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CASE REPORT

Feasibility and safety of 4 weeks of blood flow-restricted exercise in an individual with tetraplegia and known autonomic dysreflexia: a case report

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Abstract

Introduction Blood flow-restricted exercise (BFRE) appears to hold considerable potential in spinal cord injury (SCI) rehabilitation, due to its ability to induce beneficial functional changes and morphological alterations from low-intensity, low-load exercise. However, it remains unclear if this training approach is feasible and safe in individuals with autonomic dysreflexia (AD).

Case presentation A 23-year-old male with traumatic, cervical (C6), motor-complete (AIS: B) SCI and diagnosed AD completed eight sessions of BFRE for the upper extremities over 4 weeks. Blood pressure and heart rate recordings and perceptual pain responses were collected repeatedly during exercise. Blood samples were drawn pre- and post-training. Training was carried out in a neurorehabilitation hospital setting with appertaining medical staff readiness, and was supervised by a physiotherapist with expertise in AD in general as well as prior knowledge of the present patient's triggers and symptoms. Four incidences of AD (defined as systolic blood pressure increase >20 mmHg) were recorded across all training sessions, of which one was symptomatic. The patient's blood profile did not change considerably from pre- to post-training sessions. Self-reported average pain during training corresponded from "mild" to "moderate".

Discussion The patient was able to perform 4 weeks of BFRE, but encountered episodes of AD. Similarly, two AD episodes were registered during a single conventional, free-flow resistance training session. Evidence from clinically controlled safety studies is needed in order to establish if and how BFRE can be applied in a rehabilitation strategy in SCI individuals with neurological level of injury at or above T6 level.

Introduction

Cervical spinal cord injury (SCI) is a catastrophic injury that leads to complications in numerous bodily systems, including locomotor functioning. Consequently, tetraplegia reduces independence and quality of life and leads to sedentarism, physical deconditioning and increased risk of secondary health conditions [1]. Recovery of upper extremity motor function is reported as the main priority for individuals with tetraplegia [2–4]; and while some function is regained during conventional rehabilitation, considerable upper extremity impairment often persists following discharge [5]. In addition, rehabilitation appears even less rewarding for individuals with motor-complete injuries [5]. Thus, a need exists for novel therapeutic approaches in this population.

Blood flow-restricted (BFR) resistance exercise (BFRE), in which low-load (20–50% of 1-repetition-maximum) muscle contractions are performed under conditions of partial restriction of blood flow to the working muscle, has been shown to increase human skeletal muscle mass and strength to a degree that is comparable to that obtained by conventional heavy-load resistance training in healthy subjects [6]. Restriction of blood flow is typically effected by inflating a pneumatic cuff at the proximal end of the limb being trained. The potential ability to induce morphological and functional changes through BFR low-load muscle

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loading appears highly relevant in SCI rehabilitation, where atrophy, impaired neuromuscular endurance and various degrees of spasticity makes heavy-load resistance training impractical and often unattainable. Although previous case reports demonstrate functional improvements following BFRE in individuals with other neuromuscular diseases (myositis [7, 8] cerebral palsy [9], sarcopenia [10]), the technique is not well established as a rehabilitation approach.

Only a single previous study [11] has investigated the effect of BFRE in persons with SCI. Nine individuals with incomplete tetraplegia underwent 6 weeks of BFR combined with neuromuscular electrical stimulation (NMES) as training for the wrist extensors. Following the intervention period, cross-sectional area (CSA) of the extensor carpi radialis longus muscle increased by 15%, to reach a 17% greater CSA than that of the contralateral control arm that underwent a similar NMES protocol without BFR [11]. No changes in CSA were seen in the extensor digitorum communis muscle. The authors also reported functional improvements in the NMES + BFR hand only, in terms of grasp and release test performance (time to complete grasping, moving and releasing a peg over a 60 cm distance; 1 ± 0.4 vs. 0.66 ± 0.16 s, $p = 0.025$ pre vs. post).

