Author's response to reviews

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.

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Version: 3
Date: 1 March 2014

Author's response to reviews: see over
#1

**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:** 26 December 2013
**Reviewer:** claude franceschi
**Reviewer's report:**
Interesting study which could ease the treatment of lower limbs arteropathy
**Level of interest:** An article of importance in its field
**Quality of written English:** Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report

**REPLY TO THE REVIEWER #1**
We thank the Reviewer for the comment. The manuscript has been changed according to the comments of the Reviewers #2-3-4.
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: 22 January 2014
Reviewer: Ryan D. Sheldon
Reviewer's report:
In their manuscript titled “Acute oxygenation changes on ischemic foot of a novel intermittent pneumatic compression device and of an existing sequential device in severe peripheral arterial disease”, Manfredini et al. examined the acute effects of two IPC devices on limb hemodynamics and distal tissue oxygenation in patients with peripheral arterial insufficiency. This manuscript addresses a potentially important topic in that few studies have sought to examine effects of other combinations of compression characteristics (i.e. location, frequency, pressure, etc.) of IPC devices beyond the traditional 3s inflation/17s deflation at 120mmHg foot + calf devices. Additionally, the reviewer applauds the authors for examining a considerably heterogeneous clinical population, albeit the sample size is relatively small, and for examining phasic differences (i.e. inflated versus deflated phases) in their outcome measures for each treatment. However, while there is merit for studies in this area, a major limitation in the experimental approach, as is detailed below, cannot be rectified without repeating the experiments. Additionally, I have outlined other issues that the authors may choose to address going forward.

Major Compulsory Revisions
1. The major thrust of this manuscript is to compare the novel “GP” device with the traditional “SFC” device. However, as the authors state in the limitations section, treatment was performed in the supine position. The authors correctly recognize in the introduction that a major factor in the effectiveness of IPC devices in improving limb hemodynamics is the augmentation of the A-V pressure gradient. IPC accomplishes this by overcoming hydrostatic pressure to assist in venous outflow, subsequently increasing arterial inflow. In the supine position, hydrostatic pressure is virtually non-existent and there is this little impedance of venous outflow for the SFC device to overcome. That SFC devices do not augment arterial inflow in the absence of a hydrostatic column was shown to be the case by Dr. Van Bemmelen 20 years ago (J Vasc Surg 1994;19:1052–8), and virtually all studies on IPC devices as well as clinical practice employ treatment with the patient in the seated position for this reason. Additionally, in contrast to the statement in the introduction that current devices “are less effective in improving foot perfusion of ischemic limbs”, two recent trials with large sample sizes reported rather remarkable clinical improvements in patients with critical limb ischemia using traditional IPC devices in the seated position (J Vasc Surg 2008;47:543-9, J Vasc Surg 2011; 54:440-7). Thus, the conflicting findings between the current manuscript and other studies in the literature with regards to the effects of SFC are likely due to the supine position of the subjects in the current manuscript. In order to accurately compare the effects of GP vs. SFC IPC treatments it is essential that studies be repeated with subjects in the seated position to give a true comparison of the clinical utility between these two devices.
2. Blood pressure data was not reported. It is essential for interpretation of the current results that blood pressure data from before, during, and after the treatment, especially since the compression pressure of the GP device was apparently varied based on subject blood pressure. Additionally, it is conceivable that the greater amount of tissue compressed and the proximal application of the GC device relative to the SFC device could evoke central responses by affecting total peripheral resistance. It would be useful to include calculations of leg vascular conductance before, during, and after treatment.

Minor Essential Revisions.
1. There is considerable baseline variability, particularly in figure 3 and table 3. Because during treatment values are expressed relative to baseline it makes interpretation difficult. This might be
expected in a clinical population such as this, however, what was inter-day variability in baseline measurements repeated on the same limbs? It may be of use to express the during treatment data as percent of baseline within each subject to control for inter-subject variability.

2. More information regarding the specifics of the GP device are needed. What is the size of the cuff? How proximal to the knee is it placed? The actual pressure used should be reported.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests

**REPLY TO THE REVIEWER #2**

We thank the Reviewer for the positive comments but we regret for the limited interest for a novel approach to IPC. We also understand the criticisms that will be discussed.

