

Prepared for



**3rd ESM-EVBO
CONFERENCE**

ESM-EVBO
APRIL 15th-18th, 2019

MAASTRICHT, THE NETHERLANDS

**Efficacy of Transdermal CO₂
Administration Using a
Deoxyhemoglobin Vasodilator
Medical Device
to Treat Diabetic Foot Ulcers**

A preliminary study

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Disclosure

**This study was supported partially by
Circularity Healthcare USA for the supply
of CO₂ Cartridges**

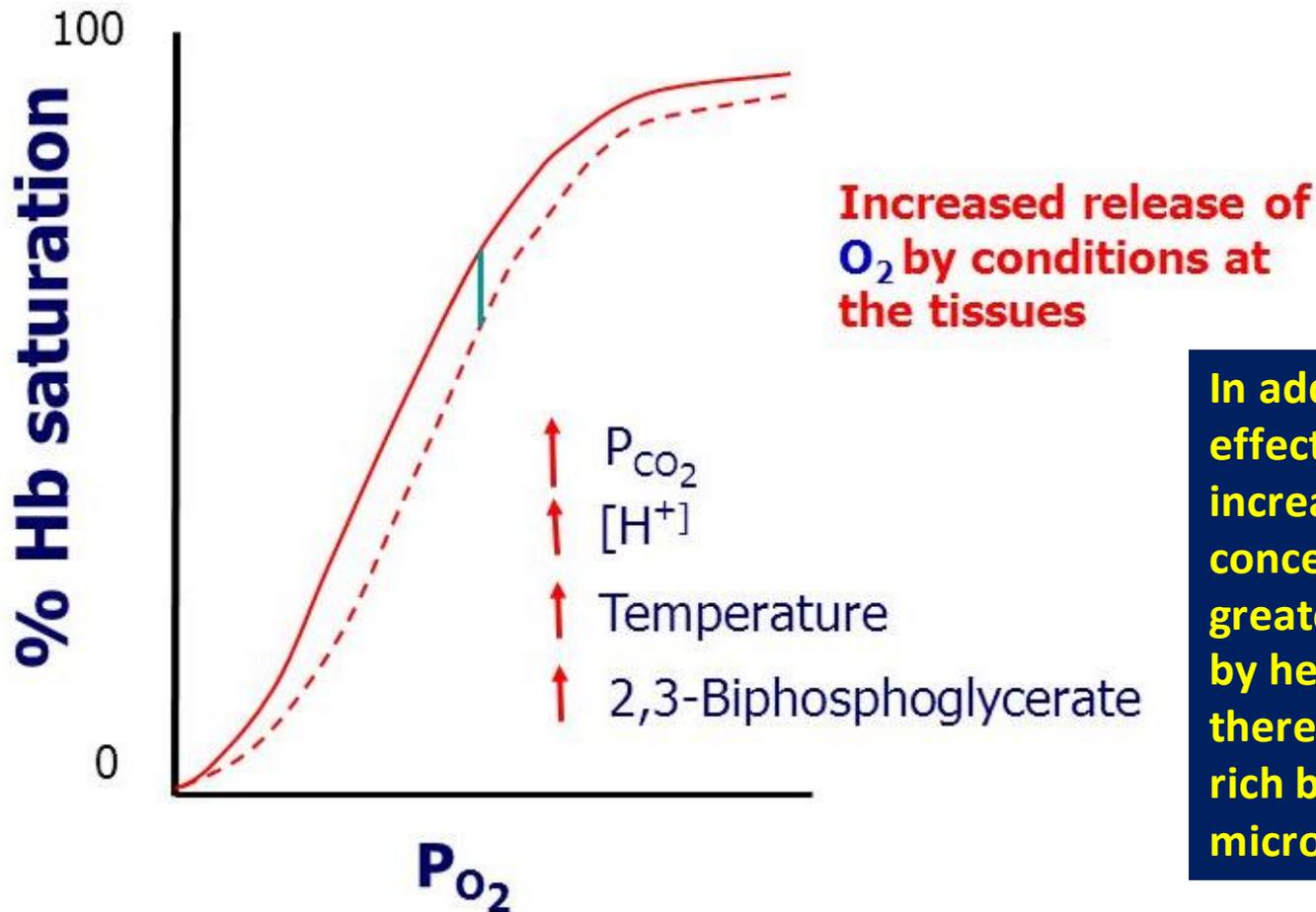
Scientific reasoning

- Introduction Medical gases have **historically** been **delivered via the inhalation** route of administration. However, in light of the physiology of human skin, it **may be possible** to deliver medical gases **transdermally**.
- Transdermal gas delivery is **non-invasive** and can interact with dermal capillary and cellular receptors near the skin, producing a **desired systemic effect**.
- The work (using transdermal CO₂ device) (*) studied a novel method for **boosting microcirculation** using diffusive non-invasive transdermal delivery of a supersaturated solution of carbon dioxide (CO₂) in water.