Although excessive, unaccustomed, high-volume BFRE may lead to skeletal muscle damage to a degree indicative of rhabdomyolysis [12], the safety of progressively adjusted BFRE has been relatively well established in healthy, able-bodied individuals as well as in individuals with a variety of physical conditions such as cerebrovascular-, orthopaedic-, cardiac-, respiratory- and neuromuscular diseases, diabetes and hypertension [13, 14]. However, in individuals with SCI ischaemia and pain associated with BFRE may trigger autonomic dysreflexia (AD). AD is a potentially life-threatening complication for individuals with neurological level of injury at or above the T6 level [15]. Therefore, the safety of this training approach needs to be further addressed in SCI. Stavres et al. [16] investigated hemodynamic changes, risk factors of deep-vein thrombosis (DVT) and the prevalence of AD during an acute bout of BFRE for the lower limbs in nine individuals with SCI (seven tetraplegics, two paraplegics). During a single exercise (3×10 repetitions of unilateral leg extension) and after 15 min follow-up, the subjects showed no signs of AD or elevated risk factors for DVT formation. However, the relatively low cuff occlusion pressures used (range: 39–110, mean: 60.1 mmHg) and the high motor function status of their participants (all AIS: D) limit the dissemination of these results for the general SCI population. Thus, more knowledge is needed about how BFRE may affect SCI individuals with various degrees of AD and neurological deficits.

The present case report is the first to describe the safety and feasibility of a BFRE training intervention in an SCI individual with a concurrent history of AD, using voluntary muscle activation.

Case presentation

The participant was a 23-year-old male patient admitted for neurorehabilitation at an SCI rehabilitation hospital. The anthropometrics and injury characteristics of the participant are presented in Table 1. At study initiation, the participant had been admitted for 9 months. No motor function was preserved below C7, whereas moderate function remained bilaterally in the upper extremities (Manual Muscle Test (MMT) scores are presented in Table 1). One month prior to initiation of the training programme the participant had a 24-h ambulatory blood pressure monitoring [17] (24-h-ABPM) performed. The participant presented with AD manifested as (1) bladder-distension-induced hypertension and tachycardia and (2) exercise-induced hypertension with compensatory bradycardia. In addition, he presented with autonomic dysfunction manifested as chronic hypotension and orthostatic hypotension. The participant completed 4 weeks of twice-weekly BFRE of the upper extremities for a total of eight sessions. The cuff (Cylindrical Tourniquet Cuff 90 mm, Zimmer Surgical, Inc., Dover, OH, USA) was systematically positioned at the most proximal end of the upper arm so that the most proximal edge of the cuff made contact with the anterior axillary fold, and inflated to a pressure of 100 mmHg using a computerized inflation device (Portable Tourniquet System II, Delfi Medical, Vancouver, Canada). The specific level of cuff pressure was

Table 1 Anthropometrics and injury characteristics of the participant.

Age	23
Bodyweight (kg)	55
Height (cm)	178
BMI	17.4
Neurological level of injury	C6
AIS classification	B
Aetiology	Traumatic
Time since injury (months)	11
Zone of partial preservation	
R-motor	C7
L-motor	C7
R-sensory	S5
L-sensory	S5
Manual muscle test scores	(R/L)
Shoulder abductors	5/5
Elbow flexors	5/5
Wrist extensors	3/3
Elbow extensors	2+/2

selected based on previous training protocols documented to improve upper extremity function and morphology in able-bodied subjects [18]. Three sets to failure (15–25 repetitions per set) were performed for each exercise with 45 s of rest between sets. The upper extremities were trained unilaterally, and all exercises were completed for the left arm before training the right arm. Cuff release was allowed between exercises only (separated by 3 min rest). Exercises were (in order): horizontal triceps extensions, biceps curls, and wrist extensions. The participant performed all exercises seated incline in his electrical wheelchair. During biceps curls, a 3 kg sandbag was secured to the palm of the participant's hand; triceps and wrist extensions were performed without additional load. For safety reasons, all training sessions were carried out in the participant's room at a neurorehabilitation hospital with appertaining medical staff and equipment kept in readiness. All training sessions were supervised by an experienced SCI physiotherapist with expertise in AD and with detailed knowledge about the participant's triggers and initial symptoms during previous episodes of AD. In six of the eight training sessions, using a portable blood pressure monitor (CardioXplorer, Medical Information Technology Inc., Westwood, MA, USA) attached to the contralateral arm, blood pressure data and heart rate recordings were obtained with high temporal resolution (approx. every 5 min) to monitor asymptomatic episodes of AD. In two training sessions where the original equipment was unavailable, another blood pressure monitor (Carescape V100, GE Healthcare, Chicago, IL, USA) with no recording function was applied manually approx. every 5 min for the same purpose. In addition, the supervising physiotherapist continuously asked the participant about symptoms related to AD. Immediately before and ~30 min after both the first and last training sessions, blood samples were drawn from the left antecubital vein and subsequently analyzed for a range of biomarkers associated with DVT, rhabdomyolysis and vascular and nerve damage (for a listing of the analyzed biomarkers, see Table 2). Pain sensation (11-point Numeral Rating Scale (NRS)) was scored by the participant before and after cuff inflation and immediately after the last set of each exercise (i.e., preceding cuff release).

