Cancer & Metabolism

RESEARCH Open Access

Pressure-adjusted static compression: aerobic metabolism and microvascular perfusion in the context of chemotherapy-induced neuropathy

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Abstract

Background Chemotherapy-induced peripheral neuropathy (CIPN) involves impaired microvascular neuronal perfusion and reduced bioenergetics. Compression and cryotherapy are potential preventive measures, yet their mechanism of acral temperature reduction remains unclear. This study aims to unravel the effects of pressure-adjusted static compression (PSC) on aerobic metabolic and endothelial responses in patients undergoing chemotherapy (CTX).

Methods Cancer patients with CTX above the CIPN-threshold dose ($n=24$, 50% male; age 64 [61–71] years) and healthy controls ($n=53$, 45% male; age 23 (18 to 87) years) had PSC applied on upper extremities. Tissue oxygenation and metabolism were derived by measuring oxygen supply (O_2Hb), oxygen demand (HHb), tissue oxygenation (TOI) and microvascular perfusion (THb) with quantitative time-resolved near-infrared spectroscopy (NIRS) and temperature with thermography. Effects were compared to cryoapplication and intermittent pneumatic compression (IPC). Endothelial function was quantified during vascular occlusion test (VOT).

Results PSC, in contrast to undersized surgical gloves (SG), uniformly creates pressure on hands and leads to a more pronounced reduction of hand temperature. Furthermore, PSC significantly increased microvascular perfusion, O_2-supply and reduced O_2-demand and aerobic metabolism, thus raised local tissue oxygenation ($p<0.05$ each). CTX lead to impaired metabolic and vascular reaction to PSC with only significant reduction of O_2-demand ($p<0.05$) during PSC. PSC is preferable regarding comfort ($p<0.05$) compared to SG. Cooling of hands (cooling gloves) had different action ($p<0.001$) to PSC with significantly reduced microvascular perfusion, O_2-supply and O_2-demand ($p<0.05$ each). Comparable local significant effects ($p<0.05$) were seen during IPC. CTX exhibited endothelial dysfunction with impaired microvascular reactivity, which limited their capacity to enhance tissue oxygenation.

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Conclusions Reduction of oxygen demand represents an important mechanism in interventions targeting prevention of CIPN. PSC, comparable to cryoapplication and IPC attenuates energy metabolism and enhances tissue oxygenation. PSC's impact on the combination of vascular and energy metabolism suggests its potential to alleviate CIPN burden. These findings support PSC's role in reducing acral CIPN through distinct mechanisms.

Keywords Chemotherapy-induced neuropathy, Compression therapy, Vascular function, Tissue oxygenation

Background

Chemotherapy-induced neuropathy (CIPN) is a disabling condition and dose-limiting for first-line chemotherapy with anti-VEGF-based antiangiogenic drugs [1]. The pathogenesis of CIPN is intricate, characterised by a complex interplay of vascular factors and an entangled imbalance in energy metabolism. Experimental data link CIPN prevention to enhanced microvascular angiogenesis of vasa nervorum induced by vascular endothelial growth factor (VEGF) [2, 3].

Both compression therapy and cryotherapy have been described as effective in reducing the risk of developing CIPN [4]. There is an ongoing debate about the mechanism by which compression therapy might be effective in secondary prevention of CIPN in hands [5–10], although it is already recommended in guidelines [11–13]. The postulated mechanism of reduced microvascular blood flow as a result of compression with two undersized latex-gloves [5–7, 9, 14], akin to cryotherapy for neuroprotection, lacks substantiation. Furthermore, it contradicts the body of evidence of autoregulatory responses, which indicate an increase in microvascular blood flow within pressure ranges of 13–40 mmHg [15–18]. We, thus, sought to unravel the underlying physiological mechanisms of pressure-adjusted static compression (PSC) as basis to evidence-based development of an urgently-needed option for CIPN-prevention in hands and feet.

Considering the intricate aetiology of diabetic neuropathy, characterised by a confluence of vascular and mitochondrial bioenergetic failure components, we hypothesized that CIPN shares similar complexities [19–21]. We postulated that one underlying effect of compression therapy in CIPN prevention involves a reduction in metabolism, in the light of an expected increased microvascular perfusion due to compression.

Near-infrared spectroscopy (NIRS) provides continuous, non-invasive metrics of tissue oxygen based on the absorption of reflected light. NIRS signals reflect both haemoglobin (in microvascular erythrocytes) and myoglobin (in muscle fibres) within superficial tissues [22–24], providing insights into the severity of disease, oxygen tension during exercise and mitochondrial capacity. NIRS signals from skeletal muscle likely originate in 60–90% from myoglobin [24]. NIRS desoxy-signal during cuff ischaemia / reperfusion corresponds dynamically to endothelial function and can thus also be used to quantify aerobic metabolism [24–27].

Materials and methods

Participants

The study population of this clinical-experimental, prospective, controlled pilot/exploratory study comprised a total of 53 subjects randomly recruited in three centres between March 2020 and December 2023. Participants recruited for the study were (a) 21 healthy middle-aged controls and (b) 24 cancer patients with different cancer types and chemotherapy doses above the threshold for CIPN-association [28]. A wide age range was included to achieve a broad variability and not limit the investigation to a specific age group. Subjects were randomly allocated to protocol type and side of intervention. All investigations were conducted with at least 8 subjects. All subjects were enrolled after careful medical history and physical examination using standard procedure for each and every investigation. Inclusion and exclusion criteria for controls and patients can be seen in supplemental material (suppl. Methods S1). All study participants gave written informed consent, and the study was approved by the ethics committee of Charité – Universitätsmedizin Berlin (EA4/075/20, Berlin, Germany).

Materials and methods

Compression and cooling products: Two undersized surgical gloves (SG; GAMMEX Latex, Ansell Healthcare, Belgium) were applied for hand compression, as described previously [5–8]. Commercially available compression garments, compression class 2 for hands were used and newly developed silicone-filled pads (all from Julius Zorn GmbH, Germany) for palmar increase of pressure in concave areas were used (PCT/WO2022/023308; suppl. Figure S1) and thus named pressure-adjusted static compression (PSC). For details, please see supplemental material (suppl. Methods S2). For intermittent pneumatic compression (IPC), the VADOplex hand pad (OPED GmbH, Germany) was used according to manufacturer´s instructions (80 mmHg every 20 s. for 1 s.). Cryoapplication was performed with ice cold gloves (Elasto-Gel Therapy Mitt TM7001, Southwestern Technologies inc., USA) cooled for at least 3 h at -18 °C.

Measuring instruments: Pressure was measured with a PicoPress pressure gauge/manometer (3 cm diameter,

M-1200, Microlab Elettronica, Italy) at the respective region of interest (ROI). Subjective perception was quantified with a standardised, validated visual analogue scale (VAS).