(*) Lee C. Rogers, D.P.M., Judy M. Muller-Delp, Ph.D., Topy A. Mudde, MSc.

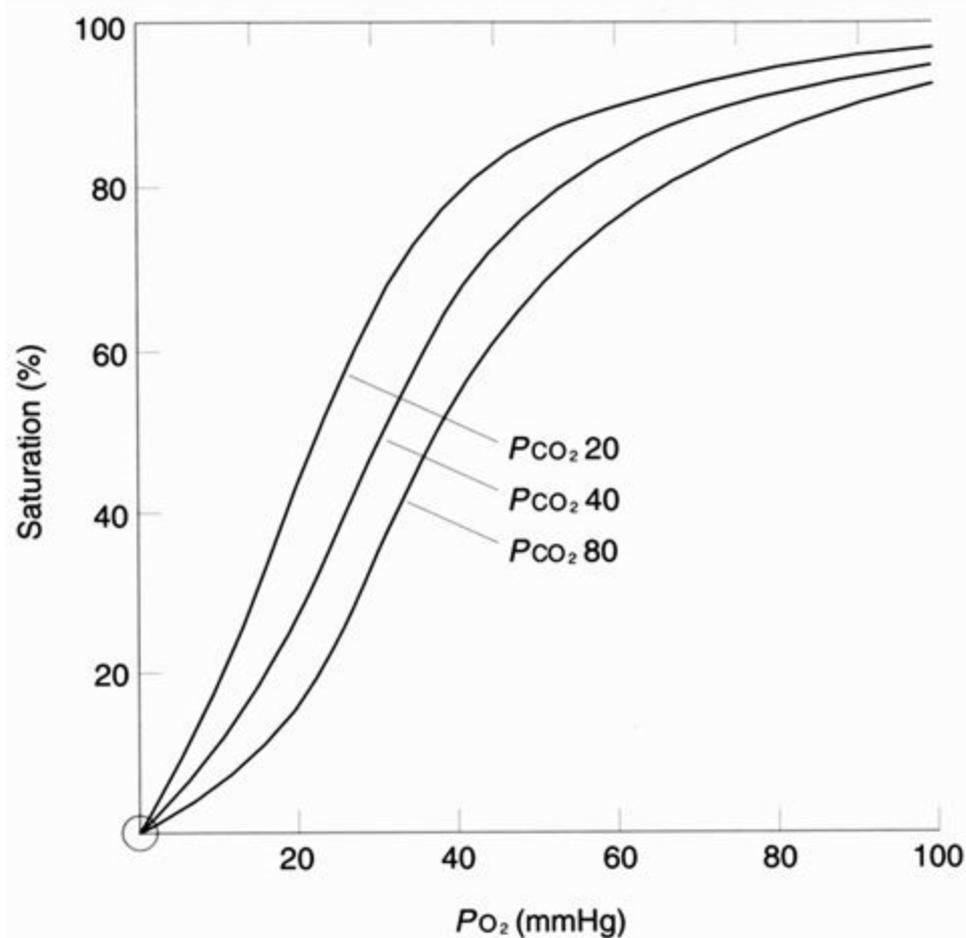
Bohr Effect

A shift of the curve to the right:- The Bohr Effect



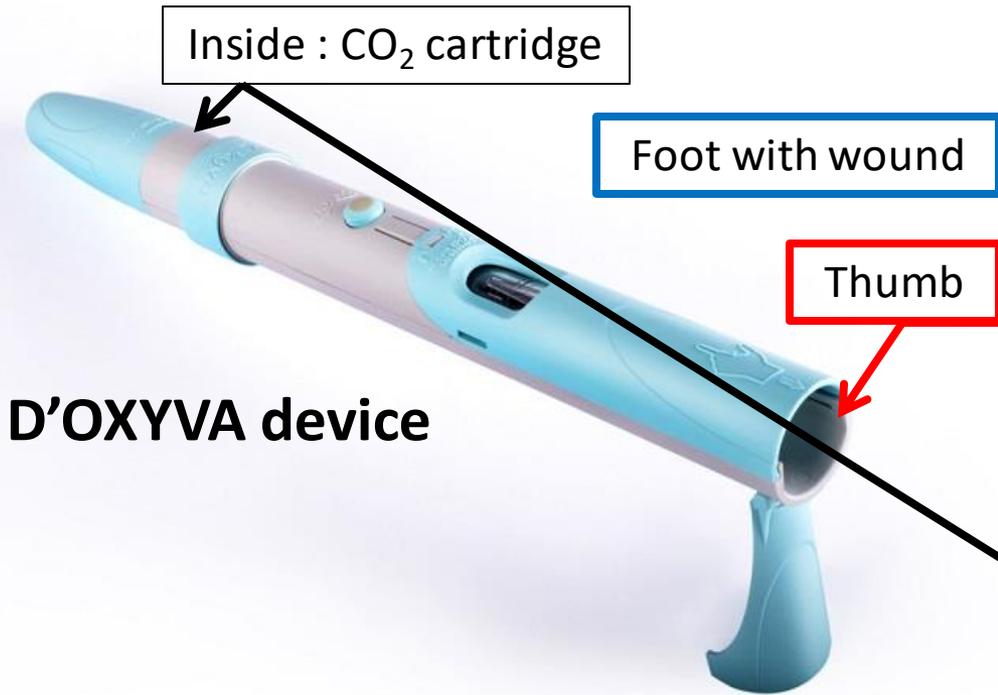
In addition, when the Bohr effect is stimulated, the increase in blood CO₂ concentration causes greater oxygen unloading by hemoglobin proteins, thereby increasing oxygen-rich blood flow in the local microcirculatory system