The inventors of the device aimed to create something conceptually different from the previous ones, on the basis that the augmentation of the A-V pressure gradient can be attained by different means. The main objective of the device was to obtain an increase in the foot perfusion in presence of severe peripheral disease, independently from existing comorbidities or position of the patients. The present study aims therefore to primarily describe the effects of the GP device. In order to evaluate the entity of these effects a comparison with the most effective device on the market was added.

**Major Compulsory Revisions**

1. **Supine position**

In our experimental setting the GP device is effective on foot perfusion both in the supine and in the sitting position. Patients able to sit undergoing experimental chronic compressive treatment with the GP device usually perform it while sitting (e.g. watching the TV).

However, in this study we opted for the supine position for different reasons:

i) It allows to evaluate the distal perfusion effect of the device independently from the hydrostatic forces that positively or negatively might affect both inflow and outflow, with a high inter-individual variability. Studies have documented that blood flow in the lower limbs decreases on assuming the erect position, sitting or standing. A significant decrease in popliteal artery systolic flow from the supine to the sitting and then to the standing position has been recently reported in patients with peripheral arterial disease, with a large intraindividual variability (5-74%) ([Anthonysamy D, Asian J Surg 2012, 35:131-135](#));

ii) It allows to minimize both the foot movements, to obtain a correct NIRS measurement;

iii) It allows to measure the foot muscle metabolism at rest during IPC treatment;

iv) It allows an easy echo Doppler evaluation of the femoral vein;

v) It allows to obtain a measurement possible for all patients, also for those who are unable to sit.

Moreover we are convinced that the study of the intermittent compression performed in a supine position is an acceptable approach, as demonstrated by other papers using or testing this technique in the supine position. Moreover, besides the respectable position of Dr. Van Bemmelen reported by the Reviewer ([now quoted, ref. # 34](#)), a different respectable point of view was reported some years later (“There appears to be physiological justification for investigating intermittent compression as a therapy for patients with intermittent claudication and rest pain in the supine position as well as seated”. [Morris R J, Woodcock JP. Effects of supine intermittent compression on arterial inflow to the lower limb. Arch Surg 2002 137:1269-1273, now quoted, ref. # 35](#)).

However we hypothesized that the hemodynamic measurements by Echo-color Doppler after SFC treatment, mostly tested by other Authors in the sitting situation, might be influenced by the position and for this reason we included a sentence in the Limitations section ([now modified in the manuscript to better explain the concept, P13-L1](#)).
A different problem is represented by the foot perfusion during IPC treatment. The issue of the foot oxygenation has been poorly studied. At the best of our knowledge no studies are comparable to the present one, therefore it is unclear which are the conflicting findings of other studies. Previous studies measured the skin blood flux or the TcPO$_2$ at the dorsum of the foot determining the partial pressure of oxygen at the skin surface and not the oxygen delivery at the site of the NIRS sensors to estimate tissue perfusion (with all the limitations of this technique to be considered). Moreover, a study with aims comparable to those of our study was performed by Ubbink et al., 2001 (ref. #20). The foot oxygenation was measured by TcPO$_2$ during IPC treatment performed by the same SFC device of our study, with patients in a sitting position. Despite this position a significant decrease of TcPO$_2$ during IPC treatment was observed (from 50.5 to 38.5 mmHg) with values, which remained lower after IPC (31 mmHg). The results are therefore comparable to our study even if patients were in a sitting position. The problem of foot perfusion with the SFC device is probably not simply related to the position of the patient under treatment. Ubbink et al. conclude that “The TcPO$_2$ reduction may be due to the pinching straps around the foot during IPC treatment” and we feel that it is a plausible hypothesis. Therefore we disagree with the necessity to modify the present study treating patients in a different position, being the aim of the study, as previously explained, to test patients in a supine position. However we agree that future studies by our group or by other researchers, with treatment performed in different positions and with an adequate sample size, will be necessary to confirm this preliminary observation (a sentence has been included in Conclusions and perspectives section P13-L22).

The sentence in the Background section related to the studies on the foot perfusion has been modified to improve the comprehension of the readers (P4-L7). The two references proposed by the Reviewer were already quoted (J Vasc Surg 2008;47:543-9, J Vasc Surg 2011; 54:440-7) (ref. #17, and ref. #18).