Near-infrared spectroscopy (NIRS) was performed using a time-resolved spectroscopy (NIRO-200, Type: C8686; Hamamatsu Photonics K.K., Japan) adapted to solve problems of absorption, scattering coefficient and mean path length [29, 30]. Furthermore, correction for blood flow/ volume for the signals was performed [27]. The probe was placed into the ROI (palm) to avoid limitations by extrapolating local and potential heterogeneous responses to other regions with different biological tissue composition [22–24].

Oxygen supply (O_2Hb), oxygen demand (HHb) [22], microvascular perfusion (THb) and tissue oxygenation (TOI) were continuously measured. NIRS optodes with an interoptode distance of 4 cm, allowing light penetration of approximately 2 cm, were placed longitudinally in the ROI. To reduce interference, the probes were taped tightly to the skin and shielded from light. All instruments were used after warmup and calibration and according to manufacturers` instructions.

Intervention protocols

All investigations were conducted under similar controlled conditions and following a standard protocol regarding preparation and conduction of investigations (see suppl. Methods S3).

After standard preparation, compression or cooling was applied for 90 min followed by a further recording period of 10 min. Investigations with CTX patients were performed during chemotherapy administration. For each investigation, NIRS and pressure were measured simultaneously. Interventions were applied unilaterally with randomisation to the dominant or non-dominant hand. To maintain a consistently low temperature, frozen gloves were changed once after 45 min.

Pressure was quantified at four specific sites, i.e. dorsum of the hand, palm, lateral edge, ventral wrist. Subjects were asked about their subjective well-being during the investigations and subjective perceptions were recorded after the interventions.

To differentiate the effects of PSC on local blood flow from venous occlusion, distal venous wrist compression was performed using a blood pressure cuff on the wrist with 30 mmHg cuff (suppl. Methods S4) [31].

With a vascular occlusion test (VOT) the endothelial function was quantified by the desaturation rate (measuring O_2Hb as proxy for oxygen supply of the muscle, downslope in first occlusion minute). Recovery periods of 60 min between repeated VOT measurements were maintained [24–27].

All investigations were conducted by trained personnel.

Analysis of NIRS-signals

NIRS parameters were continuously recorded with 1 Hz. To avoid technical artifacts and interferences automatic data smoothing was performed using the ongoing median over 5 measurement values (custom-written Visual Basic for Application in Excel, Microsoft, Version 2021, USA). All values were corrected for derivations from Zero prior to the investigation (baseline). Changes related to baseline were evaluated 5, 30, 60 and 90 min after investigation start and respectively 2 and 10 min after investigation completion each in 2-minute intervals (median and interquartile range (IQR) of measurement intervals). The VOT measurements were analysed in a similar way using the characteristics mentioned above.

Tissue oxygen uptake (mV_{O2}) was estimated by the rate of disappearance of O_2Hb and appearance of HHb, as rate of oxygen utilisation by the underlying tissue [32] during the first minute of arterial occlusion [24, 32, 33]. Correction for shifts in "blood volume" during the cuff period to obtain quantitative rate of O_2 extraction (V_{O2}) have been applied by dividing by 2 to correct for Hb_{diff} [32, 33].

Statistics

Pressure measurements were performed at least in triplicate and mean values were calculated, investigations were performed at least with 10 volunteers as independent investigations, and independent investigations on consecutive days.

Data are expressed as median and interquartile range (IQR), unless otherwise stated. Time intervals and differences over time of continuous measured variables were compared by Friedman test within one group ($p < 0.1$) before a post-hoc analysis was performed. Intraindividual comparisons between baseline and follow-up measurements were analysed by Wilcoxon test (2-sided). Continuous variables were compared by the Mann-Whitney-U test for group comparison.

Statistical significance was assumed, if a null hypothesis could be rejected at $p \leq 0.05$. All statistical analysis was performed with SPSS (IBM) in the current version and "R Studio, Version 2021.09.2" (Posit PBC, Boston, USA).

Results

Characteristics of healthy controls and CTX patients

The baseline characteristics of healthy controls and cancer patients undergoing chemotherapy are summarised in Table 1 and cumulative doses of chemotherapy are shown in suppl. data Table S1.

In addition to chemotherapy, 5 patients received immune checkpoint inhibition (ICI), 13 patients received monoclonal antibodies (not ICI), 3 patients received hormonal treatment, and 6 patients received steroids as part of their treatment.

Table 1 Baseline characteristics of controls and patients

	Controls	CTX
N	21	24
Age	23 [21–24], (from 18–87 years)	64 [61–71]
m: f	24:29	12:12
No. of CVRF	1.0 [0.0–1.0]	2.0 [1.0–3.0]
BMI [kg/m^2]	21.6 [20.1–23.0]	24.2 [19.4–28.0]
No. of chemotherapy substances per patient [1, 2]	-	3.0 [2.0–4.0]
No of treatment lines [2, 3]	-	1.5 [1.0–3.0]
No. of chemotherapy substances inducing CIPN [4]	-	2.0 [1.0–2.0]
No. of other chemotherapy substances	-	1.0 [0.25-2.0]
pts with: without CIPN [5]	-	12:12

[1] Number of substances are given irrespective of treatment lines

[2] A switch from Cisplatin to Carboplatin during the same treatment line is considered one line of treatment and one chemotherapy substance

[3] Chemotherapy followed by switch maintenance is considered one treatment line

[4] the following chemotherapeutic agents were considered CIPN inducing: (Nab-)Paclitaxel, Carboplatin, Cisplatin, Vincristine, Docetaxel, and Oxaliplatin. Polatuzumab vedotin, enfortumab vedotin and trastuzumab emtansine are antibody drug conjugates with MMAE or mertansin payload and therefore considered CIPN inducing

[5] according to CTCAE 4.0 including sensory symptoms; cut-off CIPN grade 2

Abbreviations: CVRF: cardio-vascular risk factors (age, gender, hyperlipidaemia, arterial hypertension, diabetes, smoking, family history); BMI: body mass index; CIPN: chemotherapy-induced peripheral neuropathy; CTX: chemotherapy; pts: patients. Data presented as number or median with [interquartile range]

The cancer cohort had mixed tumour entities: lymphoma ($n = 6$), breast ($n = 5$), gastrointestinal ($n = 5$), head and neck ($n = 3$), urothelial ($n = 2$), NSCLC ($n = 1$), prostate ($n = 1$) and testicular ($n = 1$) cancer.

PSC reduces temperature, enhances palmar pressure and is more comfortable compared to undersized surgical gloves and cryoapplication

Similar to results with surgical gloves from other groups [5, 6, 8] hand temperature was reduced from 32.9 °C [25.0–34.8] to 28.1 °C [24.4–32.9] by 4.8 °C [CI 3.0–6.6], ($p = 0.05$) with PSC.