The Bohr effect



Three Oxygen Dissociation curves illustrating the Bohr Effect.

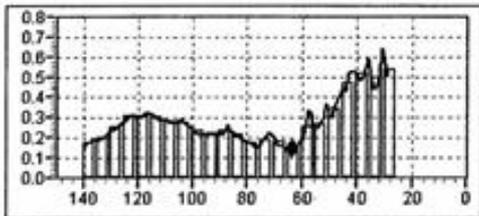
Increased carbon dioxide in the blood causes a right-shift in the curves, such that the haemoglobin more easily unloads the oxygen it is carrying.



D'OXYVA device



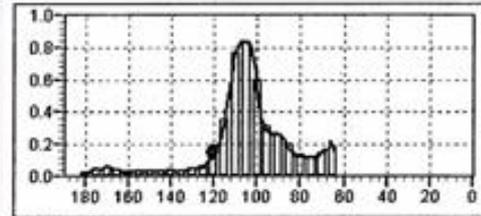
Following are Skin Perfusion Pressure sample results conducted by U.S. FDA cleared Vasamed® Sensilase® 3000 and measured on a healthy female volunteer with a single D'Oxyva™ therapy applied.



Right Digit - Hallux

64 mmHg

5 minutes before D'Oxyva™ therapy:
Healthy capillary blood flow at
64 mmHg



Right Digit - Hallux

121 mmHg

2 minutes after D'Oxyva™ therapy:
89% capillary blood flow increase
from 64 to 121 mmHg



the effect of transdermal CO₂ delivery on remote microvascular perfusion in subjects with and without diabetes by assessing skin perfusion pressure of the foot after bathing the thumb in CO₂.



**Measurement of PI (Perfusion Index) Masimo[®],
Pulse Rate (PR), and O₂-Sat (%SpO₂)
by means of gadget (Android or Apple)**

Aim of the preliminary study

- This clinical study was designed to observe
- 1) the effect of transdermal CO₂ administration using the D'OXYVA[®] medical device on peripheral capillary oxygen saturation (SpO₂), Pulse Rate, and perfusion index (PI) and
 - 2) the efficacy of transdermal CO₂ administration to treat diabetic foot ulcers.

Table 1. Wagner Ulcer Classification System

Grade	Lesion
1	Superficial diabetic ulcer
2	Ulcer extension involving ligament, tendon, joint capsule, or fascia with no abscess or osteomyelitis
3	Deep ulcer with abscess or osteomyelitis
4	Gangrene to portion of forefoot
5	Extensive gangrene of foot

Patient's DFU treated : Wagner's Class 1 & 2

Variable	Control, n=15	Treatment, n=15	p-value
Gender; n(%)			0,109
- Male	2 (13,3)	7 (46,7)	
- Female	13 (86,7)	8 (53,3)	
Age (years); Mean±SD	55,13±6,39	58,07±7,79	0,269

