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The FlowOx device for the treatment of peripheral artery disease: current status and future prospects

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1. *Introduction*

In peripheral artery disease (PAD), arterial blood flow to the extremities is impeded. Clinically, the severity of PAD ranges from asymptomatic disease to intermittent claudication or atypical extremity pain during exercise, and to critical limb ischemia characterized by rest-pain, tissue loss and gangrene. Patients with PAD have increased risk of cardiovascular morbidity and mortality, and the treatment strategy consists of cardiovascular risk modifying treatments, and treatment of leg symptoms. Exposure of the affected leg to cyclic pressure changes increases the macro- and micro circulatory blood flow and may be used for the treatment of PAD [1, 2]. The principles of this treatment have been described since the early 20th century, however, has more recently become a treatment option for selected patients, as a new treatment device has been developed [3, 4, 5].

FlowOx 2.0 is a CE-marked medical device designed to apply intermittent negative pressure (INP) to the extremity to improve arterial and skin blood flow. The foot and lower leg are treated in a pressure chamber made of hard Polyethylene Plastics (fig. 1). The foot arch rests on a positioner in the bottom of the pressure chamber, that is movable to adjust the lower leg's angle inside the pressure chamber. A padding between the pressure chamber and the lower leg becomes inflated when INP is started. The pressure chamber is sealed around the lower leg below the knee using a customized thermoplastic elastomer seal. A pump unit generates INP by removing air from and venting the pressure chamber in cycles of 10 s of -40 mmHg negative pressure and 7 s of atmospheric pressure. The FlowOx device is made of lightweight components (control unit 3 kg, pressure chamber 2.5 kg) making the system mobile, and can easily be operated by most patients at home. The physiological, clinical, and health-economic implications of FlowOx treatment have been investigated in multiple studies (table 1).

2. *Circulatory effects*

INP causes an increase in arterial and skin blood flow when applied to the lower leg [1, 2, 6]. However, if constant negative pressure is applied, there is an initial increase, followed by a decrease in arterial and skin blood flow [6]. The reduced arterial flow during constant negative pressure is caused by a veno-arterial reflex response, causing vasoconstriction of the arterioles when the veins become distended. Physiologically, the veno-arterial reflex counteracts hemodynamic changes when moving from a supine to a standing position, limits the rise in hydrostatic pressure and prevents edema. By applying INP, the effect of the veno-arterial reflex is avoided.

Because of the different mechanical properties of the arteries and the veins, exposure of the leg to INP have different impact on the arterial and venous side of the capillary bed. The negative pressure phase of the INP cycle has a small effect on the arterial pressure, but causes a drop in venous pressure in the exposed extremity, similar to the level of the negative pressure applied [7]. This causes an increase in the arteriovenous pressure difference, promoting increased arterial flow.

Increased arterial flow increases the share stress on the endothelium of the arterial wall, leading to a local release of vaso-active substances causing vasodilation. The fluctuations in share stress patterns generated by INP improves flow-mediated dilation, which explain the hyperemia that is observed after the INP session has ended [1, 8]. In patients with PAD, normal fluctuations in arterial flow are reduced, which leads to less stimulation of the endothelial cells and deterioration of normal endothelial activities. It is likely that the repetitive fluctuation in arterial flow caused by INP is favorable for patients with PAD, as it mimics the vasomotion observed in healthy subjects.

3. *Clinical implications*

Several studies of INP treatment for patients with PAD have suggested positive effects on leg pain, walking capacity and wound healing [3, 5, 7, 9, 10]. However, more recently, two randomized controlled trials did not find additional effects of INP treatment in patients with intermittent claudication, hence the effect of INP treatment in patients with PAD has been debated [11, 12]. There are large differences in treatment frequency, length of INP cycles, and the levels of INP applied among the previous studies. Common for most of the studies was that the application of INP was based on in-hospital treatment, because the treatment devices were immobile or too difficult for the patients to handle. Hence, the treatment duration and frequencies in most previous studies were rather low.

In a recent randomized controlled trial of 72 patients with intermittent claudication, we showed that treatment with FlowOx one hour twice daily for 12 weeks increased pain-free walking distance compared with sham treatment [13]. For the patients with the most symptomatic disease there was an increase in both pain-free and maximal walking distance. This was the first double blind, randomized sham-controlled trial to show that INP treatment increases walking capacity in patients with intermittent claudication, and the first randomized controlled trial that documented clinical effects of FlowOx treatment. In patients with intermittent claudication, cardiovascular prevention and exercise therapy are the first-line treatment. Participation in supervised exercise therapy (SET) programs have positive effects on leg symptoms, general health, and cardiovascular risk. However, the use of SET in the management of patients with intermittent claudication is limited by low accessibility and poor compliance. A systematic review from 2016 concluded that only one third of the patients with PAD were suitable for and willing to undertake SET [14]. Hence, treatment with FlowOx might be a

relevant adjunct to standard care for patients with intermittent claudication. Especially for patients with disabling claudication and high risk of complications from endovascular or open surgical treatment, FlowOx treatment seems to be a reasonable alternative.

For patients with critical limb ischemia, early endovascular or open surgical revascularization is the cornerstone treatment. However, revascularization is dependent on the severity and extent of the disease, patient comorbidities, and the risk of procedural related complications. For patients with critical limb ischemia not amenable for revascularization, amputation has been the only option. In a case study of four patients with critical limb ischemia, FlowOx treatment one hour, twice daily for eight weeks had beneficial effect on wound healing [10]. Based on promising results, a pilot trial investigating the effects of FlowOx treatment in patients with non-option critical limb ischemia was initiated (Ref: ISRCTN51433523). However, patients with critical limb ischemia are often severely comorbid with a one-year mortality of 25% [15]. Hence, a proper sample size of patients with non-option critical limb ischemia treated with FlowOx over weeks, turned out to be very difficult to achieve. As a very low number of patients were treated according to protocol before the trial was terminated, no clear conclusions on the treatment effect could be drawn from that trial. Unpublished feedback from early market introduction (n=99 patients) in the UK, Germany and Scandinavia indicate that FlowOx treatment could reduce pain and improve wound healing in more than 50% of the treated patients with critical limb ischemia (Iacob Mathiesen, CSO, Otivio AS, unpublished observations).