Wearing two undersized surgical gloves (SG), as used in CIPN prevention, lead to pressure values between 4 and 45 mmHg in different parts of the hand (palm, dorsum, lateral edge and ventral wrist), with the highest pressures at the lateral edge (see suppl. data Figure S2). Fabric compression gloves with an inserted palmar pad (PSC) resulted in values between 13.5 and 36.5 mmHg, with less variation between the different hand positions. PSC statistically significant increased pressure in the hand palm compared to SG (SG: 4.0 mmHg [2.0–5.0] vs. PSC: 14.0 mmHg [11.8–15.3], $p = 0.002$).

Table 2 Subjective perception quality during compression and cryoapplication rated by controls and patients

Perception quality [VAS]	A) SG Controls	B) PSC Controls	C) PSC CTX	D) Cryoapplication Controls
Sensitivity loss	6.2 [5.2–7.2]	3.9 [2.3–5.6]	0.4 [0.0-2.8]	3.4 [1.6–7.2]
Movement restriction	8.2 [7.0-8.6]	5.6 [4.1–7.1]	1.6 [0.6–4.4]	2.4 [1.0–8.0]
Sweating	7.6 [5.5–8.6]	1.7 [1.0-2.1]	0.2 [0.0-0.6]	0.0 [0.0–0.0]
Pressure	7.7 [6.1–8.5]	4.6 [4.2–6.5]	2.6 [1.6–3.6]	1.0 [0.6–1.4]
Pain	6.4 [2.2–7.1]	2.0 [0.8–2.6]	0.0 [0.0-0.4]	2.2 [0.8–4.2]

Perception quality during 20 min of compression A, with two undersized surgical gloves (SG), B, under pressure-adjusted static compression (PSC), C, by CTX patients during 90 min of PSC and D, by controls during 90 min of cryoapplication. Data is presented as median with interquartile range; respective quality was rated between 0 and 10, where 0 is the maximum positive and 10 is the maximum negative perception; controls: $n = 12$, CTX: $n = 24$; Abbreviations: CTX, chemotherapy; PSC, pressure-adjusted static compression; SG, surgical glove; VAS, visual analogue scale

PSC showed compared to SG better subjective ratings regarding sensitivity loss ($p = 0.037$), movement restriction ($p = 0.033$), sweating ($p = 0.003$), pressure ($p = 0.026$) and pain ($p = 0.008$), and therefore higher comfort and improved wearability. PSC was also well tolerated by cancer patients (Table 2). Interestingly, CTX patients rated the comfort of PSC very high, probably due to the very invasive and burdensome nature of their therapy.

Compression with surgical gloves and PSC enhances microvascular perfusion and reduces oxygen demand

Replicating the setting of previous groups [5, 6, 8], we first analysed the effect of compression with 2 undersized SG as well as with PSC worn for 90 min on oxygen supply (O_2Hb) and oxygen demand (HHb), microvascular perfusion (THb) and tissue oxygenation (TOI) in controls. Unilateral SG compression over 90 min compared to ipsilateral baseline resulted in a non-significant increase of oxygen supply (A: O_2Hb, + 3.5 µM/s [2.7–13.7], p = 0.161), a reduction of oxygen demand (B: HHb, -3.9 µM/s [-6.0 - -0.3], p = 0.018), and increased tissue oxygenation (D: TOI, + 5.2% [3.2–8.9], (p = 0.006), but no change in microvascular perfusion (C: THb,+1.8 µM/s [-7.0–11.7], p = 0.56,Fig. 1). Immediately after taking the SG off, all values returned to baseline. With locally increased pressure in the palm, unilateral PSC over 90 min compared to baseline ipsilaterally lead to increase of oxygen supply (A: O_2Hb, + 10.9 µM/s [4.8–14.0], $p < 0.001$), reduction of oxygen demand (B: HHb, -3.4 µM/s [-8.0–1.7], p = 0.026), increased microvascular perfusion (C: THb, + 4.6 µM/s [1.6–12.7], p = 0.001) and tissue oxygenation (D: TOI, + 8.9% [5.2–11.9], $p < 0.001$,Fig. 1). Remarkably, after 90-minute PSC treatment, the changes in O_2Hb (p = 0.012), THb (p = 0.004) and TOI (p = 0.004) persisted for at least 10 min.