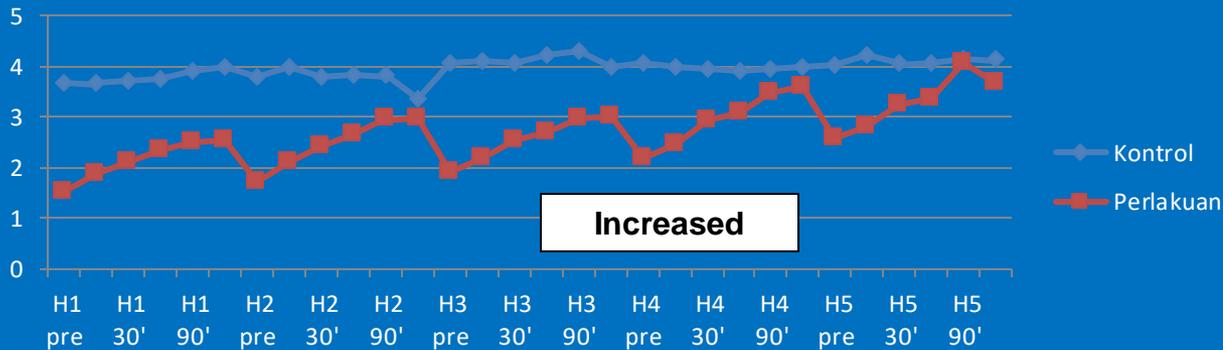
Subject's characterisation

Variable	Control, n=15	Treatment, n=15	P-value
Hemoglobine (gram%); Mean±SD	9,93±1,66	8,56±1,99	0,052
O2-Saturation; Mean±SD	97,67±1,59	98,80±1,42	0,049
PR; Mean±SD	104,93±12,89	95,67±11,70	0,049
PI; Mean±SD	3,69±2,22	1,52±1,36	0,003

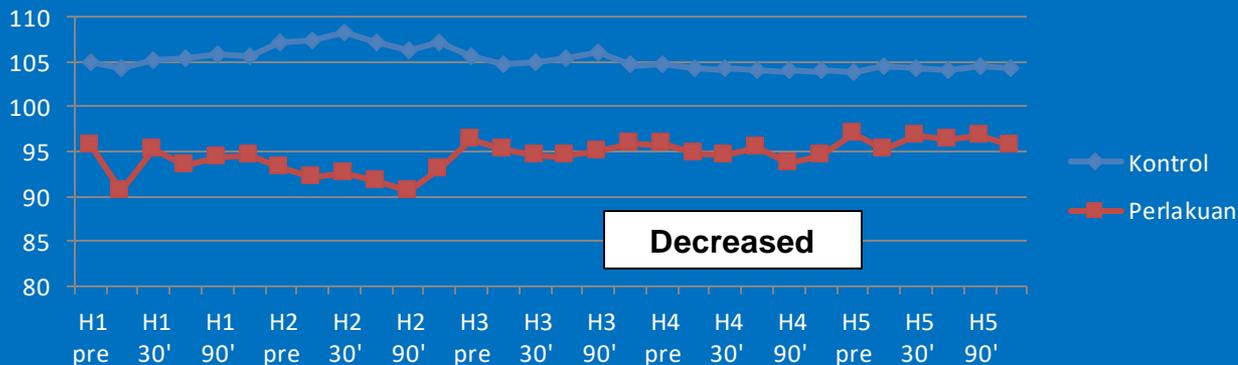
Subject's clinical condition

Variable	Pre	Post	p-value
Control, n=15			
O2-Saturation	97,67±1,59	97,33±2,06	0,430
PR	104,93±12,89	104,33±12,86	0,676
PI	3,69±2,22	4,15±2,03	0,309
Treatment, n=15			
O2-Saturation	98,80±1,42	98,40±1,24	0,395
PR	95,67±11,70	95,60±14,19	0,976
PI	1,52±1,36	3,68±1,89	<0,0001

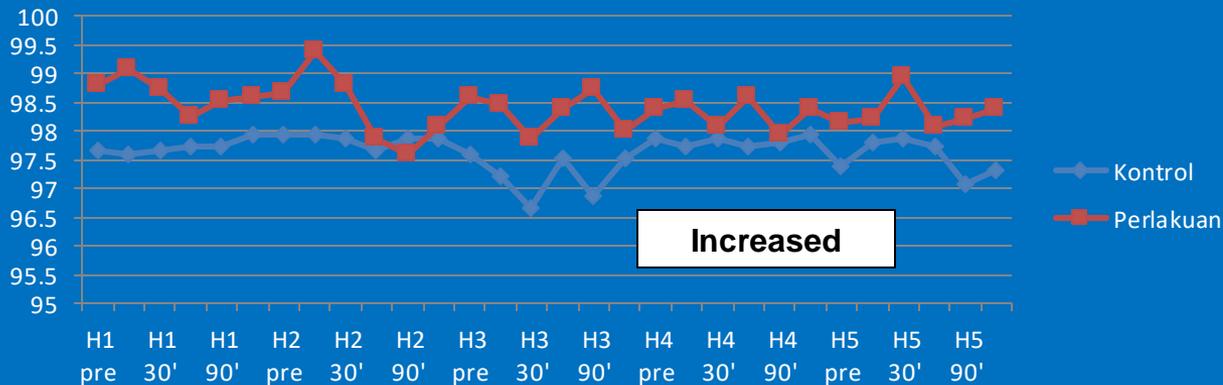
RESULT



Changes of Perfusion Index (PI)



Changes of Pulse Rate (PR)



Changes of Oxygen Saturation (SpO₂)

DFU Wagner-2

Pre-



5 days' after



DFU Wagner-1

Pre-



5 days' after



Conclusion of the study for clinical use

- Application of transdermal CO₂ produces a remote **vasodilation** that may be mediated through **release of a circulating humoral agent**
- Transdermal Delivery of Carbon Dioxide Boosts Microcirculation (Lee C. Rogers¹, D.P.M., Judy M. Muller-Delp³, Ph.D., Topy A. Mudde², MSc.)
- Impairments in microcirculation are detrimental to skin repair and regeneration
- the delivery system of transdermal carbon dioxide **improves parameters of dermal microcirculation.**
- using the device shows promise for improving the microcirculation in multiple disease states and may improve skin repair or **delayed wound healing.**

Second Study

AUTHORS

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AIM OF THE STUDY :

This clinical study was designed to **(1) quantify the effect of transdermal CO₂ administration** using the D'OXYVA[®] medical device on transcutaneous carbon dioxide (tcPCO₂), peripheral capillary oxygen saturation (SpO₂), and perfusion index (PI) and **(2) to evaluate the efficacy and safety** of transdermal CO₂ administration to treat diabetic foot ulcers.

METHODS

- Adults with clinically-confirmed type II diabetes mellitus (DM) and an active Wagner class 1-2 foot ulcer (≥ 30 days) were recruited to one of two cohorts.
- In cohort one, patients were given a 5-min transdermal application of CO₂ using D'OXYVA[®]; spO₂, tcPCO₂, and PI were measured at baseline and up to 120-min post-administration.
- In cohort two, patients were trained to self-administer CO₂ twice daily for 8 weeks. Each patient returned to the clinic twice-weekly to document the wound healing processes by a certified physician.

Table. 1**General characteristic of Group-1**

		Gender	
		Male (N=9)	Female (N=6)
N = 15			
Age (average yrs)		54.3 (std + 8.0)	66.6 (std + 5.5)
DFU Wagner Class.			
	1	3 (33%)	1 (16.6%)
	2	6 (67%)	5 (83.4%)

Table. 2**General characteristic of Group-2**

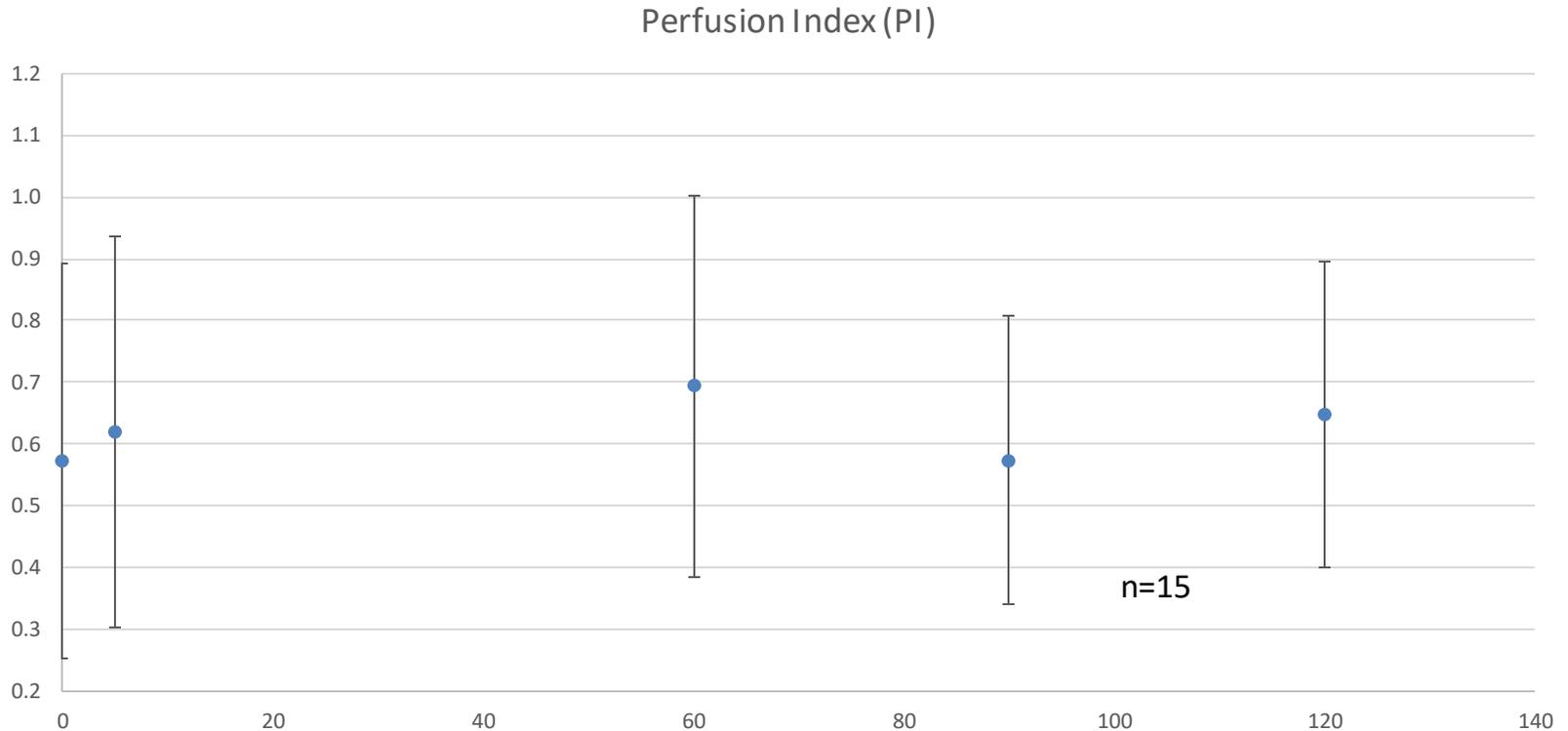
		Gender	
		Male (N=2)	Female (N=4)
N = 6			
Age (average yrs)		53 (std + 8.0)	63.3 (std + 5.5)
DFU Wagner Class.			
	1	1 (50%)	1 (25%)
	2	1 (50%)	3 (75%)

RESULTS

- Fifteen and six patients in cohort one and cohort two, respectively, enrolled and **completed the study**. Following CO₂ administration, **average PI was increased from baseline at all time points** and maximally peaked 23% above baseline after 60 min (p<0.05). **Average SpO₂ appeared to increase by ~0.5% 5-min post-administration**, followed by a steady decline towards baseline; however, these results were not statistically significant from baseline (p>0.05). **tcPCO₂ and pulse rate were unchanged.**
- In cohort two, **improved wound-healing processes were observed** following the first day of CO₂ treatment. These improvements included the **appearance of granulation tissue, clean and well defined ulcer borders and decreases in observable inflammation and edema**. In one patient, **complete resolution** of a DM foot ulcer (Wagner stage 2) located on the great toe occurred after 3 weeks. **No adverse events or safety signals associated with use of the device were observed.**

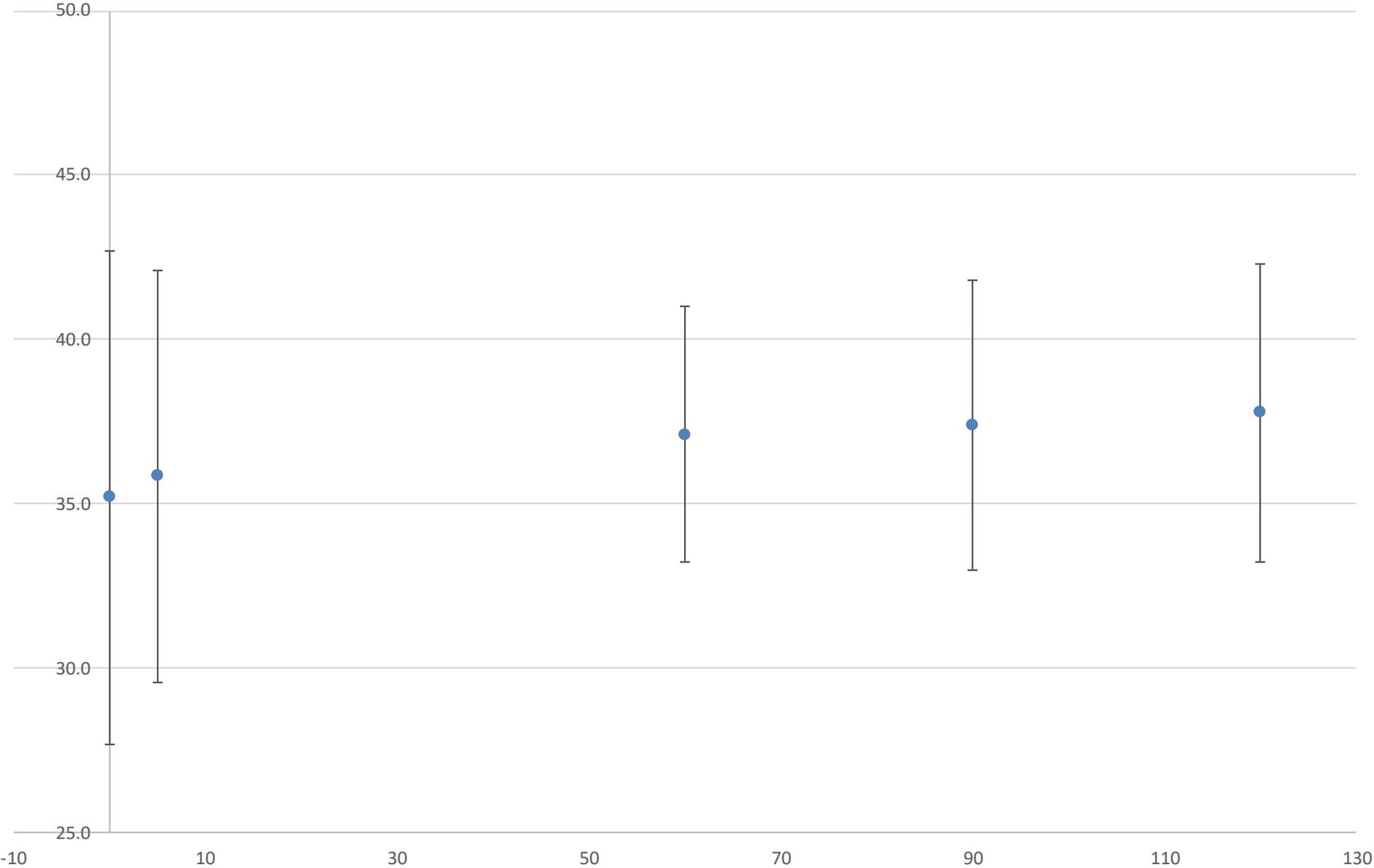
Perfusion Index

AFTER 0, 5, 60, 90 AND 120 MINUTES OF CO2 TRANSDERMAL DELIVERY WITH D'OXYVA APPARATUS

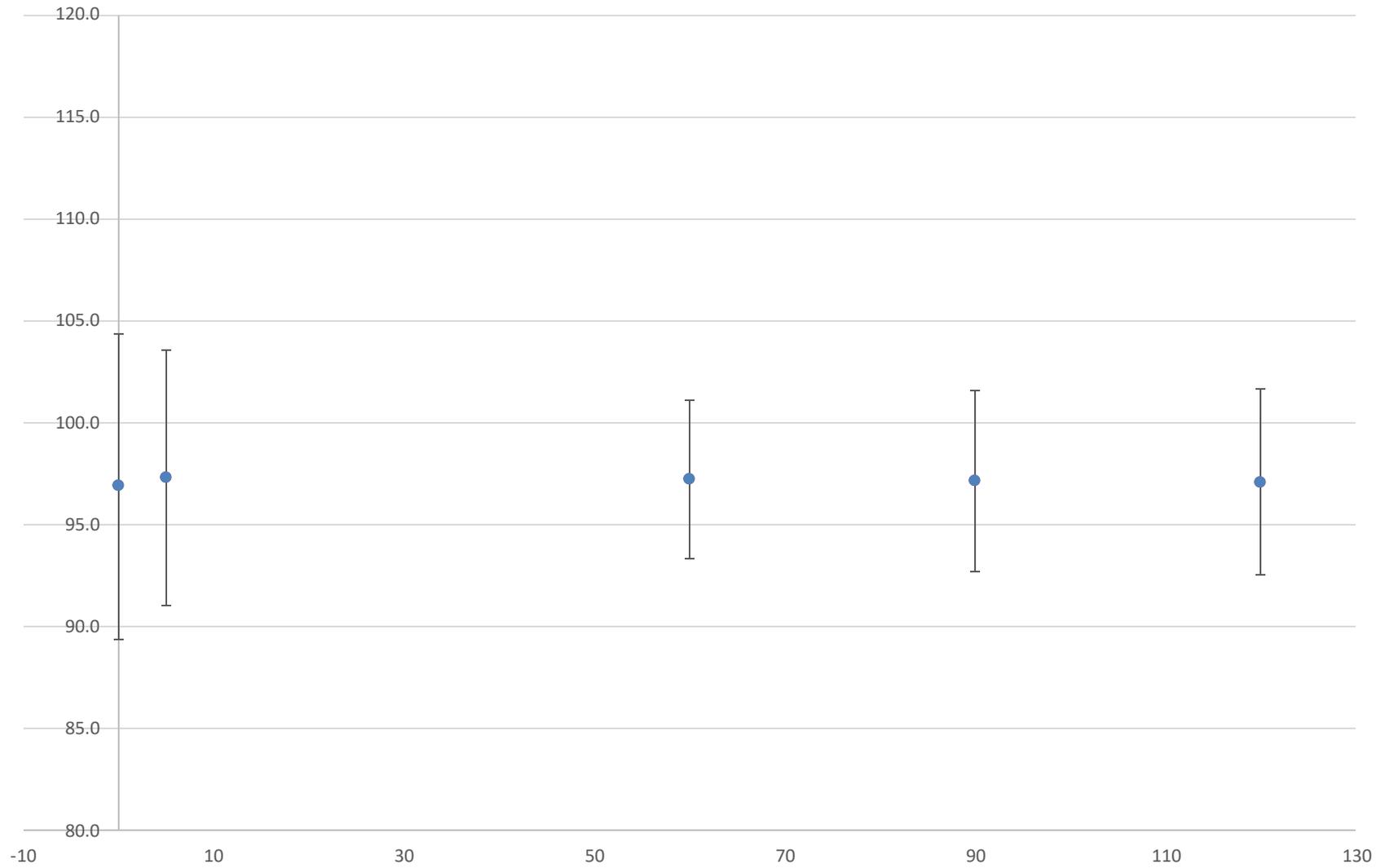


Time (min)	Average (value)	Standard Deviation
0	0.6	0.3
5	0.6	0.3
60	0.7	0.3
90	0.6	0.2
120	0.6	0.2

