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Sildenafil as a Therapeutic Option for Digital Ischemic Ulceration: Case Report

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Abstract

Unilateral Raynaud's phenomenon is a rare clinical condition caused predominantly by a thoracic outlet syndrome and characterized by significant morbidity that can lead to digital ulceration associated sometimes with deep tissue necrosis, gangrene and amputation. Recent studies showed the beneficial effect of PDE-V-inhibitor sildenafil in Raynaud's phenomenon and limb ischemia of improved microcirculation. We report for the first time, a case where oral sildenafil permitted amputation avoidance in a woman presenting severe acute digital ischemia caused by a 'cervical rib'. Therefore, therapy of ischemia with sildenafil could be an effective treatment option in patients not responding to classical drugs.

Keywords: sildenafil, unilateral Raynaud's phenomenon, digital necrosis, thoracic outlet syndrome, cervical rib

Introduction

Unilateral Raynaud's phenomenon is a rare clinical condition caused most of the time by a thoracic outlet syndrome. Vascular complications of this syndrome arise as a result of the intermittent but long-term compression of the subclavian artery by cervical rib, cartilage or fibrous band. They can lead to digital ulceration, necrosis and even amputation for the worst cases (1, 2).

We report a case of unilateral Raynaud's phenomenon secondary to cervical rib in which distal thromboembolism occurred. Due to the major vascular limitation, it was proposed to amputate the mid-forearm. Parallel, the patient saw a German television show where Viagra® was used for ulcerations of the digits in cases of scleroderma, and asked her doctors if this might be an option.

Case Description

We present the case of a 37-year-old woman who developed critical upper limb ischemia for whom we introduced sildenafil (Viagra®, Pfizer AG), a PDE-V-inhibitor, to avoid amputation of the lower forearm. In August 2001, she was admitted to the Emergency Unit (University Hospital of Lausanne) complaining of increasing pain in the right forearm and frigid hand extremity. Her past medical history included a non-treated Raynaud's phenomenon of the right hand diagnosed 5 months before with multiple associated risk factors including heavy smoking (46 pack-year), oral contraception (over 20 years), manual labor as a waitress and the cold climate of Switzerland.

Initially, the angiography showed occlusions of the radial and ulnar arteries at the level of the distal third of the right forearm (Figure 1A). The patient was therefore diagnosed with stage IV acute ischemia with no specific etiology. Therapeutic heparin anticoagulation (Liquemine®, Drossapharm AG; 20,000 U/24h) was introduced as well as i.v. nitroglycerine, and sub-cutaneous morphine for pain management. Since there was no improvement of symptoms, thrombolytic therapy with urokinase (Pharma Consulting AG; 40,000 U/h) was introduced but failed. The clinical situation deteriorated with the appearance of small necrotic lesions on the thumb and index finger of the right hand. Therefore, a treatment with Iloprost (Ilomedin®, Bayer AG; 0.5 slowly increased to 2 µg/kg/min) was begun but tissue necrosis kept advancing. The decision was taken to perform a bypass between the brachial and the interosseous arteries with interposition of a reversed great saphenous vein graft. Initially, clinical features improved but a few days later, an extensive thrombosis of the whole arterial network, including the bypass and the brachial artery developed. Given the dramatic

evolution, a neuro-stimulator was implanted with the aim to diminish pain and allow vasodilatation of upper-limb capillary network. Slight clinical improvement evolved and the patient could leave the hospital but with full therapeutic anticoagulation with acenocoumarol (Sintrom®, Novartis AG) and heavy dose morphine. Despite the remaining critical ischemia, the situation remained stable during a few months. However, during winter, clinical deterioration occurred with extensive necrosis of the distal phalanx of the right thumb and index finger, which were complicated with local infection.

Consequently, amputation of partial distal phalanx of right thumb and index was performed. Recovery was not easy since the amputation stumps had become necrotic, leaving the bony part of the proximal phalanx of the thumb and the intermediate phalanx of the index finger exposed. An amputation above the elbow was considered, a site where trans-cutaneous oxygen pressure was still compatible with wound healing. At this time, the patient asked to be treated with sildenafil after having seen a German television program about reimbursement polemic on Viagra® and his use as treatment in patients suffering scleroderma. Sadly, this treatment alternative was not considered as serious by most health professionals. A multi-disciplinary council took place, where angiologists and plastic surgeons stated for this option against others. The decision was then made to treat the patient with low dose Viagra® (25 mg, three times a day for six weeks) under strict medical supervision.