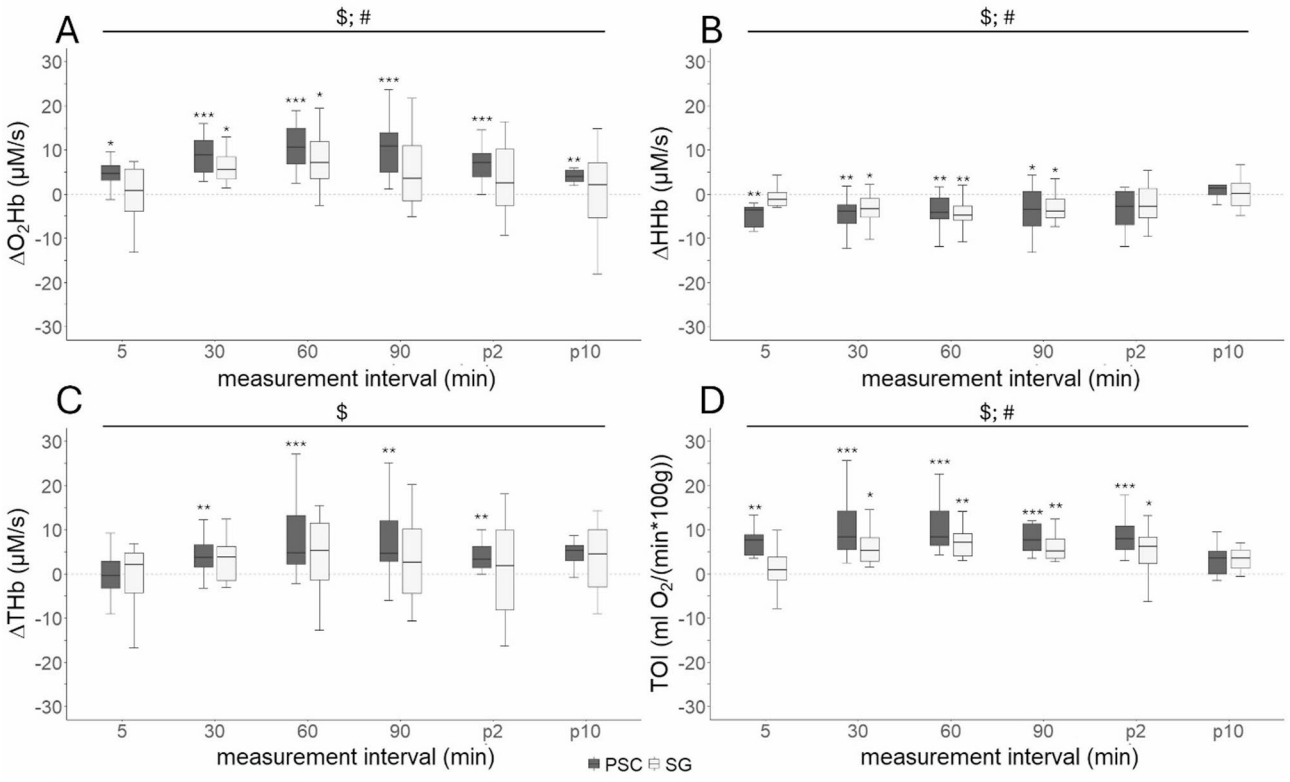

Fig. 1 Effect of pressure-adjusted static compression (PSC) and surgical glove (SG) compression on tissue oxygenation parameters in controls. **A**: O_2Hb, **B**: HHb, **C**: THb, **D**: TOI. Unilateral PSC ($n = 12$) and SG ($n = 10$) compression was performed in hands over 90 min. Tissue oxygenation parameters were measured by NIRS at baseline and after 5, 30, 60 and 90 min and during post-compression after 2 min (p2) and 10 min (p10). Data were standardised by the baseline values and presented in box plots showing the median and interquartile range. Dotted line: standardised baseline value at start of measurement (0 min)

Statistics: Analyses of differences over time in each group by Friedman test (PSC: $ and SG: #, $p < 0.05$), and post-hoc comparison of each time-point to baseline within each group by Wilcoxon test (2-sided), $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Intermittent pneumatic compression improves tissue oxygenation without direct effect on microvascular perfusion

Since there are supportive findings of intermittent pneumatic compression (IPC) increasing tissue oxygenation with clinically relevant effect in critical limb ischaemia [34], we directly compared the effect of 30 min unilateral PSC with IPC. Similarly to the effects of PSC (compare Fig. 1), during IPC in controls, oxygen supply was increased (A: O_2Hb, + 3.4 μM/s [-0.9–6.9], $p = 0.05$), oxygen demand reduced (B: HHb, -5.2 μM/s [-6.7 - -3.7], $p = 0.008$), and tissue oxygenation increased (D: TOI, + 5.3% [1.7–7.4], $p = 0.003$, Fig. 2) with no changes of microvascular perfusion (C: THb). Thus, intermittent compression with IPC, like static compression with SG and PSC, similarly showed a reduction in oxygen demand.

Venous occlusion increases oxygen demand

To further substantiate our rejection of the previously postulated mechanism of "reducing microvascular flow" [5, 6] caused by SG compression, we showed that unilateral venous occlusion at the wrist had no effect on oxygen supply or microvascular perfusion. With this classical venous occlusion pressure intervention, oxygen demand (HHb) increased by 3.5 μM/s [2.0–5.1] ($p = 0.0017$) and consecutively, tissue oxygenation (TOI) was statistically significant reduced by -2.3% [-4.9 – -1.1] ($p = 0.012$) in contrast to PSC ($p = 0.012$). Contrary to the postulated mechanism so far [5, 6, 9, 11, 14], PSC increases microvascular oxygenation and reduces oxygen metabolism.

Cryoapplication reduces microvascular perfusion, oxygen demand and tissue oxygenation

Cryotherapy over 90 min during CTX-application is evidence-based for prevention of CIPN [35], but not well tolerated [36, 37]. Subjective rating during 90 min wearing frozen gloves (-18 °C) are shown in (Table 2). In control, cryoapplication was not perceived as inconvenient during the study. No data are available on its effect on oxygen supply and demand, microvascular perfusion or tissue oxygenation.

Unilateral cryoapplication statistically significant reduced oxygen supply (A: O_2Hb, -8.9 μM/s [-12.3 - -4.9], $p = 0.002$), microvascular perfusion (C: THb, -11.4 μM/s

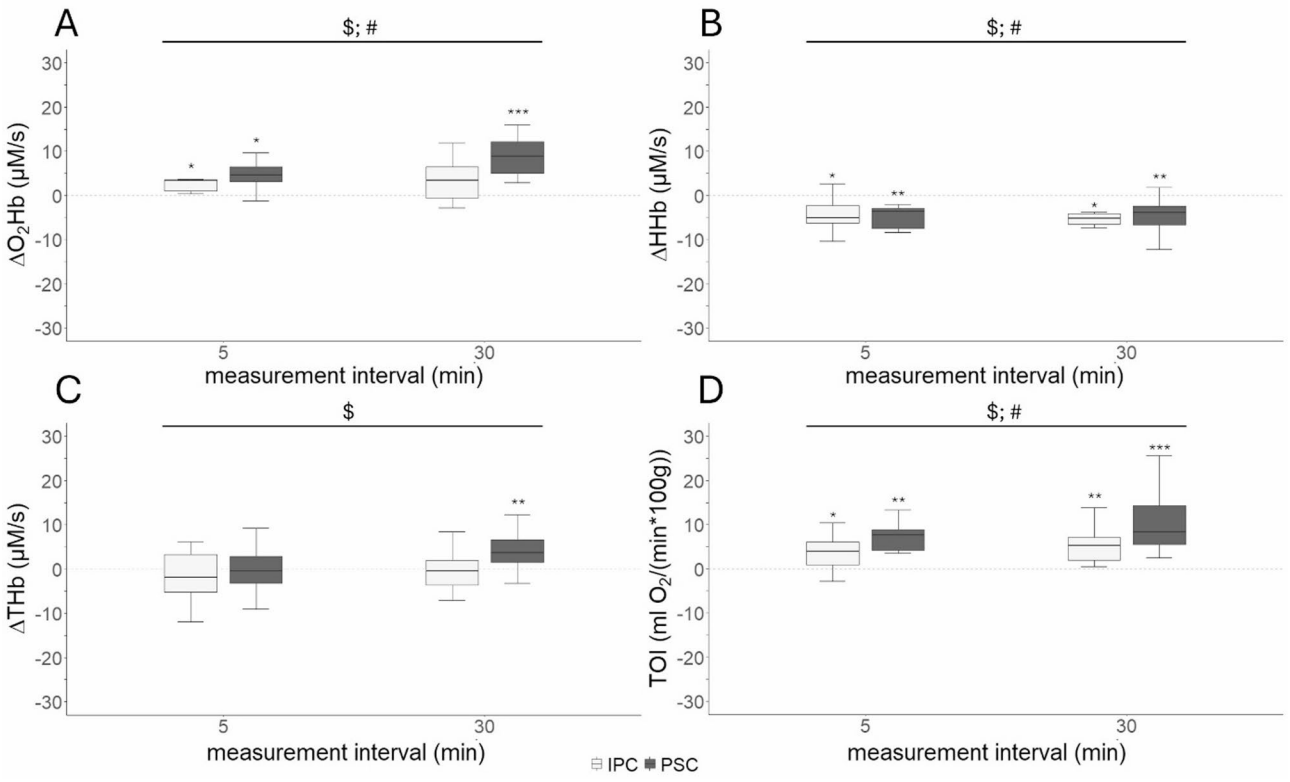

Fig. 2 Effect of intermittent pneumatic compression (IPC) compared to pressure-adjusted static compression (PSC) in controls. **A**: O_2Hb, **B**: HHb, **C**: THb, **D**: TOI. Unilateral IPC ($n = 10$) and PSC ($n = 12$) was performed in hands over 30 min. Tissue oxygenation parameters were measured by NIRS at baseline and after 5 min and 30 min. Data were standardised by the baseline values and presented in box plots showing the median and interquartile range. Dotted line: standardised baseline value at start of measurement (0 min)

Statistics: Analyses of differences over time in each group by Friedman test (IPC: # and PSC: $, $p < 0.05$), and post-hoc comparison of each time-point to baseline within each group by Wilcoxon test (2-sided), *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[-17.5 - -4.8], $p = 0.002$) and tissue oxygenation (D: TOI, – 4.0% [-7.8 - -4.9], $p = 0.019$, Fig. 3) in contrast to PSC (see also Fig. 1, $p < 0.001$). However, oxygen demand was reduced (B: HHb, -2.5 µM/s [-4.8 - -0.2], $p = 0.015$), as also observed for compression interventions (PSC, SG, IPC).

Chemotherapy impairs aerobic metabolism and damages the endothelium

We tested the hypothesis of endothelial dysfunction in CTX-patients and CTX impairing aerobic metabolism [20, 21]. Endothelial function of patients receiving chemotherapy with CIPN-inducing substances was compared to controls and PAD (peripheral arterial disease, as positive controls). Metabolism and endothelial function were statistically significant impaired with – 55% desoxygenation ($p < 0.001$) in patients receiving CTX (Fig. 4), comparable to PAD (data not shown).

Restricted reactivity of aerobic metabolism to PSC with impaired microvascular perfusion and oxygen supply in chemotherapy

Controls responded to PSC by increasing oxygen supply, decreasing oxygen metabolism and increasing tissue oxygenation. To analyse whether chemotherapy might influence manner and magnitude of responses to PSC, these were evaluated in CTX (patients with and without CIPN) and compared to controls. Statistically significant and similar changes in CTX compared to controls were seen only in the effect of PSC on oxygen demand (HHb: -0.5 µM/s [-5.7–0.7], $p = 0.006$). The impaired microvascular reactivity in CTX was reflected by the absence of PSC effects on oxygen supply, microvascular perfusion and tissue oxygenation (Fig. 5).

PSC reduces aerobic metabolism

In controls muscle oxygen consumption (VO_2) was reduced after PSC intervention compared baseline ($p = 0.015$,Fig. 6), confirming that indeed PSC reduces aerobic metabolism.

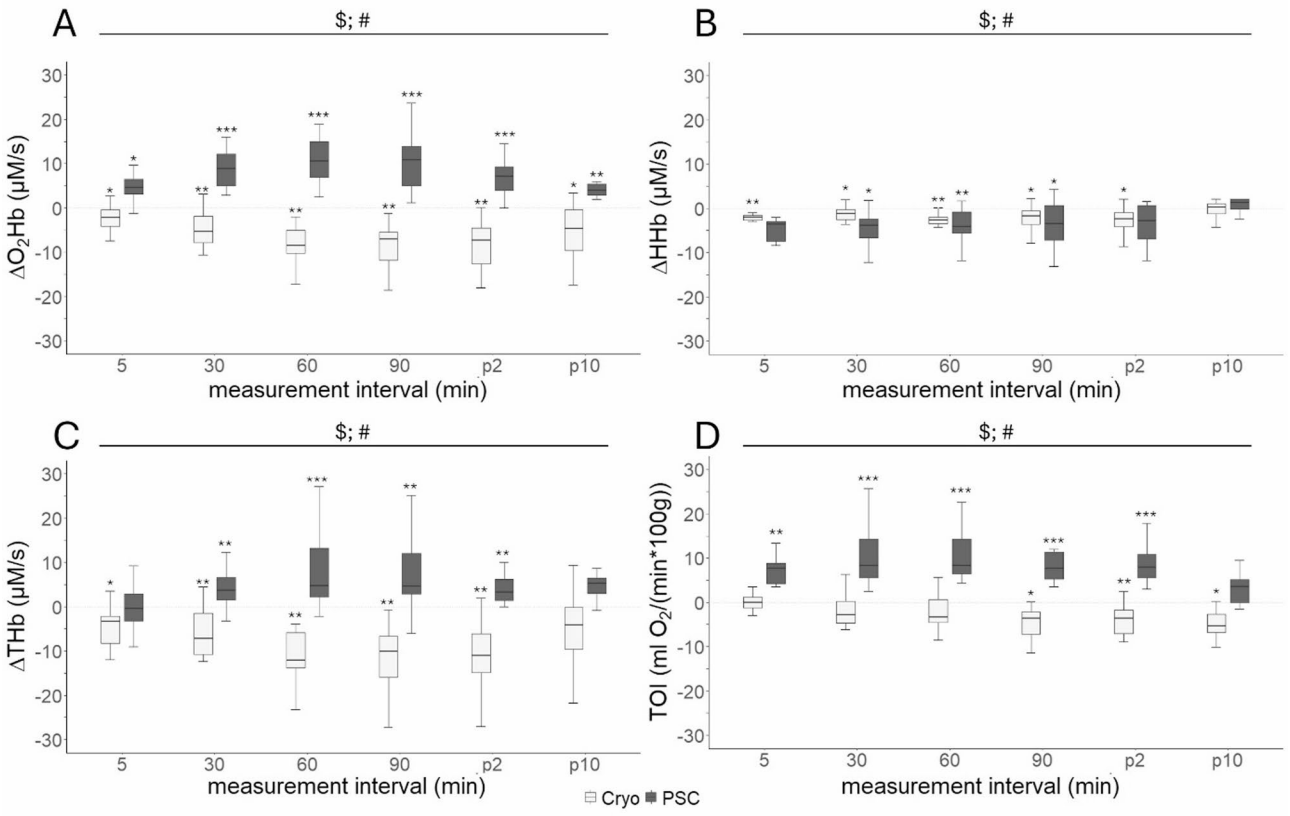

Fig. 3 Effect of cryoapplication (Cryo) compared to pressure-adjusted static compression (PSC) in controls. **A**: O_2Hb, **B**: HHb, **C**: THb, **D**: TOI. Unilateral cryoapplication ($n=12$) and PSC ($n=12$) was performed in hands over 90 min. Tissue oxygenation parameters were measured by NIRS at baseline and after 5, 30, 60 and 90 min and during post-intervention after 2 min (p2) and 10 min (p10). Data were standardised by the baseline values and presented in box plots showing the median and interquartile range. Dotted line: standardised baseline value at start of measurement (0 min). Statistics: Analyses of differences over time in each group by Friedman test (Cryo: $ and PSC: #, $p<0.05$), and post-hoc comparison of each time point to baseline within each group by Wilcoxon test (2-sided), *$p<0.05$, **$p<0.01$, ***$p<0.001$

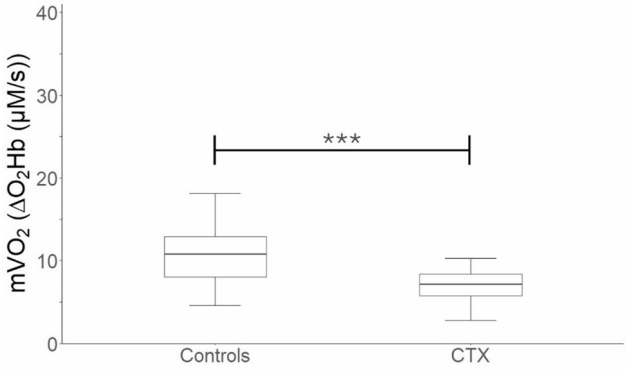

Fig. 4 Effect of chemotherapy in CTX patients ($n=23$) compared to controls ($n=21$) on tissue metabolism derived from vascular occlusion tests. Tissue oxygen consumption (mVO_2) was measured by NIRS and presented as desaturation rate (downslope of O_2Hb during the first minute of occlusion). Data are presented in box plots showing median and interquartile range

Statistics: Mann-Whitney U-test (2-sided), ***$p<0.001$

Discussion

In this study addressing the mechanism of action of an alternative therapeutic option for primary and secondary prevention of CIPN, the primary findings are: (1) compression therapy for CIPN prevention reduces cellular oxygen demand and increases tissue oxygenation; (2) chemotherapy chronically impairs not only aerobic metabolism but also vascular, more specifically, endothelial cell function comparable to atherosclerotic artery disease with reduced oxygen supply; (3) PSC with higher pressure in the region of interest showed more pronounced effects on tissue oxygenation and was superior regarding comfort compared to the currently used surgical glove compression; and (4) compression therapy, cryotherapy and IPC have completely different working mechanisms, albeit all three interventions reduce aerobic metabolism demand.

Vascular and energy metabolism with bioenergetics failure components have been implicated in the complex pathogenesis of CIPN with resultant endoneuronal hypoxia being sufficient to cause functional alterations [2, 3]. Results from our studies demonstrate

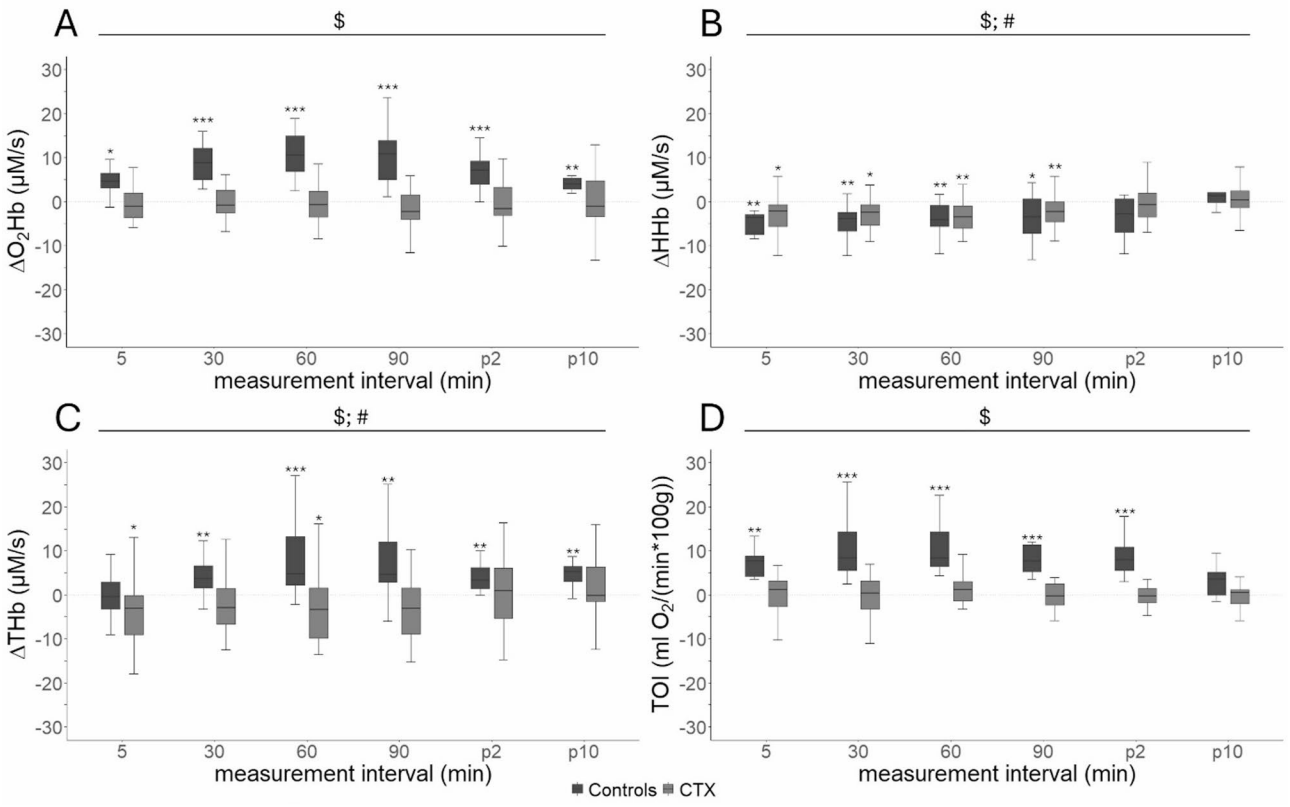

Fig. 5 Effect of pressure-adjusted static compression (PSC) in controls ($n = 12$) and CTX ($n = 24$). **A**: O_2Hb, **B**: HHb, **C**: THb, **D**: TOI. Unilateral PSC was performed in hands over 90 min. Tissue oxygenation parameters were measured by NIRS at baseline and after 5, 30, 60 and 90 min and during post-compression after 2 min (p2) and 10 min (p10). Data were standardised by the baseline values and presented in box plots showing the median and interquartile range. Dotted line: standardised baseline value at start of measurement (0 min)
Statistics: Analyses of differences over time in each group by Friedman test (controls: $, CTX: #, $p < 0.05$), and post-hoc comparison of each time point to baseline within each group by Wilcoxon test (2-sided), $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

that compression therapy decreases aerobic metabolisms with a consequent increase in tissue oxygenation. Thus, the previously postulated working mechanism of reduced microvascular flow [5, 6, 9, 14] responsible for the clinical effect of compression therapy appears less likely based on our data. Likewise, we refute the assumption that any effect from glove compression might be related to a potential venous occlusion, since the latter leads to marked increase of desoxygenated haemoglobin and reduced tissue oxygenation, in contrast to PSC. Rather, our results are consistent with prior studies showing that compression in the pressure range evoked by undersized latex gloves and optimised by PSC, results in increased perfusion [17, 38].