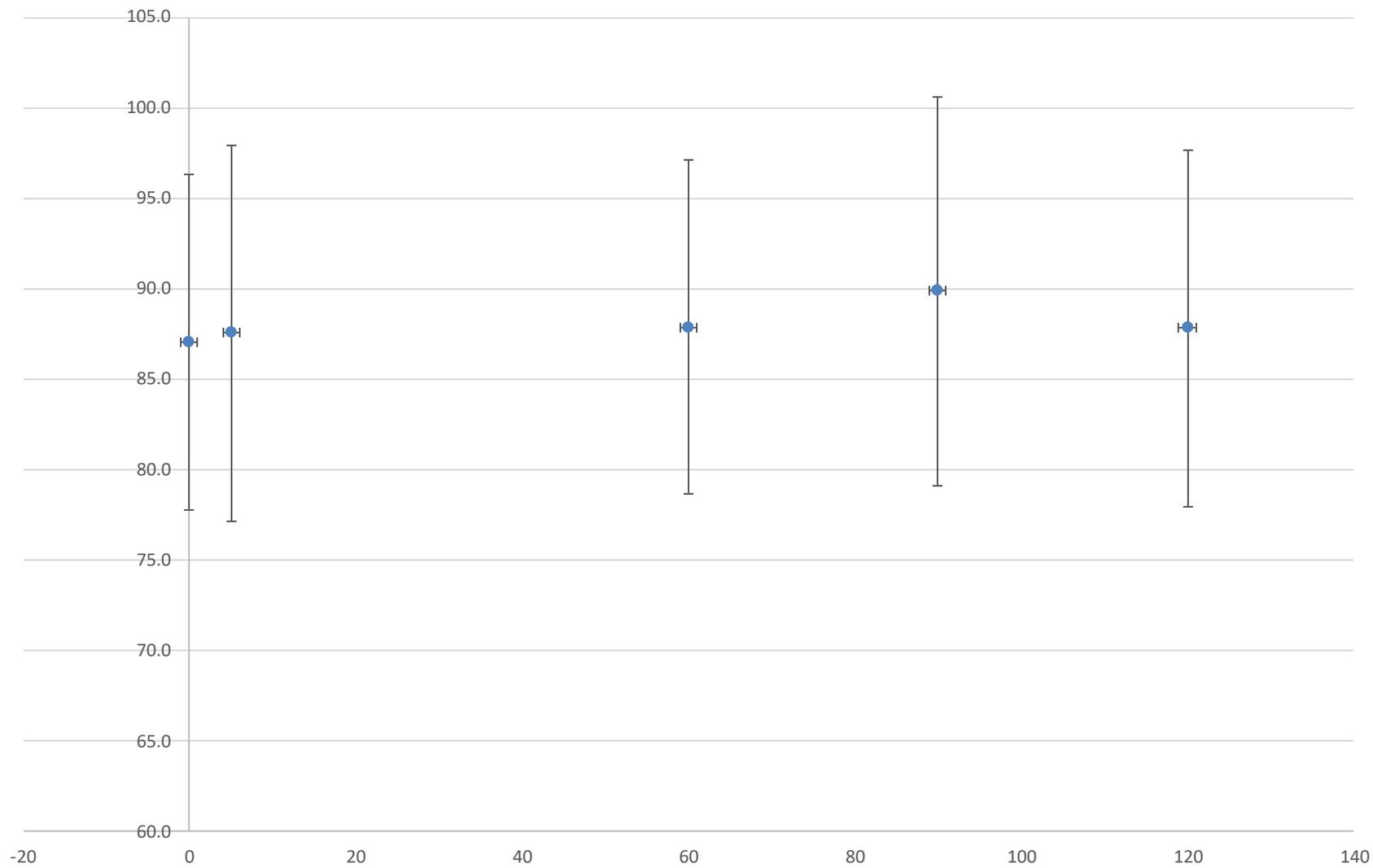
TcCO2



SaO2



PR



Summary of the results

- The use of D'OXYVA[®] transdermal CO₂ delivery system seems to be a safe method with no adverse effect shown in this study
- An increase of perfusion index (PI) could be a way to boost the wound healing process
- This method could be recommended to be used in the treatment of diabetic foot ulcer

Future direction

- There appears to be a time-dependent effect, with the largest treatment affect occurring at 30 or 60 min post administration, depending on the day
- A larger sample is needed to generalize the study results to the general population. It did showed that there is a better outcome of the wound healing process as compared with the other group of patients
- Larger populations and assessing participants' daily general health experiences are required to support the potential of this medical device to prevent future diabetic foot

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