2. Blood pressure data/leg vascular conductance

Blood pressure data: The treatment was really set according to the blood pressure of the subject at the beginning of the treatment and then maintained constant. According to the inventors this is a crucial issue for the device. As requested, blood pressure values before and after treatment have been included in the text (Results section, P8-L17).

Leg vascular conductance: We understand the comment, however this small pilot study only aimed to measure a possible effect on foot oxygenation during acute treatment not to explore the mechanisms of action. This is an interesting hypothesis for future studies (a sentence was included in Limitations section, P13-L8, and also in Conclusions and perspectives section, P13-L25).

Minor Essential Revisions

1. We agree with the Reviewer. Inter-day variability in baseline measurements on the same limbs was not previously studied. This was included in the Limitations section, P13-L6.

We understand the comment in relation to the inter-subject variability. For this reason we decided to show the data of each subject during treatment (in this case only in relation to the tHb, being consistent with HbO$_2$).

We opted for the absolute change of the area under curve instead of the percentage change considering the high percentage variations during treatment in some subjects and being the results almost superimposable (as shown below). For this reason the figures have not been modified in the manuscript.

2. More detailed informations about the GP device have been added in the manuscript (Section Methods, P5-L8).
The original figures from the manuscript (left), and the modified one considering the percentage variations (right) are shown.
#3

**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

**Reviewer's report:**

**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 Bemmelen 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 as 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 Bemmelen 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

REPLY TO THE REVIEWER #3

We thank the Reviewer for the comments. We also understand the criticisms that we will discuss in the present replies.

1) Supine position
We understand the criticism of the Reviewer. However the inventors of the device aimed to create a tool able to increase the foot perfusion in presence of severe peripheral disease, independently from the existing comorbidities. Even if all the patients of our study were able to sit we all know that not all can sit, thus the device should work in any position and in any patient. In our experience the GP
device has the same effect in the supine as in the sitting position and patients (able to sit) undergoing experimental chronic compressive treatment with the GP device usually perform it while sitting (e.g. watching the TV).

However, in the present study we opted for the supine position for different reasons:

i. It allows to evaluate the pure hemodynamic effect of the device independently from the hydrostatic forces that positively or negatively might affect both inflow and outflow, with a high inter-individual variability. Studies have documented that blood flow in the lower limbs decreases on assuming the erect position, sitting or standing. A significant decrease in popliteal artery systolic flow from the supine to the sitting and then to the standing position has been recently reported in patients with peripheral arterial disease, with a large intraindividual variability (5-74%) (Anthonysamy D, Asian J Surg 2012, 35:131-5);

ii. It allows to minimize both the foot movements, to obtain a correct NIRS measurement;

iii. It allows to measure the foot muscle metabolism at rest during IPC treatment;

iv. It allows an easy Echo Doppler evaluation of the femoral vein;

v. It allows to obtain a measurement possible for all patients, also for those who are unable to sit.

Otherwise we are convinced that the study of the intermittent compression performed in a supine position is an acceptable approach, as demonstrated by other papers using or testing this technique in the supine position. Moreover, besides the respectable position of Dr. Van Bemmelen reported by the Reviewer (now quoted, ref. # 34), an other respectable different point of view was reported some years later (“There appears to be physiological justification for investigating intermittent compression as a therapy for patients with intermittent claudication and rest pain in the supine position as well as seated”. Morris R J, Woodcock JP. Effects of supine intermittent compression on arterial inflow to the lower limb. Arch Surg 2002 137:1269-1273, now quoted, ref. # 35).

Therefore we do not agree with the Reviewer’s opinion that body position is a critical issue for the study. Moreover we don’t see any critical issue in the translation of the findings of the study to the clinical setting considering the solid clinical experience of the Authors in vascular surgery, hemodynamics, rehabilitation and management of PAD patients. The invention and the study are strictly finalized to a translation to the clinical setting.

