Reviewer's report

Title: Acute oxygenation changes on ischemic foot of a novel intermittent pneumatic compression device and of an existing sequential device in severe peripheral arterial disease.

Version: 2 
Date: 23 January 2014

Reviewer: Bruno Roseguini

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Major comments:

Manfredini and co-workers sought to contrast and compare the effects of two IPC devices on leg blood flow, foot oxygenation and patient compliance in individuals with critical limb ischemia. A recently developed device that compresses the thigh progressively over 20 s (Gradient Pump) is compared to the ArtAssit pump, that applies intermittent, rapid compressions to the foot and calf (4 s inflation/16 s deflation). The authors report that the GP device was more effective in improving leg venous blood flow and foot oxygenation than the ArtAssit pump. Further, GP obtained a higher score of patient compliance.

The authors must be commended for studying such an important and clinically relevant subject. Most therapeutic approaches for PAD have unsatisfactory cost-effectiveness and are not accessible to the vast majority of patients. As IPC therapy has the potential to be used in the home setting without direct medical supervision, this novel approach is beginning to gain acceptance as a potential therapeutic aid in the treatment of patients with PAD. The optimization of these devices to improve the clinical effect and increase patient’s adherence is therefore highly desirable.

The manuscript is well written and easy to follow and the methods chosen to evaluate the outcomes are appropriate. I do have, however, a number of concerns regarding the study design and interpretation of the results.

1) Body position: The authors choose to determine the effects of IPC pumps with the patients in the supine position. This choice is critical not only for the interpretation of the results but especially for the potential of these findings from this study to be translated to the clinical setting. The vast majority of clinical studies with IPC, including those that employed thigh compression cuffs (Delis Kt et al. Surgery 129(2):188–195, 2001) have been conducted with the patients in the sitting position. The rationale for this choice is well known for at least 20 years: the magnitude of changes in arterial-venous pressure difference during IPC application is far greater with the limb in a dependent position. In fact, Dr. Paul van Bemmelen showed us nearly 20 years ago that IPC devices do not evoke meaningful hemodynamic changes when the pump is applied with the subject laying supine (van Bemmlen et al. J Vas Surg 19(6):1052-1058, 1994).
The authors argue that they chose to apply the pump in the supine position so the device could be used in patients restricted to bed. Were any of the patients included in the study in this condition (i.e. restricted to bed)? If not, then the study should be performed in a different clinical population. In my view, if the goal is for the pump to be used in patients with CLI that are able to sit, then the pump should be employed in the sitting position as to maximize the hemodynamic effects of the therapy. As highlighted above, patients in the available randomized clinical trials have been instructed to use the pumps while sitting. Whether the well-documented benefits of IPC applied in the sitting position hold true for long-term supine application, remains to be determined.

2) Blood flow changes: As stated by the authors in the introduction, the most salutary hemodynamic effects of IPC application are believed to be the repeated increases in arterial blood flow and wall shear-stress. Strategies that increase shear-stress typically lead to a number of beneficial adaptations in the vasculature, including improved conduit-artery vasodilatory capacity as well expansion of the collateral network (Laughlin et al. J Appl Physiol 2008;104(3):588-600). IPC application is known to provoke marked changes in blood flow and shear stress in healthy subjects (Sheldon et al. J Appl Physiol 2012;112(12):2099-109) as well as in patients with PAD (van Bemmlen et al. J Vas Surg 19(6):1052-1058, 1994). Foot and calf compression increase blood flow by two to threefold in the legs of patients with PAD (Delis Kt et al. J Vasc Surg. 2005 Oct;42(4):717-25). Typically, blood flow and shear stress are reduced during cuff inflation and markedly increased following cuff release (Sheldon et al. J Appl Physiol 2012;112(12):2099-109). Interestingly, the arterial blood flow changes during IPC application observed in the present study differ substantially from the aforementioned profile. First, blood flow does not increase during cuff deflation in both devices. Second, cuff inflation to pressures up to 120 mmHg did not seem to reduce blood flow. These observations likely stem from the fact that the pump was applied in the supine position and confirm the notion advanced by van Bemmelen and co-workers that the pump is not effective in the supine position.

Minor comments:

- Duration of application: It is unclear why the GP device was applied for 35 minutes while the ArtAssit was applied for two hours. As there are documented changes in the blood flow responses to IPC application over time (Sheldon et al. J Appl Physiol 2012;112(12):2099-109), it would be important to characterize the hemodynamic changes at similar time points for both devices.

- Foot oxygenation: According to the authors, one of the most important end-points in this study was the evaluation of changes in foot oxygenation. However, it is unclear to what extent foot oxygenation is impaired in the selected patients. Measurements of toe pressure or transcutaneous oximetry (TcPO2) would help to better define the severity of the disease and therefore the magnitude of improvements triggered by IPC application.

- NIRS measurements: Among the variables obtained during NIRS
measurements, deoxy-hemoglobin has been the variable of choice in most studies that employ this technology because this variable is not sensitive to changes in blood volume and can be used as a proxy for fractional oxygen extraction in the tissue. This variable was not reported in the present study.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests