Vascular therapy by external stimulation in patients with type 2 diabetes

Summary of the publication

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Situation in the context of diabetic disease

Type 2 diabetes affects more than 537 million people worldwide. The vascular complications of diabetes affect the large vessels (arteriopathy) and the microcirculation (retinopathy, nephropathy, neuropathy). Type 2 diabetes and its complications are major public health issues, both in terms of management and prevention. In particular, in the so-called developed countries, one amputation occurs every 30 seconds due to diabetes.

Endothelial cells play a key role in proper physiological function. In particular, they release nitric oxide (NO), a potent vasodilator, in response to mechanical forces generated by increased blood velocity and longitudinal shear forces in the vessels (so-called shear-stress forces) ,[23] . Endothelial function is known to be impaired in a variety of conditions, including type 2 diabetes patients where endothelial cells play an important role in the progression of diabetic disease,[45] .

It has also been shown in diabetic patients that mechanical stimulation of the vessels (shear stress) and NO release from the endothelium are decreased, impairing blood microcirculation[6] .

There is a strong relationship between endothelial function and insulin resistance and sensitivity. Indeed, systemic blockade of NO bioavailability in healthy subjects significantly impairs glucose tolerance by increasing clearance and decreasing insulin secretion. These data support the fact that glucose homeostasis is linked to vascular health and that an alteration of the latter is involved in the pathogenesis of type 2 diabetes[7] .

Finally, it has been shown that the postprandial response of skeletal muscle micro vessels is impaired in diabetic patients, and that this impairment, probably related to insulin resistance of the microcirculation, is also involved in the pathogenesis of type 2 diabetes[8] . This is consistent with the muscle weakness often reported by type 2 diabetes patients.

Therefore, vascular therapy (any means that stimulates endothelial cells to increase circulating NO and maintain micro vessel blood flow) may have a place in the management of the type 2 diabetic patient, provided it is non-invasive, has demonstrated a direct beneficial effect on the vascular endothelium and is available and accessible to patients.

Thus, a vascular therapy by external stimulation reproducing the shear-stress, associated with oral or injectable anti-diabetic treatments, is likely to slow down the evolution of the pathology, considering that

- The NO and endothelial function have an impact on glucose homeostasis,
- The uptake of glucose by the muscles is correlated, in type 2 diabetic patients, to the insulin resistance of the microcirculation,
- The vascular function is involved in the pathogenesis of type 2 diabetes.

Vascular therapy by external stimulation is therefore a good potential candidate for stabilising or preventing diabetic complications and in particular neuropathy of the lower limbs with the risk of diabetic wounds and amputations, which represent a major challenge for the diabetic population.

The Stendo device

The Stendo device was developed to stimulate endothelial cells non-invasively. It consists of a console connected to a pneumatic suit consisting of four layers including a gel layer and a layer containing pulsed air. The device applies diastole-synchronized compressions/decompressions (DSCD) to the lower body.

The pressure applied is 60 mm Hg and the cardiac synchronization is performed by means of a finger pulse oximeter.

A first study in 24 **healthy** volunteers showed that DSCD induced a doubling of the blood flow in the microcirculation of the skin recorded by laser-Doppler of the forearm[9] .

As lymphatic vessel cells are similar in nature to blood vessel cells, a second study was conducted in 24 **patients with** Lymphoedema. This randomised controlled trial demonstrated that the Stendo device significantly reduced the volume of the lower limbs[10] , which led to CE marking in 2018. Stendo has since been used successfully by physiotherapists and is very well tolerated. It should be noted that there is also impairment of lower limb lymphatic function in obesity and type 2 diabetes, with an association between interstitial albumin retention and the presence of peripheral neuropathy[11] .

Stendo medical device, exercising the DSCD

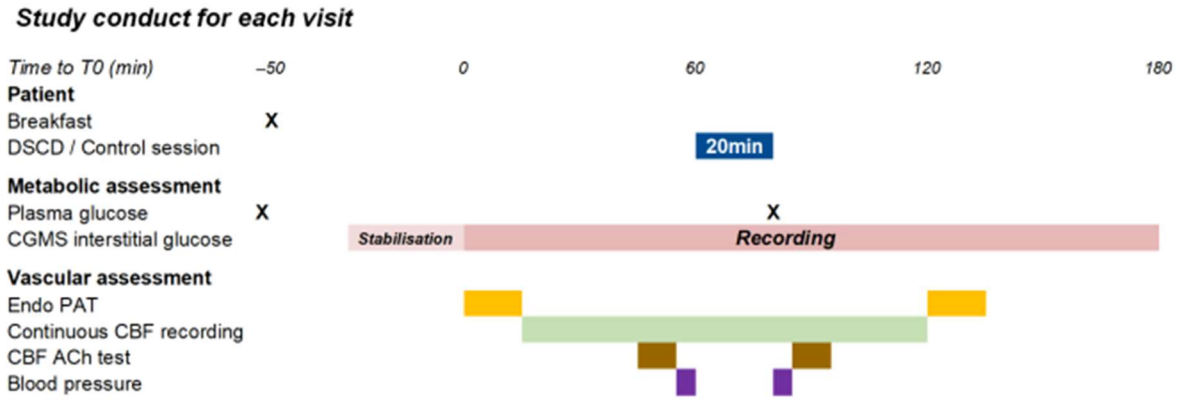
Studies in type 2 diabetes patients with the Stendo device

Two single-centre, randomised, controlled, cross- over studies were conducted:

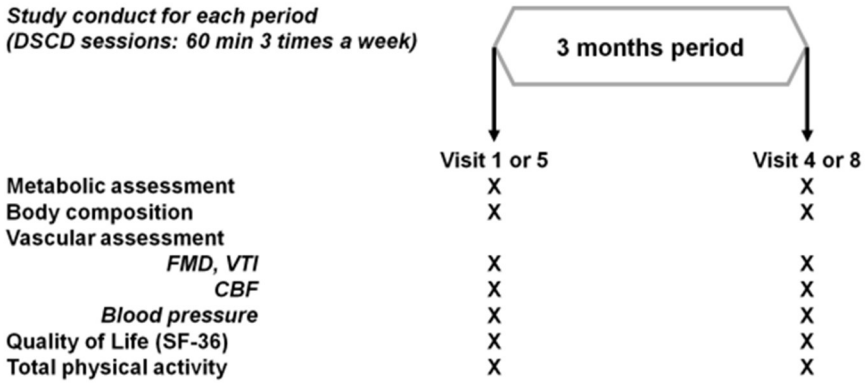
- A study evaluating the acute effects in 16 patients (Study 1). The effects of a Stendo DSCD session (*verum* session, 20 minutes) were evaluated in comparison with a subsequent control session (simulated DSCD session, 20 minutes) applied after a two-week wash-out period, or *vice versa* (CHU Jean Verdier, Professor Paul Valensi).
  Interstitial glucose (CGM) and skin blood flow (laser-Doppler, Periflux) of the forearm were continuously recorded before, during and after the DSCD *verum* or simulated sessions. Endothelial function was assessed before and after the sessions.
- A study evaluating the chronic effects on 38 patients (Study 2). The effects of three one-hour sessions of DSCD per week for 3 months were evaluated in comparison with a subsequent control period of 3 months (no DSCD sessions), the two periods being separated by a wash-out period of 4 to 6 weeks, or *vice versa, i.e. control period followed by the DSCD period* (Clermont Ferrand University Hospital, Professor Martine Duclos)
  Assessments of endothelial function, microcirculation, metabolism, body composition and physical activity were performed before and after each 3-month period.

In both studies, skin microcirculation and endothelial reactivity were assessed by laser-Doppler, either on the forearm or on the palmar surface of the hand, these sites being a good reflection of the functions and alterations of the microcirculation within other organs and tissues , ,[121314] .

Study 1 drawing (for each visit)

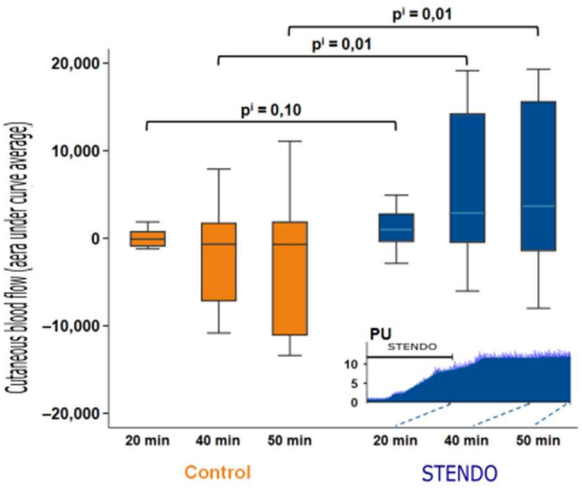


Study 2 drawing (for each period)

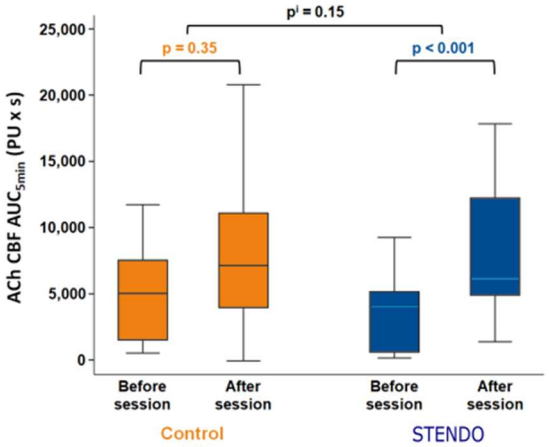


Results

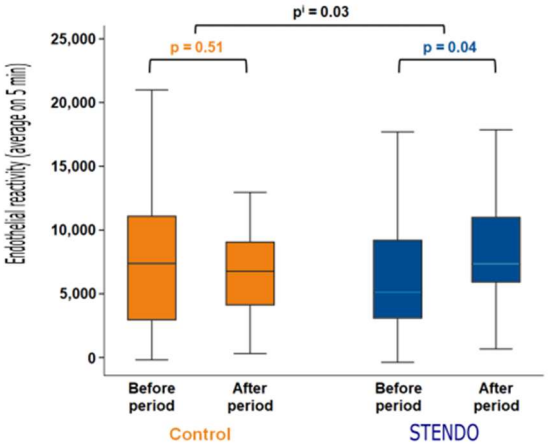
- **A 20-minute Stendo DSCD session induces an immediate effect on microcirculation flow that increases significantly and persists for more than 30 minutes after the session has ended**. The area under the flow curve measured by laser-Doppler (Periflux) on the forearm is on average six times higher 30 minutes after stopping the DSCD *verum* session (at T= 50 minutes) than after a control session.



- **A 20 min DSCD Stendo session induces an improvement in endothelial function**, as assessed by endothelium-dependent vasodilation in an acetylcholine (AC h) test in the forearm. The increase in the area under the curve recorded for 5 minutes after local iontophoretic administration of AC h is 35% higher after a *verum* DSCD session than after a control session.



More than 24 hours after the last 3-month DSCD *verum* session, endothelial function is significantly improved compared to the 3-month control period. Endothelial function is measured here by laser-Doppler (Periflux) recording of the area under the reperfusion flow curve of the microcirculation of the palmar surface of the hand for 5 minutes after release of the brachial artery occlusion.



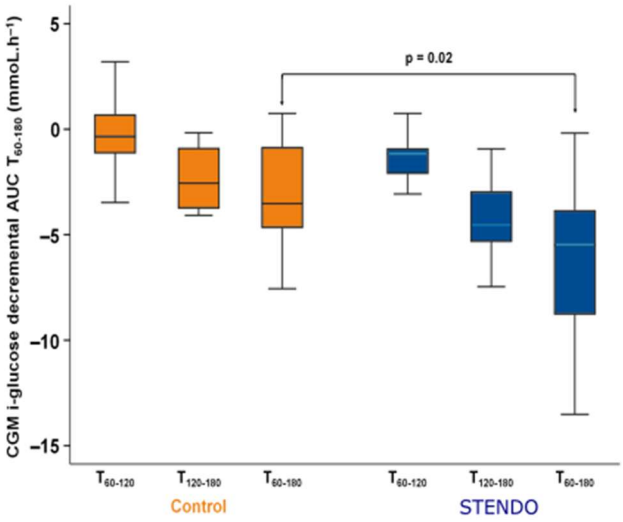
The vascular effects of Stendo DSCD are observed without changes in other cardiovascular parameters, in particular, arterial pressure, heart rate and left ventricular ejection volume remain unchanged.

