

Summary of Key Clinical Outcomes: 9 trials involving +450 patients

Published Studies with PVR system

Microcirculation

1. Microcirculation Improvements

RCT (n = 42 patients with DFUs):

Patients receiving transcutaneous CO₂ therapy showed statistically significant improvements ($p < 0.01$) in both endothelial and neurogenic regulation of skin blood flow. No changes were observed in the control group.

Finžgar M, Frangež HB, Cankar K, Frangež I. Transcutaneous application of the gaseous CO₂ for improvement of the microvascular function in patients with diabetic foot ulcers. *Microvasc Res.* 2021 Jan;133:104100. doi: 10.1016/j.mvr.2020.104100. Epub 2020 Nov 10. PMID: 33181169.

2. Microcirculatory Flow (Healthy Volunteers)

RCT (n = 33, healthy male participants):

One lower limb of each participant was treated while the other served as control. Blood flow (LD flux) in the treated limb increased significantly from 5.8 PU to 30.3 PU (5 fold increased < 0.001), with no changes in the control limb.

Finžgar M, Melik Z, Cankar K. Effect of transcutaneous application of gaseous carbon dioxide on cutaneous microcirculation. *Clin Hemorheol Microcirc.* 2015;60(4):423-35. doi: 10.3233/CH-141898. PMID: 25261433.

Wound Healing

3. A double-blind RCT

RCT (n = 57 patients with DFUs):

In the treatment group, 67% of ulcers achieved complete closure within 4 weeks. The remaining ulcers showed a 96% reduction in surface area and a 99% reduction in volume. In the control group, no ulcers healed completely; reductions in surface area and volume were only 25% and 27%, respectively.

Macura M, Ban Frangež H, Cankar K, Finžgar M, Frangež I. The effect of transcutaneous application of gaseous CO₂ on diabetic chronic wound healing-A double-blind randomized clinical trial. *Int Wound J.* 2020 Dec;17(6):1607-1614. doi: 10.1111/iwj.13436. Epub 2020 Jul 7. PMID: 32633896; PMCID: PMC7949258.

4. Multicenter RCT DFU Study

n = 115 (76 ulcers in treatment group, 36 in control group)

- 64,47% of ulcers (49/76) in the treatment group achieved complete closure in 4 weeks. The remaining ulcers showed an average surface area reduction of 89.88 %.
- In the control group, only 3 ulcers (7.7%) healed completely; 5 worsened, and the others showed an average area reduction of 48.2%.

-The odds of complete wound closure within 4 weeks were approximately 35 times higher in the transcutaneous CO₂ therapy group compared to SoC (OR ≈ 35.1).

Frangež, I.; Potkonjak, M.; Veliu, S.; Metelko, Ž.; Badanjak, A.; Križaj, J.; Ban Frangež, H.; Poljičanin, T.; Meloni, M.; Papanas, N.; et al. Transcutaneous Carbon Dioxide Therapy

5. **Wound Recurrence After 12 Months (n = 40 DFUs)**

- A total of 40 diabetic foot ulcers was treated; of these, 27 (67.5%) reached complete closure within 4 weeks. The remaining 13 showed surface area reductions 89.88%.

- At 12-month follow-up, only 7 cases (17.5%) showed recurrence — substantially lower than the global average of ~40% per year.

Standard neurological assessment and plantar temperature measurement were performed before the first therapy and after completion of the twentieth session.

Results demonstrated:

- statistically significant improvement in protective sensation in Semmes–Weinstein monofilament testing ($p < 0.001$)

- improvement was observed irrespective of ulcer etiology (ischemic, neuropathic, neuroischemic).

- statistically significant improvement in vibration perception ($p = 0.021$)

- statistically significant improvement in plantar skin temperature (first toe; ($p < 0.001$))

The restoration of protective sensation is clinically relevant because LOPS is a major independent predictor of first and recurrent ulceration. The parallel improvement in sensory function and plantar temperature supports a neurovascular mechanism, consistent with capillary-level perfusion

Bulum, T.; Poljičanin, T.; Badanjak, A.; Držić, J.; Metelko, Ž. Effect of Transcutaneous Application of Carbon Dioxide on Wound Healing, Wound Recurrence Rate and Diabetic Polyneuropathy in Patients with Neuropathic, Ischemic and Neuroischemic Diabetes-Related Foot Ulcers. *Life* 2025, 15, 618.