4. Safety

Patients with PAD are at risk of developing wounds and often have a delayed or impaired wound healing process. The areas of the lower leg and foot that are in contact with the pressure chamber during FlowOx treatment, could theoretically be at risk of tissue damage. As part of the safety

assessment, pressure measurements at contact points between the leg and the pressure chamber were performed during INP, concluding that the skin areas were not exposed to pressures, neither level nor duration, that impose a risk to PAD patients. The pressure levels were lower than those imposed by other interventions or treatments for PAD, diabetes, or critical limb ischemia (Dr. Daniel Parker, University of Salford, Manchester, UK, unpublished report).

Measurements of the effects of FlowOx treatment on the central circulation indicates a physiologically insignificant effect on mean arterial pressure during INP treatment [1, 2]. This is important as a large proportion of the patients with PAD have concomitant coronary or cerebrovascular disease and may be sensitive to rapid systemic circulatory changes.

During the clinical studies on FlowOx 2.0, no serious adverse events were reported, indicating that FlowOx treatment is safe for patients with PAD.

5. Conclusion

FlowOx treatment increases walking capacity and may be a useful adjunct to standard care for patients with disabling intermittent claudication. Whether the beneficial effects observed in patients with intermittent claudication are generalizable to patients with more severe stages of PAD should be investigated in a larger trial, however, observational data indicate a positive effect in selected patients with critical limb ischemia not amenable for revascularization. Treatment with FlowOx seems safe for patients with PAD and has few side effects. The system offers a new tool for the treatment of PAD, it enables patients to treat themselves at home.

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Declaration of Interest

H Hoel is employed by Otivio AS with funding from The Research Council of Norway. Otivio AS has the commercial rights to the INP technology discussed in this paper. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Table 1. Completed studies of the physiological, clinical, and health-economic implications of FlowOx.

AUTHOR	N	STUDY DESIGN	STUDY POPULATION	MAIN CONCLUSION
Sundby et. al. 2016 [6]	23	Experimental	Healthy subjects	INP of – 40 mmHg induced rhythmical fluctuations in blood flow and increased both arterial blood flow velocity and skin blood flow.
Sundby et. al. 2016 [10]	4	Case report	Peripheral artery disease	INP treatment should be investigated further as a potential non-invasive treatment option for patients with peripheral arterial disease and hard-to-heal leg ulcers.
Sundby et. al. 2017 [1]	20	Experimental	Peripheral artery disease	INP increases foot macro- and microcirculatory flow pulsatility. Application of INP resulted in increased mean arterial blood flow velocity.
Sundby et. al. 2018 [16]	24	Experimental	Spinal cord injured	INP induced an increase in arterial blood flow in the foot, followed by a decrease. This fluctuation was observed following the onset of negative pressure, without any significant changes in heart rate or mean arterial pressure.
Sundby et. al. 2018 [17]	9	Clinical crossover pilot	Spinal cord injury and chronic lower limb ulcers	INP can be used as a home-based treatment for patients with SCI and chronic lower limb ulcers. Its efficacy should be tested in an adequately sized, randomized clinical trial.
Holder et. al. 2019 [8]	15	Experimental	Healthy subjects	INP induce fluctuations in blood flow and shear rate that improve endothelial function. This may represent a hemodynamic stimulus that improve vascular health.
Hoel et. al. 2019 [2]	16	Experimental	Peripheral artery disease	INP of -40 and -60 mmHg applied in cycles of 10 sec of negative pressure and 7 sec of atmospheric pressure induced acute increase in arterial and skin blood flow.
Hoel et. al. 2020 [13]	72	RCT	Peripheral artery disease and intermittent claudication	Treatment with -40 mmHg INP for one hour twice daily for 12 weeks increased PWD compared with sham treatment. For patients with baseline PWD < 200 m, treatment with -40 mmHg INP increased both PWD and MWD compared with sham treatment.

Ezeofor et. al. 2021 [18]	62	Health-economic study	Peripheral artery disease	FlowOx therapy delivered as a single annual dose may be a cost-effective treatment for peripheral artery disease. It improved health outcomes and reduced treatment costs in this modelled cohort.
Hoel et. al. submitted 2021	72	RCT	Peripheral artery disease and intermittent claudication	A significantly proportion of the patients had a reduction in vWF, and the concentration of vWF was significantly reduced after treatment with -40 mmHg INP for one hour twice daily for 12 weeks. This may indicate a beneficial effect on endothelial activation and endothelial injury.
Hoel et al. submitted 2021	10	Clinical follow-up trial	Peripheral artery disease and intermittent claudication	Both PWD and MWD improved after treatment with – 40 mmHg INP for one hour twice daily for 24 weeks, compared with baseline. The main improvement in PWD occurred during the first 12 weeks of treatment, whereas the main improvement in MWD occurred between 12 and 24 weeks of treatment.

INP intermittent negative pressure; SCI spinal cord injury; RCT randomized controlled trial;

PWD pain free walking distance; MWD maximal walking distance; vWF von Willebrand factor.

Figure 1. The FlowOx device for lower extremity intermittent negative pressure treatment. Intermittent negative pressure is generated in a pressure chamber sealed around the patient's lower leg by a pump unit that is removing air from and venting the pressure chamber. Source: Otivio AS/Bastian Fjeld.