Clinical Case Report

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Nonrevascularizable buttock claudication improved with Sildenafil

A case report

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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 ($tcpO_2$) 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. $tcpO_2$ 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, DROPmin = minimal DROP value, MWD = maximum walking distance, PAD = peripheral arterial disease, PDE5i = phosphodiesterase-5-inhibitor, QoL = quality of life, $tcpO_2$ = transcutaneous oxygen pressure, VEGF = vascular endothelial growth factor.

Keywords: angiogenesis, buttock claudication, exercise-$tcpO_2$, pain, peripheral arterial disease, Sildenafil, treadmill walking test

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Key Message: Sildenafil, a phosphodiesterase-5-inhibitor, may represent a new therapeutic option in addition to the conventional optimal medical therapy in patients with arterial claudication. Transcutaneaous oxygen pressure ($tcpO_2$) measurement during exercise is a promising technique for the diagnosis and monitoring of patients with peripheral arterial disease.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current case report.

LO: the investigator–coordinator of a crossover, double-blind, prospective, randomized, monocenter study (ARTERIOFIL-NCT02832570) and a double-blind, prospective, randomized, multicenter study (VALSTAR-NCT02930811), contributed to the management of the patient, treatment strategy including the original aspect of using Sildenafil, literature search, data collection, data analysis, data interpretation, figures, and writing the report. AC contributed to patient care and writing of the report. SH contributed to patient care. PA contributed to patient care, data collection, data analysis, data interpretation, and writing the report.

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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 ($tcpO_2$) measurement during exercise was performed to argue for the vascular origin of the walking impairment. During exercise-$tcpO_2$, chest $tcpO_2$-change is subtracted from limb $tcpO_2$-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. The treadmill test is performed using a constant load procedure (10% slope and 3.2 km/h speed) up to 15 min and an incremental load thereafter according to the Bruce Protocol.[1]

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, $tcpO_2$ 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, antiplatelet, angiotensin converting enzyme [ACE] inhibitor) and advice to walk, a 5-week supervised rehabilitation did not significantly increase the walking capacity. Exercise-$tcpO_2$ after the training was not improved, and MWD was 223 m (the test was stopped because of buttocks pain and proximal ischemia). A new test performed in 2009 showed isolated proximal ischemia, an MWD of 91 m and buttock and back pain. Ultrasound confirmed the normal permeability of the bypass with no significant stenosis in the lower limbs arteries. The ankle brachial index (ABI) was 0.99 in the right side and 0.93 in the left side. Postexercise ABI was normal. The patient divorced, was depressed and reported severe quality of life (QoL) impairment. In 2010, attempt to treat the patient with Cilostazol (phosphodiesterase-3-inhibitor) had to be stopped because of side effects (headache and nausea). A new walking test showed no improvement (MWD: 56 m, and isolated bilateral proximal ischemia).

3. Interventions

Mid February 2015, a new $tcpO_2$ 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 2 h after the first oral intake and stopped at 310 m for thigh fatigability but without the usual buttock 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).

Attempt to reduce by half the daily dosage of Sildenafil, during April 2015, resulted in a decrease of MWD at 399 m and reappearance of buttock pain. Thereafter, the daily dose was increased back to 100 mg/d. One week later MWD was 883 m. Here, it must be noted that our treadmill procedure is no longer a constant load test after 900 s (800 m at 3.2 km/h) but changes to an incremental load.[1] The patient felt better, most of his depression treatment was stopped. MWD were 1102 and 1209 m in November and December 2015 (Fig. 1, panel 3), respectively. In early February 2016, MWD progressed to 1253 m despite slight buttock discomfort (Fig. 1, panel 4). DROP stabilized to approximately −25 mm Hg on both buttocks throughout the constant load phase of the walking test, and further decreased only at peak exercise (7.3 km/h and 16% grade). Finally, after about 2 years of treatment, in January 2017, the MWD stabilized to 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 (Fig. 1, panel 5).

4. Outcomes

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

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,[2] and is frequently under-reported by the patients.[2] Differential diagnoses for proximal claudication include hip arthritis and lumbar spine stenosis. Exercise-$tcpO_2$ 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.[3] As expected from the patent aorto-bi-femoral bypass, calf $tcpO_2$, 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[4] on the diagnosis and treatment of PAD including antiplatelet, 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[5] 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[6] and through spinal adenosine A1, A2A, A2B, and A3 receptors.[7] 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