- **In the chronic study, the improvement in endothelial function was associated with an approximately 3% decrease in extracellular fluid measured by impedancemetry**, which is consistent with the decrease in lower limb volume observed in patients with lymphoedema.
- The effects of DSCD on vascular function were recorded on the forearm or hand, at a distance from pulsatile compressions on the lower body. These effects persist after stopping DSCD (30 minutes after stopping a single session, more than 24 hours after the last session after 3 months of DSCD), showing a prolonged effect on endothelial cells as well as a systemic effect probably through the release of vasoactive substances, including NO.

Thus, Stendo pulsatile compressions appear to reproduce and/or amplify the shear stresses necessary for proper vascular function, which is impaired in patients with diabetes.

- Furthermore, the improvement in endothelial function is accompanied by a metabolic improvement:

A session of DSCD *verum* significantly **improves the decay of blood glucose and interstitial glucose after the postprandial blood glucose peak.** Interstitial glucose was recorded by CGM (Navigator II®, Abbott), with the area under the curve calculated from the start of the DSCD session or the control session (T=60) for two hours (up to T=180).
In addition the decrease in interstitial glucose correlated with the increase in endothelium-dependent vaso-dilation.



After 3 months of DSCD sessions the lipid profile is significantly improved: increase in HDL - cholesterol, decrease in LDL- cholesterol and non- HDL cholesterol and a marked tendency to decrease triglycerides.

- Repeated use of **DSCD also significantly improves vitality** (SF-36 quality of life questionnaire) **and overall physical capacity (measured by the International Physical Activity Questionnaire IPAQ),** criteria that are impaired in diabetic patients.

Conclusion and outlook

- **For the first time these studies demonstrate that a non-invasive vascular therapy procedure (here DSCD sessions applied by the Stendo device) is able to improve endothelial function and increase microcirculation in type 2 diabetic patients.**
- **The improvement of endothelial function by the Stendo device is demonstrated without inducing any adverse effects.**
- **The studies carried out underline the promising interest of this new type of therapy to improve the endothelial function of type 2 diabetic patients and its potential in the prevention of vascular complications in the medium and long term.**
- **In addition, the improvement in vascular function under the effect of Stendo DSCD is coupled with a metabolic improvement:**
  - **Stendo DSCD induces a greater decrease in blood glucose in postprandial period, which correlates with improved endothelial function.**
  - **The lipid profile is significantly improved after three months of DSCD and extracellular fluid is reduced,**
- **As mentioned earlier, the improvement in endothelial function and microcirculation observed here in type 2 diabetic patients should contribute to improving circulatory flow in tissues and thus**
  - **improve oxygenation and tissue nutrition, with a reduction in extracellular fluid retention.**
  - **improve glucose homeostasis, by its better uptake by muscle cells, the increase in skin blood flow reflecting an increase in muscle blood flow.**
- **Furthermore, all the results acquired with the DSCD with the Stendo device plead in favour of the role of the physio pathological function of the endothelium on the genesis and the evolution of type 2 diabetes, and support the interest of any means allowing to preserve and improve the functional components of the endothelium and the microcirculation in the management of the diabetic patients.**

  In particular, DSCD sessions could be particularly beneficial in type 2 diabetic patients with lower limb symptomatology of heaviness, swelling, oedema and muscle weakness, clinical evidence of impaired endothelial function.

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Link to the original study: https://cardiab.biomedcentral.com/articles/10.1186/s12933-022-01710-6