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A Quick Fix for Better Walking? That's Probably a Bit of a Stretch

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Management of patients with symptomatic lower-extremity peripheral artery disease (PAD) remains challenging. There are limited evidence-based options that provide significant functional improvement. There are only two US Food and Drug Administration-approved medications for the indication of claudication in PAD: cilostazol and pentoxifylline. Cilostazol offers only modest improvement in PAD-associated walking impairment and is not well-tolerated by patients because of its adverse effect profile. Furthermore, the most recent US as well as European PAD management guidelines do not recommend the use of pentoxifylline because of lack of evidence for efficacy [1,2]. Supervised exercise therapy (SET) has been shown to improve claudication symptoms and walking in multiple randomized controlled trials [3]. More recently, the CLEVER trial demonstrated that SET provides durable improvement in functional status and in quality of life for up to 18 months when compared to stent revascularization [4]. Therefore, the Centers for Medicare and Medicaid Services issued a memorandum on May 25, 2017, to establish coverage for SET in PAD patients with claudication. Recent randomized clinical trials have also demonstrated benefits from (non-supervised) home-based walking programs [5,6]. Despite clear benefits, compliance remains very poor with exercise programs, especially in elderly patients. SET is not widely available, and when available, there are barriers of affordability, accessibility, and transportation. In a recent review of more than 1500 patients with stable symptomatic PAD by Harwood *et al.*, 50% showed no interest and refused participation in SET, and an additional 19% reported that attending SET is too inconvenient [7]. Thus, approximately 70% of patients declined SET, even when it was available at no cost to them. Elderly patients are also more likely to have limited mobility due to other comorbidities, such as arthritis, coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease, affecting their exercise capacity. Thus, obviously, more options are needed for PAD patients suffering from intermittent claudication.

In the current issue of *Cardiovascular Revascularization Medicine*, Hotta *et al.* present a prospective randomized non-blinded crossover study assessing the effect of passive muscle stretching on popliteal artery dilatation and walking function among 13 elderly patients (age 60-85) with stable PAD [8]. Passive stretching of calf muscles (soleus and gastrocnemius) was achieved by an ankle dorsiflexion brace applied for 30 minutes every day for 5 days per week for a total of 4 weeks. Patients were randomized into 4 weeks of passive stretching or 4 weeks of no stretching and then crossed over to the other intervention. The authors measured endothelium-dependent flow-mediated dilatation (FMD) and endothelium-independent nitroglycerine-induced dilatation (NID) of the popliteal artery. They also measured symptom-free, continuous, and total walking distance on a 6-minute walk test (6MWT). The authors reported that passive stretching is associated with significant improvements in FMD as well as continuous and total walking distance on the 6MWT but did not affect the NID. Another interesting finding is the modest sustenance of improvement at 4 weeks in muscle function as tested by 6MWT but cessation of improvement of endothelial function as tested by FMD. After 4 weeks of washout period, muscle function as tested by the 6MWT was sustained, even after any improvement in FMD had disappeared.

The results are intriguing, but the study is not without limitations. A sham brace to keep the ankle in a neutral position as a control could have enabled blinding of patients to minimize a possible placebo effect, which may have also allowed the blinding of clinicians performing the 6MWT to reduce observer bias. A larger sample size may have helped in detecting the effect size and would have increased the robustness of these findings.

The authors hypothesized that the primary mechanism for improvements in continuous and total walking distance is from the improvement in FMD (from stretching) leading to an increase in calf muscle blood flow during exercise. However, it has been shown that stretching

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improves range of motion as well as muscle strength [9,10], and it is possible that the improvement in walking from stretching could have improved FMD instead of the authors' suggestion of FMD-related walking improvement. As the authors mentioned, it is unknown whether endothelial dysfunction is the primary contributor to the functional limitation seen in PAD. The Cardiovascular Health Study [11] and the Multi-Ethnic Study of Atherosclerosis [12] have suggested the role of FMD in predicting adverse cardiovascular events. Therefore, this hypothesized mechanism requires further testing, especially if there is potential to elucidate novel therapies for these patients.

Nonetheless, these findings are noteworthy for their potential future implications in the treatment of stable symptomatic PAD patients, especially if confirmed by randomized controlled trials. Having said that, and without taking away from the need to find ways to tailor treatment to patient needs, passive stretching may have another limitation. This limitation may have to do with compliance. In a study of 50 patients prescribed an arm abduction brace post-surgery, Grubhofer *et al.* showed that about half of the patients did not use the brace for at least 80% of the recommended time [13]. They also showed that self-reported patient compliance with a brace was unreliable when compared to a temperature-sensitive sensor in the brace.

In summary, these findings are promising. While the current study has limitations, stretching could become a safe, and cheap, modality in improving quality of life in stable PAD patients. Hopefully, a prescription of a brace to keep the ankle at 15-degree dorsiflexion for 30 minutes every day for 5 days every week (which can be implemented at home) may have better tolerance and hence may have better compliance in elderly patients with symptomatic PAD than SET currently has.

Conflicts of interest

The authors report no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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