Reproducing previous effects of SG compression on temperature reduction [5, 6, 9, 14], we extend the knowledge of the mechanisms of action using NIRS for the context of CIPN prevention. The effects of PSC with commercially available products show similar, but more pronounced effects compared to SG, especially in the arterial region of interest for microvascular neuronal perfusion of the palm. With great attention to standardisation and validation in iterative investigations, effect of adjustment of pressure in the delineated microvascular region for neuronal perfusion of the sensory acral neurons was scrutinized. We postulate that the reduction in temperature induced by compression therapy is largely attributable to reduced aerobic metabolism, with increased oxygen delivery and consequently improved tissue oxygenation in healthy individuals. Reduced aerobic metabolism appears as the largest contributor to the clinically relevant neuronal protection in the prevention of CIPN through different therapeutic options.

Whereas PSC and SG compression showed similar reduction in temperature in the ipsilateral hand, higher pressure in the region of interest with PSC induced more pronounced changes in oxygen supply and consumption, perfusion and tissue oxygenation during compression. Evidencing reduced energy consumption with PSC, this is the most likely reason for reduction of limb temperature in compression therapy. Thus, the effect of CTX on cellular energy metabolism contributing to CIPN [20, 21] might offer an additional therapeutic target for neuroprotection for PSC in CIPN prevention.

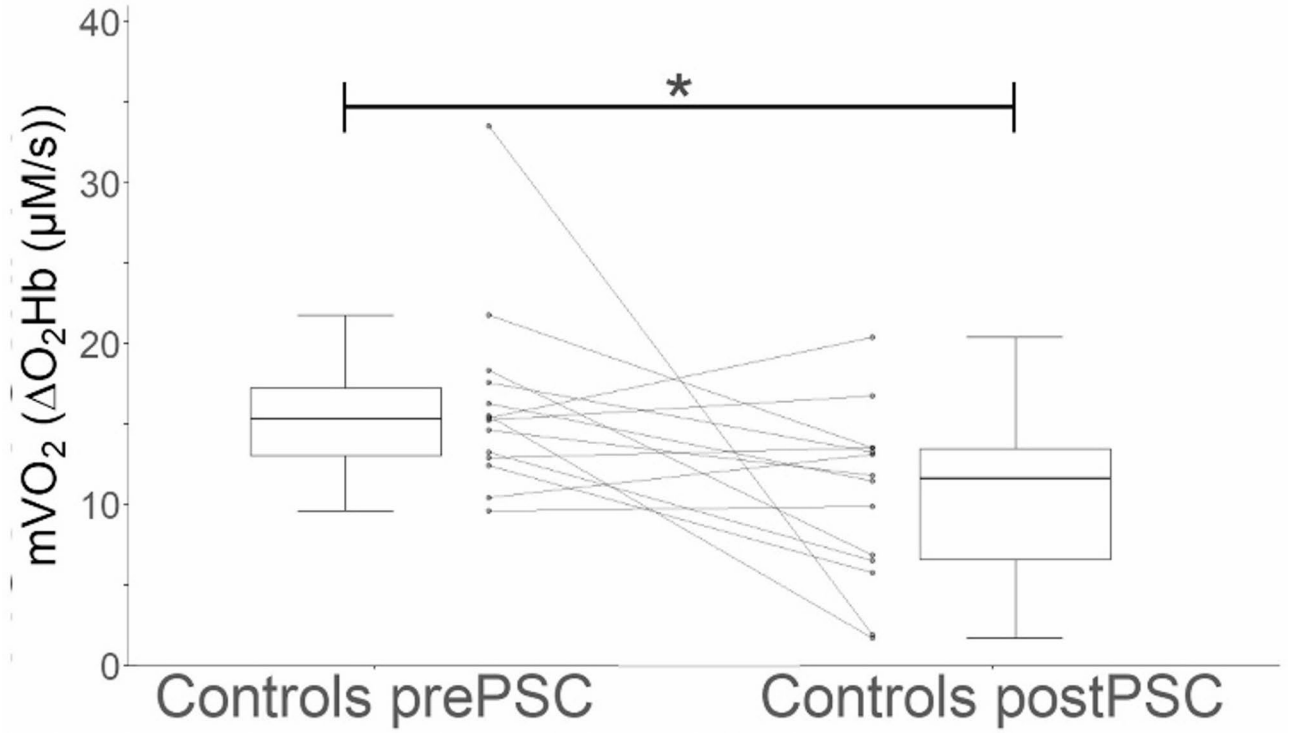

Fig. 6 Reduced aerobic metabolism in controls ($n = 14$) during unilateral pressure-adjusted static compression (PSC). Tissue oxygen consumption (mVO_2) was measured by NIRS and presented as desaturation rate (downslope of O_2Hb during the first minute of occlusion). Data are presented in box plots showing median and interquartile range. Lines represent the individual pre- and post-PSC values
Statistics: Wilcoxon test (2-sided), $*p < 0.05$

Additionally, the above-mentioned changes persist after the actual compression period in PSC only, suggesting a yet unidentified underlying mechanism. This should be considered, when discussing the duration of compression therapy, which logically should not be restricted to the duration of application of the different substances with much longer half-times, but should consider the potential underlying mechanisms and the needs of patients.

Since the predominant effect of cryoapplication was blood flow reduction, simultaneous reduction of oxygen supply prevented optimisation of tissue oxygenation.

The administration of chemotherapy induces vascular rarefaction, contributing to CIPN [2, 3] and endothelial dysfunction due to direct damage [39] and senescence [40]. Endothelial aging, marked by microcirculatory dysfunction and neurohypoperfusion of nerves aligning vessels [41], underscores the importance of optimising microvascular perfusion. However, reduced deoxygenation may not solely reflect endothelial dysfunction. Differences in medication regimens (e.g., vasoactive drugs or anti-inflammatory medications), systemic inflammation related to cancer or its treatment, and variations in baseline tissue composition (such as differences in muscle mass, fat content, or microvascular density) can also influence tissue oxygenation signals [42]. Our finding of endothelial cellular damage in patients receiving CIPN-inducing chemotherapy accentuates the importance to consider the vascular component in this complex pathophysiology. PSC may play a role in enhancing therapeutic effects by increasing oxygen delivery, microvascular perfusion, and tissue oxygenation in the microvasculature.