In addition we are not convinced that the supine position was critical in the different results in term of foot perfusion observed with the two devices. A study with aims comparable to those of our study was performed by Ubbink et al, 2001 (ref. # 20) by the same SFC device of our study, on patients in a sitting position. The foot oxygenation was measured by TcPO2 at the dorsum of the foot during IPC treatment. Despite the sitting position a significant decrease of TcPO2 was observed during IPC treatment (from 50.5 to 38.5 mm) with values that remained lower after IPC (31mm Hg). The results are therefore comparable to our study even if patients were in a sitting position. The problem of foot perfusion with the SFC device is probably not related to the position of the patient under treatment but to other factors, as the pinching straps around the foot during IPC treatment as hypothesized by Ubbink et al.

However, a sentence dealing with the necessity that future studies performed by our group or by other researchers, with a different patients’ position and with a adequate sample size will be necessary to confirm this preliminary observation is included in Conclusions and perspectives section (P13-L22).

2) Blood flow changes: The considerations are interesting. It probably depends on the pump. We have discussed that the concept is different but we still have not studied the related causes of the effects (a sentence has been included in Conclusions and perspectives section P13-L24).
Minor comments:
- Duration of application:
As we shown in Fig. 1 (schematic description of the study design), the effects of both IPC devices were tested after 35’. The SFC device was maintained up to 2 hours because most of the literature deals with a prolonged treatment with this IPC device. This concept is explained in the text (P6-L2). We therefore aimed to observe whether a better response was obtained after a prolonged treatment. However the comparison of results has been performed after 35’.

- Foot oxygenation:
We agree with the Reviewer. We limited our measurements to NIRS measurement, being this methodology more sensitive to monitor real oxygen status. However, we realize that also a parameter of wide clinical use and therefore more familiar to the readers would have been helpful to better define the severity of the disease. A sentence has been included in the Limitations section (P13-L9).

- NIRS measurements:
We agree with the Reviewer. The local muscle oxygen extraction as the change in HHb concentration has been considered by other Authors the parameter better reflecting the dynamic balance between O\textsubscript{2} delivery and O\textsubscript{2} utilization during dynamic exercise as well less influenced by blood volume changes, as the Reviewer says. However, the study aimed to evaluate the foot oxygenation during the GP device and we preferred to focus on other parameters for different reasons. We mainly focused on the parameter HbO\textsubscript{2}, or the amount of Hb with oxygen in the tissue under the sensor, because better describing the degree of oxygen available in the foot. In addition we have discussed data of tHb showing that the blood volume under the sensor was modified consistently with HbO\textsubscript{2}. Finally HHb, or oxygen extraction, theoretically might vary among subjects according to the muscle mass of the patient’s foot, limited and variable (e.g in diabetic subjects). Nevertheless in the present study we have evaluated all the 3 parameters measured by the NIRS device, and superimposable results were also obtained analysing HHb AUC values (the pattern of HHb has been added in Fig.3). A comment has been added in Discussion section (P11-L4, and two references have been also quoted (ref. # 31 and ref. # 32).
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: 28 January 2014
Reviewer: Peter Klein-Weigel
Reviewer's report:
Major revision: s. attached file
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
no conflicting or competing interests, actually I’m not working in this field and I do not have any financial or non-financial relations to producers of products described in the patients and methods-section

Strength of the article:
Interesting topic, of high interest for all vascular specialists and wound managing faculties.
Basic methodology is adequate.
Weaknesses:
Patients: too less and too heterogenous. Unfortunately authors mixed non-critical and critical PAD-stages as well as acute symptomatic and stable diseases with very different short and mid-term prognoses and vascular and microcirculatory compensation mechanisms.
Authors should further work in that field, increase the number of patients, should perform an analysis, how many patients they would need for adequate power and should homogenize patients on the basis of PAD-Stages and acuity of symptoms

REPLY TO THE REVIEWER #4

We agree with the Reviewer and we thank him for the suggestions. In a previous version of the manuscript we separated the effects according to the severity of the disease with a better haemodynamic and foot oxygenation response for patients with critical limb ischemia. Unfortunately, for the limited sample size in the present manuscript we preferred to avoid the subgroups analysis.
The present study is a spontaneous study to evaluate whether an improved foot perfusion occurs using a novel device in patients with severe peripheral disease. In addition for the first time at the best of our knowledge, the NIRS technique was used to measure the effects on foot perfusion. Next step will be a clinical study to determine the effectiveness of the device reducing the numerous biases of the present manuscript. The suggestions have been included in Conclusions and perspectives section, P13-L23.