<https://doi.org/10.3390/life15040618>

6. **Randomized controlled trial patients with recurrent hard-to-heal diabetic foot ulcers (n=30)**

Potkonjak et al. (2026) evaluated transcutaneous CO₂ therapy in addition to standard of care versus standard of care alone. After 4 weeks, complete ulcer healing was achieved in 46.7% of patients in the CO₂ group compared with 0% in the control group ($p = 0.005$), while median wound-area reduction was 85.7% versus 17.2%, respectively ($p < 0.001$).

Tissue oxygenation (StO₂) increased significantly in the CO₂ group by $29.6 \pm 19.6\%$, compared with a decrease of $2.2 \pm 6.9\%$ in controls (between-group difference 31.8%; $p < 0.001$).

Pain intensity also decreased significantly in the CO₂-treated group ($p = 0.002$).

Potkonjak M, Ančimer B, Lázaro-Martínez JL, Brodmann M, Papanas N, Frangež I. Transcutaneous CO₂ Therapy Improves Tissue Oxygenation, Ulcer Healing and Pain in Recurrent Hard-to-Heal Diabetic Foot Ulcers: A Randomized Controlled Trial. *International Journal of Lower Extremity Wounds*. Published online July 9, 2026. doi: 10.1177/15347346261468402.

DSPN- Distal Symmetrical Polyneuropathy

7. **Multicenter DSPN Study** n = 120 patients with diabetes (80 in study group (40 with DFU and 40 without DFU), 40 in control group). Results in the study group – treated with CO₂ therapy:
- Protective sensation improved by 53% in patients without ulcers and 34% in those with chronic ulcers;
 - Vibration perception improved by 30% (no ulcers) and 23% (with ulcers);
 - Plantar foot temperature increased by 5.1°C (no ulcers) and 3.9°C (with ulcers).

No clinically relevant changes were observed in the control group.

Frangž I, Papanas N, Đermanović Dobrota V, Ban Frangž H, Lukinović-Škudar V. Transcutaneous Application of Gaseous CO₂ Improves Diabetic Distal Symmetrical Polyneuropathy in Patients with and Without Chronic Wounds. Int J Low Extrem Wounds. 2025 May 6:15347346251338680. doi: 10.1177/15347346251338680. Epub ahead of print. PMID: 40326000

8. **DSPN**

RCT (n = 60 patients with DSPN and DFUs):

Among 30 patients in the treatment group, statistically significant improvements were observed (p < 0.001) in monofilament testing, vibration perception, and skin temperature. No such improvements were seen in the control group.

Ban Frangž, H.; Rodi, Z.; Miklavčič, J.; Frangž, I. The Effect of Transcutaneous Application of Gaseous CO₂ on Diabetic Symmetrical Peripheral Neuropathy—A Double-Blind Randomized Clinical Trial. Appl. Sci. 2021, 11, 4911. <https://doi.org/10.3390/app11114911>

Post surgical and post-traumatic hematoma, Edema and Pain

9. **Ratano S, Jovanovic B, Choudja Ouabo E. Effects of the Percutaneous Carbon Dioxide Therapy on Post-surgical and Post-traumatic Hematoma, Edema and Pain. Journal of Orthopaedic Case Reports 2023 December, 13(12): 11-17; <https://doi.org/10.13107/jocr.2023.v13.i12.4058>**

Additional device-specific supportive evidence of microvascular effect is presented in a 2025 professional symposium contribution by Potkonjak M, describing case-based capillary density assessment before and after treatment with the PVR System. In that report, capillary density increased following repeated transcutaneous CO₂ therapy, including an increase from 40/mm² to 64/mm² (60% increase) and from 14/mm² to 31/mm² (121.4% increase), providing further supportive physiological evidence consistent with improved local microvascular function. Because this source represents a professional symposium contribution and case-based material rather than a peer-reviewed controlled clinical study, it was assigned supportive evidentiary weight only.

Ref: Potkonjak M. Microvascular disease – a key risk factor for the development of chronic wounds and a barrier to successful healing. In: Proceedings of the 18th Wound Care Symposium, Portorož, Slovenia; 15–16 May 2025. Symposium organizer: University Medical Centre Ljubljana.