Our findings are in line with results from compression used in other fields to improve perfusion [15, 38]. To verify this therapeutic option, large-scale well-designed randomised controlled trials are needed.

Based on these data, for patients undergoing chemotherapy with CIPN, PSC could be a therapeutic option for CIPN-prevention. This work provided indications for the proof of principle and since our investigations were done in a group of patients with and without CIPN, the use of PSC could be relevant for both, primary and secondary prevention of CIPN. Furthermore, modification of all modifiable cardiovascular risk factors and investigating the effect of e.g. vascular protection in these patients is needed in well-designed prospective clinical trials [43–45].

In perspective, our results encourage further research into the causal relation of vascular and moreover, endothelial damage in CIPN progression, into prevention of CIPN by reducing mitochondrial metabolism, and open the field to vascular, and more specifically, for endothelial

protection, i.e. statin therapy, with the hope of offering therapy to prolong symptom-free and high-quality life expectancy [44]. Similarly, it may be worth investigating whether PSC could delay diabetic neuropathy, an equally complex pathology involving reduced mitochondrial bioenergetics and microvascular disease [19–21] to ameliorate this chronic debilitating condition.

Strengths and weaknesses

Careful attention was always given to sex distribution and age matching in the control groups. However, the patient group consisted of older individuals leading to an age mismatch between healthy controls and patients. Since age is likely to be a contributing factor, this heterogeneity represents a limitation. Moreover, the sample size was small, as the investigation was a clinically-experimental pilot study and no a priori power calculation was possible. Future studies with larger cohorts based on these data and accounting for an even age distribution will be necessary to confirm and extend these observations and prove the generated hypotheses with adequate statistical power.

The uniform application of all study procedures, using state-of-the art standard procedures and protocols for the measurement of physiological variables with NIRS with iterative protocols and independent investigations with randomisation of intervention and control for each step, and using automatic analysis are key elements of this work. Choice of the NIRS system, optode characteristics and placing them into the ROI [29, 30] and correction for blood flow/ volume are considered state-of-the art [24, 46].

Duration of occlusion was chosen to be as convenient as possible for later CTX-patients as compromise between the shorter, but reliable time frame of 3 min and discomfort to the subjects, the true zero plateau was not required for this scientific purpose.

Clearly, the clinical nature of our studies precludes further insight into the interdependence of the metabolic and vascular defects in the pathogenesis of this condition.

Influenced on reduction of EF parameters by 90 min PSC point towards a reduction of NO bioavailability that might be caused by release of NO during PSC with consequent reduced reactive hyperaemia amplitude and duration, comparable to the effect seen by repetitive VOT [47].

The investigations focused on evaluating the mechanisms of action, and only single applications without prolonged observation periods and repeated treatments were analysed. Future studies should also focus on evaluating the clinical symptoms of CIPN before and after PSC treatment at different frequencies and durations of use in order to assess the clinical course of CIPN, and to draw conclusions on the potential of PSC usage for primary and secondary prevention of CIPN. In this context, it would be interesting to examine the various compression methods in terms of their effect on the clinical endpoint of CIPN and thus gain resilient information about the optimal application.

Conclusion

In conclusion, our findings highlight the critical role of reducing cellular oxygen demand as a central mechanism in interventions aimed at preventing the incidence and progression of chemotherapy-induced peripheral neuropathy (CIPN). PSC, alongside cryotherapy and IPC, demonstrates efficacy in reducing aerobic metabolism, although each employs distinct mechanisms. Ultimately, PSC emerges as a promising therapeutic option by enhancing tissue oxygenation and microvascular perfusion, underscoring the importance of vascular health in CIPN prevention and suggesting avenues for further research into endothelial protection and neuroprotection strategies.

Abbreviations

BMI	Body mass index
CIPN	Chemotherapy-induced neuropathy
CTX	Chemotherapy
CVRF	Cardio-vascular risk factors
HHb	Desoxygenated hemoglobin
IPC	Intermittent pneumatic compression
IQR	Interquartile range
NIRS	Near infrared spectroscopy
O_2Hb	Oxygenated hemoglobin
PAD	Peripheral arterial disease
PSC	Pressure-adjusted static compression
ROI	Region of interest
SG	Surgical glove
THb	Total hemoglobin
TOI	Tissue oxygenation index
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VOT	Vascular occlusion test

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40170-025-00409-y.

Supplementary Material 1

Acknowledgements

We are grateful to Max Brunner, Lilli Scheil, Kiril Krantchev, Varinia Donat, Meline Meinköhn and Janina Renk for expert technical assistance. We are indebted to Dr. Ana Pekanovic for help with study conduct. We are very grateful to the entire team at the Interdisciplinary Medical Oncology (IMT) outpatient clinic at Charité Benjamin Franklin, and especially to Dr. Kathrin Rieger for her medical leadership, Irina Höpfner for her nursing leadership, and Meret Erbe for her excellent patient management. We would also like to thank the dedicated team at the Clinic for Haematology, Oncology and Tumour Immunology (CBF), in particular Prof. Björn Chapuy, PD Antonia Busse, PD Konrad Klinghammer, Prof. Dr. Kathrin Rieger for their medical leadership and Dr. Clarissa Heck for her support. Furthermore, we are obliged to all patients and volunteers for participating in this trial.

Author contributions
AH: Conceptualisation, Formal analysis, Investigation, Visualisation, Project administration; AS: Writing - Original Draft, Writing - Review & Editing, Supervision; ASL: Investigation, Writing - Review & Editing; BL: Conceptualisation, Validation, Formal analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualisation, Supervision, Project administration; CSL: Conceptualisation, Methodology, Validation, Formal analysis, Resources, Writing - Original Draft, Writing - Review & Editing, Supervision, Funding acquisition; HH: Conceptualisation, Methodology, Writing - Review & Editing; JM: Conceptualisation, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualisation, Project administration; RR: Conceptualisation, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualisation, Project administration; SO: Investigation, Writing - Review & Editing; UK: Investigation, Resources, Writing - Review & Editing.

Funding
Knitted gloves, stockings and pads were kindly provided by JUZO GmbH, Germany.

Data availability
No datasets were generated or analysed during the current study.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All study participants gave written informed consent, and the study was approved by the ethics committee of Charité – Universitätsmedizin Berlin (EA4/075/20, Berlin, Germany).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 30 April 2025 / Accepted: 15 September 2025
Published online: 02 October 2025

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