Differential diagnoses for proximal claudication include hip arthritis and lumbar spine stenosis. Exercise-tcpO2 is a renewed technique that has proved efficiency to argue for a vascular origin of walking-induced proximal pain. Here, it has allowed to follow-up over a long period of time the presence and severity of buttock ischemia. As expected from the patent aorto-bi-femoral bypass, calf tcpO2, ABI at rest and after exercise were normal. Cilostazol has been proposed in addition to optimal medical treatment as recommended by the European Society of Cardiology on the diagnosis and treatment of PAD including antplatelet, lipid lowering drugs, ACE inhibitors and advice to walk to improve functional capacity in patients with claudication but removed from the market in France due to frequent side effects. A double-blind study found no difference between Sildenafil versus placebo on walking distance, but for incremental workloads and after a single oral intake. Beyond its vasodilator effect, Sildenafil was suggested to have a direct antinociceptive effect via the L-arginine/nitric oxide/cyclic guanosine monophosphate pathway and through spinal adenosine A1, A2A, A2B, and A3 receptors. Whether decreased nociception could explain the spectacular and very early effect and absence of usual pain noted under treatment in our patient (Fig. 2), is a fascinating but unproved hypothesis for research. A particular point of interest is the single oral high-dose intake proposed. This was done in an attempt to “optimally cover” the period of activity while limiting the total daily dose.
and decreasing the risk of hypotension by night. Another finding of this single observation is the synergic effect of daily walking exercise and Sildenafil on angiogenesis. In fact, walking induced vascular endothelial growth factor (VEGF) expression, and the concomitant administration of Sildenafil significantly and dose-dependently enhanced this effect. Previous studies have described the proangiogenic effect of Sildenafil in vitro, in cultured endothelial cells, and in vivo, at both capillary and
arteriolar levels in an experimental model of ischemia reperfusion.[9] Finally, we can hypothesize that Sildenafil has an acute effect on the pain caused by ischemia and in the long term, a synergistic effect on angiogenesis and tissue oxygenation as we were able to put in evidence by exercise-tcpO₂ on treadmill test.

6. Main lessons to learn

Sildenafil, a PDE5i, may represent a new therapeutic option in addition to the conventional optimal medical therapy in patients with arterial claudication. tcpO₂ measurement during exercise is a promising technique for the diagnosis and monitoring of patients with PAD. A crossover, double-blind, prospective, randomized, monocenter study (ARTERIOFIL-NCT02832570) and a double-blind, prospective, randomized, multicenter study (VALSTAR-NCT02930811) are ongoing to confirm our original observation.

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