Vascular evaluation pre- and post-sildenafil treatment was conducted. The plethysmographic pressures of the right hand were well below normal values (Table 1), as well as trans-cutaneous oxygen pressure (data not shown). Sildenafil was introduced gradually and was well tolerated without any undesirable effects. Clinical situation improved rapidly with a clear decrease in pain and heavy analgesic medication could also be completely withdrawn. One week after introducing sildenafil, granulation tissue appeared in the extremities and bleeding occurred when bandages were changed. One month later, the right thumb and index were nearly completely covered with granulation tissue (Figure 2A). Two months later, a Doppler ultrasound examination showed arterial collateral development between humeral and interosseous arteries at the proximal third of the forearm. The radial artery was only distally perfused collaterally from the interosseous artery and the ulnar artery was also perfused with a very weak flow (data not shown).

Because of the promising evolution, the decision was made to continue treatment for several months to allow collateral vascularization to develop and provide maximal cover before the cold winter months. Eventually, sildenafil treatment was reduced and stopped (total of 6 months) and no complications were observed during or after treatment. Functional limitation

of the metacarpophalangeal and interphalangeal joints continued until the end of the treatment and severe bone-muscle atrophy was also the consequence of the ischemia. Even though oral anticoagulant therapy with acenocoumarol (INR target of 2-3) was continued, another episode of arterial thrombosis occurred. Vascular imaging follow-up showed thrombosis of the right subclavian artery and truncus brachiocephalicus. CT scan portrayed a right cervical rib articulating with the first rib and compressing the subclavian artery (Figure 1B&C).

Unfortunately, this diagnosis was initially not given and the cervical rib was only found after a second thrombotic event 2 years following the first episode. Retrospectively, there was some evidence before that time that compression of the right subclavian artery was suspected upon Doppler ultrasound and the same malformation was noted after a vascular examination. Fortunately for our patient with relation to the chronic situation, she had already developed collateral arteries that provided a detour so the thrombosis had limited clinical effect. Overall, the cervical rib could explain both the unilateral Raynaud's phenomenon, diagnosed a few months earlier, as well as the unsuccessful outcome of the vascular by-pass performed after the first vascular occlusion. The effect of anticoagulation medication in this case was negligible and despite its administration from the very beginning, the clinical situation continued to decline. Furthermore, the anticoagulation was stopped later considering the thrombosis was a consequence of a mechanical problem. Still today, our patient has not been operated for the problem of cervical rib, since she has been without vascular symptoms for more than 12 years.

Discussion

Sildenafil seems to have important effects in peripheral ischemia, particularly for the upper limb. Until now, Sildenafil has mainly been used for erectile dysfunction and pulmonary hypertension (3, 4). Recently, there have been promising reports of other uses for sildenafil, such as peripheral ischemia as well as primary and secondary Raynaud's phenomenon, but findings are still in preliminary stages (5, 6).

Sildenafil activates the nitric oxide (NO)/protein kinase G (PKG) pathway, which has an important role in vascular tone regulation and an important role in neovascularization especially favouring arteriogenesis. Moreover, it is regarded as a powerful vasodilator in ischemia (5, 7).

In addition, different studies have shown a beneficial effect of sildenafil in the treatment of peripheral vascular problems. Roland Fries *et al.* (2005) showed that sildenafil significantly

increased microcirculation and diminished symptoms in patients with Raynaud's phenomenon resistant to classical vasodilator treatments. The study showed that after administration of 50 mg of sildenafil for 4 weeks, the flow velocity increased by more than 400% (8).

Different cases of treatment with sildenafil in patients with digital ulcers due to scleroderma are reported, as in the article by Friedrichson *et al*. (2008), which showed that after 5 weeks of treatment with 75 mg of Sildenafil, digital ulcers disappeared (9).

In the present paper, we report the first case where sildenafil has led to a rapid improvement of symptoms of acute ischemia, including pain, wound healing and amputation avoidance, caused by a malformation of the subclavian artery. The improvements began already from the 7th day of treatment with sildenafil which was the time needed for the development of effective angiogenesis revascularization of the ischemic limb as shown in experimental works (5).

Unfortunately, description of treatment of ischemic limb by sildenafil is lacking. Retrospectively, we believe that treatment could probably have been stopped sooner because of improvement related to the development of an effective angiogenesis and as soon as the value of tissue oxygen pressure was stabilized. The long-term monitoring confirms our hypothesis, since 12-year follow-up for the vascular parameters remain stable and identical to that found at the discontinuation of the sildenafil treatment.

The upper limb of this patient was saved but due to late introduction of sildenafil and therefore prolonged ischemia, a functional limitation of the metacarpophalangeal and interphalangeal joints persists and has not improved for the last 12 years. The patient is unable to work and therefore has ever since been on welfare and following professional reinsertion programs without success.

Conclusion

In conclusion, acute ischemia of the superior limb is a rare and dramatic complication of a cervical rib. Our clinical case would show that through its effect on angiogenesis, sildenafil was responsible for saving the limb of our patient from amputation and also responsible to avoid surgical intervention for resection of the cervical rib. Importantly, no side effects of sildenafil were detected. This case shows the important role of sildenafil in the treatment of ischemic extremities that often happens in vascular diseases, diabetes, and arthritis. Due to sildenafil's value in possible amputation avoidance, further work is merited to clarify mechanisms and modalities of treatment. With television emissions specializing in medical topics, the public can actively participate in their treatment regimens. This scenario happened

recently when a patient with a degrading metal hip prosthesis had cobalt poisoning and saw a similar situation in the TV series with Dr. House (10). Importantly, the open discussion with patients can sometimes be profitable.

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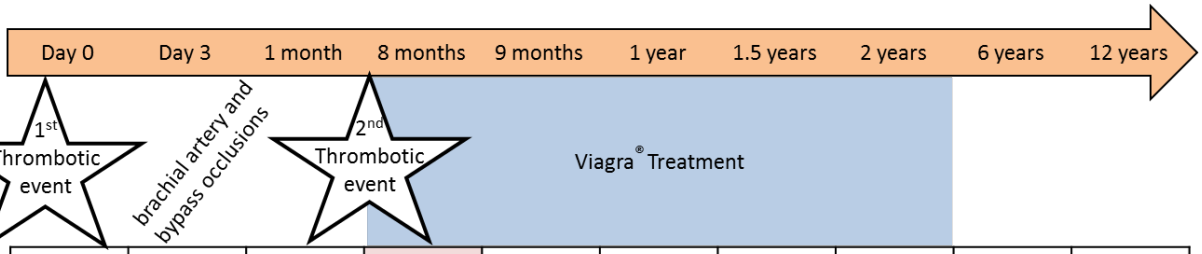
Table 1: Patient Vascular Data.



Right brachial AT*	130/80	110/70	#	Not measured (unbearable pain)	70[a]	80[a]	80[a]	80[a]	88/65	80/63
Right index finger	55	60	#		30	45	80	60	86	50
Right thumb	#	#	#		Not measured /Thumb wounded				66	45
Left brachial AT**	130/80	130/75	130/70	105/71	120/72	115/70	119 [b]	125/77	107/67	100/63
Left index finger	140	normal	normal	n.d.	105	100	125	115	102	105

[a] systolic; interosseous a.;[b] systolic; # Undetectable; n.d. not done due to unbearable pain; (; **): After brachial artery occlusion, the artery tension is measured at the interosseous artery level, using an echo-Doppler.*