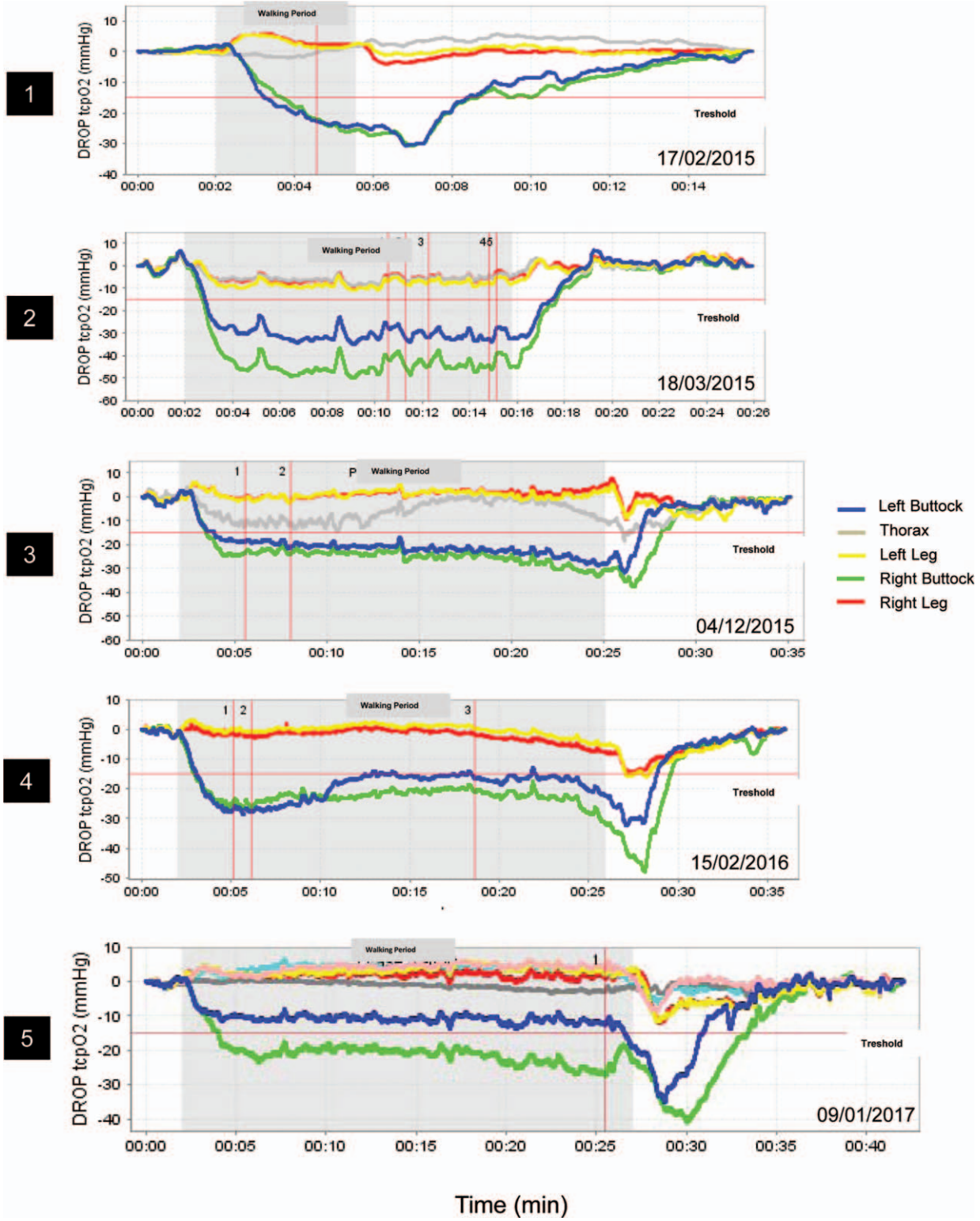

Figure 1. Typical example of exercise-tcpO_2 recording showing bilateral proximal but no distal ischemia during the walking period, before (February 2015; panel 1), after 1 month treatment (March 2015; panel 2), then after 10 months treatment (December 2015; panel 3), follow by 1 year treatment (February 2016; panel 4), and finally after 2 years treatment (January 2017; panel 4) with Sildenafil 100 mg/d. Note that from minute 15, speed and slope of the treadmill are progressively increased.

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.[8] Previous studies have described the proangiogenic effect of Sildenafil in vitro, in cultured endothelial cells, and in vivo, at both capillary and

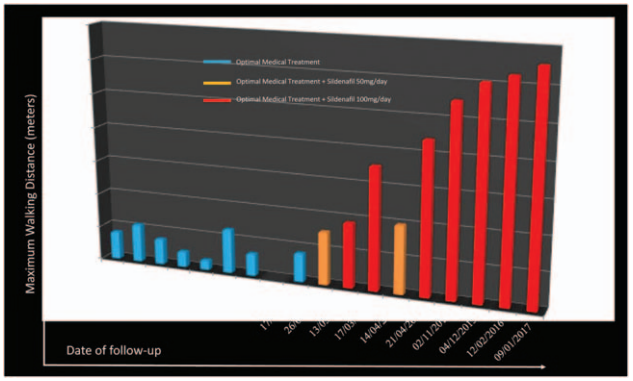

Figure 2. Evolution of the walking capacity on treadmill as maximal distance, before (blue squares) or after (orange and red squares) the introduction of Sildenafil during the follow-up period (2003–2017).

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-tcpO_2 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. tcpO_2 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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