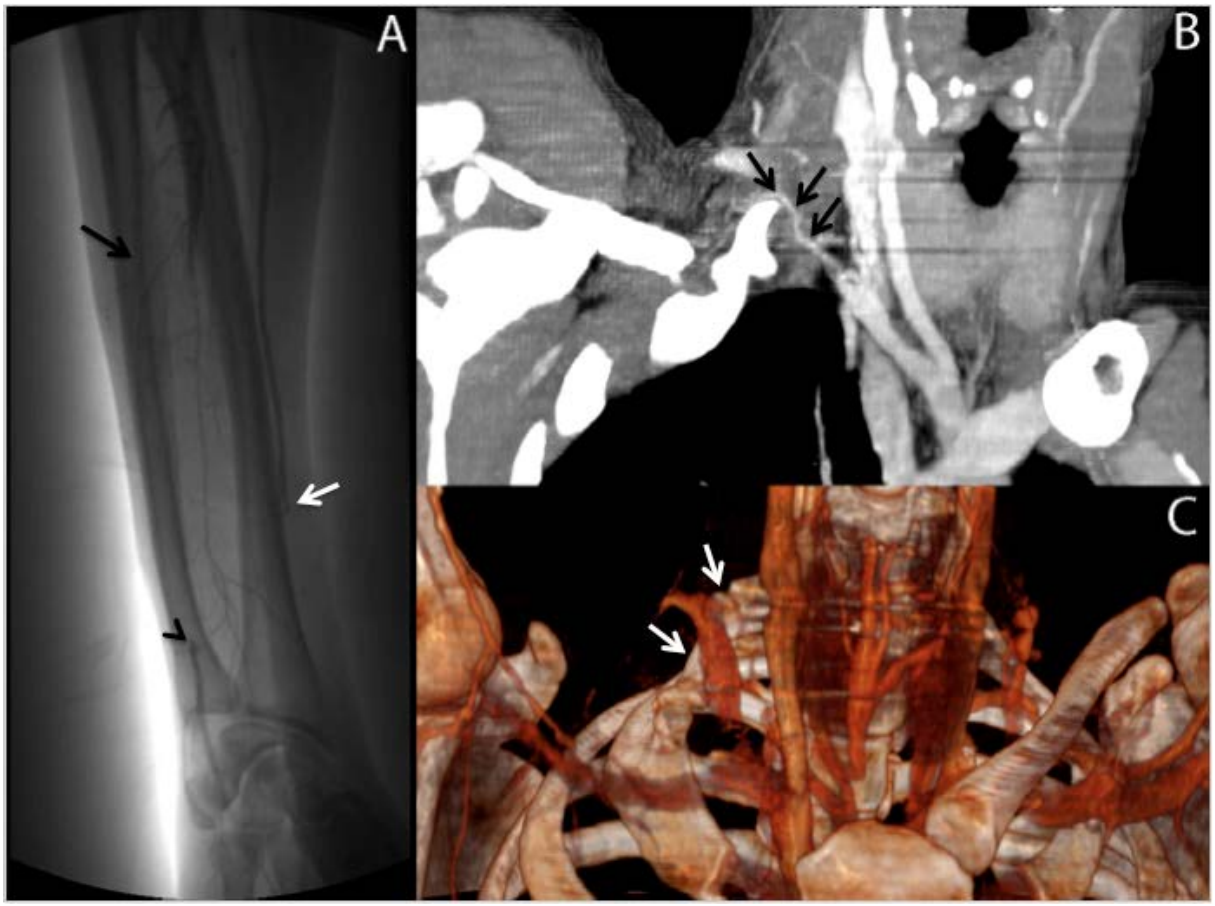


Figure 1.

Radiologic studies A. Angiographic study of the vasculature of the right forearm, executed in August 2001 when the patient was first admitted to the hospital. Radial artery is occluded at the distal third (white arrow). The proximal two third of the ulnar artery is occluded (black arrow) and only little vascularized by small collateral arteries from the interosseous artery permitting a slight a reprise of the ulnar artery at the carpal portion third (black triangle). **B.** 2D reconstruction of a CT-scan done in 2003 showing a thrombosis of the subclavian artery (black arrows). **C.** 3D reconstruction from the same CT scan showing the right cervical rib (white arrows) in with relation to the vasculature.

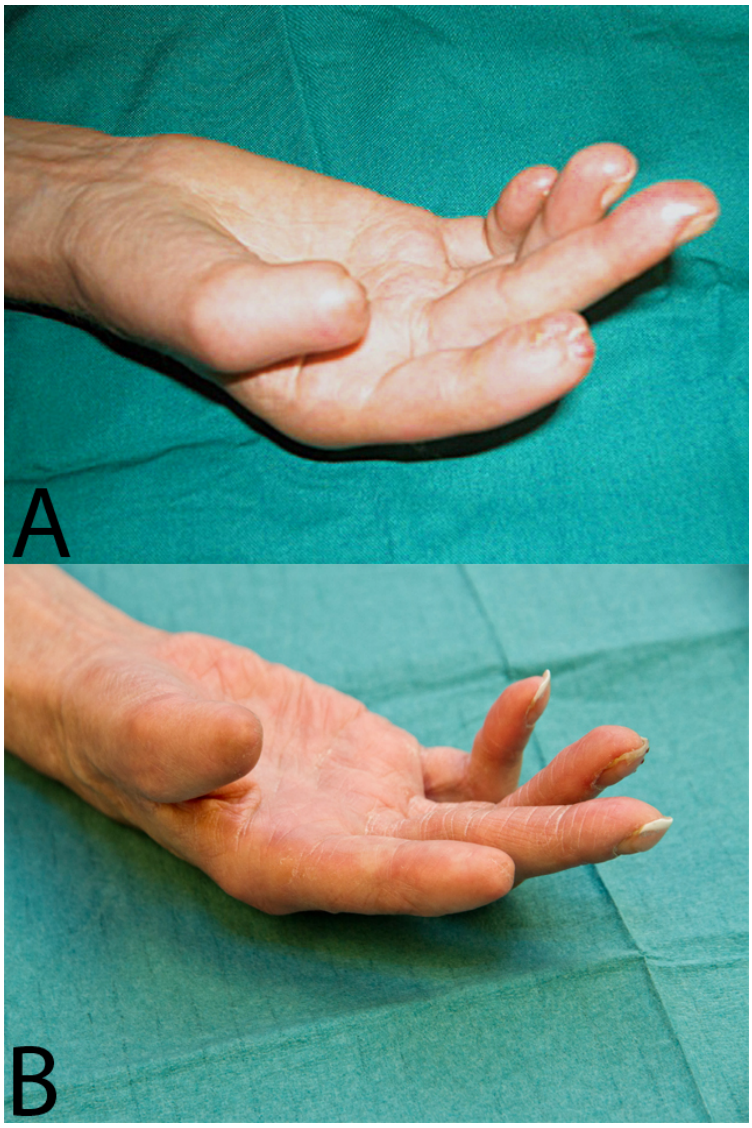


Figure 2.

Topical aspect of the hand. A. One month after introducing sildenafil, the right thumb and index were nearly completely covered with granulation tissue. **B.** Twelve years later.