In addition, the participant underwent a 24-h-ABPM 2 months after the BFRE intervention period, using the same portable blood pressure monitor (recordings performed every 15–30 min). From these 24-h-ABPM recordings, data from (1) a conventional training session performed without BFR (note that the temporal resolution of the BP recordings in this free-flow training session was

Table 2 Blood profile of the SCI participant assessed immediately before and after the first and last training session, respectively.

Analysis	Unit	Marker of	Reference interval	Pre-first training session	Post-first training session	Pre-last training session	Post-last training session
Troponin T	ng/l	Acute coronary syndromes	<14	113	114	107	103
Creatine-kinase	U/l	Muscle damage/ rhabdomyolysis	50–270	319	318	288	286
Myoglobin	µg/l	Myoglubinuria/ rhabdomyolysis	<75	80	71	41	45
Lactate-dehydrogenase	U/l	Tissue damage	105–205	160	165	182	159
Protein	g/l		62–78	69	68	68	69
Potassium	mmol/l	Hyperkalaemia	3.5–4.6	3.6	3.7	3.8	3.6
Sodium	mmol/l	Hyponatremia	137–145	142	141	141	139
Free calcium-ions	mmol/l	Cell damage/death	1.18–1.32	1.25	1.28	1.27	1.27
Albumin	g/l	Hepatic stress	34–45	37	37	37	37
Creatinine	µmol/l	Renal stress	60–105	43	40	41	46
Estimated glomerular Filtration rate (eGFR)	ml/min	Renal stress	>60	>90	>90	>90	>90
C-reactive protein (CRP)	mg/l	Inflammation	<8	31.9	30.1	5.7	5.8
Lymphocytes	10^9/l	Immune system dysfunction	1.3–3.5	1.57	1.42	–	–
Haemoglobin	mmol/l	Anaemia	8.1–10.3	7.2	7.2	7.7	7.5
Thrombocytes	10^9/l	Vascular damage	145–350	234	238	291	287
Fibrin D-dimer	mg/l	Thrombosis	<0.5	0.90	COA	0.87	1.0

COA = Blood sample analysis unattainable due to coagulation of the sample. Reference intervals from a Danish database are based on healthy males aged 18–55 years.

lower than for the BFRE sessions) and (2) a sterile intermittent catheterization was extracted.

The study was reported to The Scientific Ethical Committees of Region Central Jutland (case no. 1-10-72-348-18), but the board deemed it unnecessary to obtain Ethical permission, as they considered the intervention regime as individual treatment initiative for a single patient. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. The participant gave verbal and written consent to participate in the study.

The training protocol was completed successfully and without any major modifications in the experimental procedures, with the exception of five intra-exercise cuff releases on spontaneous request of the participant. During eight training sessions and 341 min of supervised BFRE the participant experienced a single episode of symptomatic AD, which he characterized as "beginning headache and discomfort" accompanied by a distinct autonomic response (SBP: +42 mmHg DBP: +46 mmHg HR: −21 bpm, compared to a recording performed 6 min prior to this event) following which the cuff was immediately released and the participant rested. The episode occurred during the last set of the last exercise in session 2 (Fig. 1); therefore, training was not resumed subsequently. Two minutes later, when the participant reported no remaining symptoms, a new blood pressure recording was performed and all values had normalized (Fig. 1). Subsequently, the participant resumed to

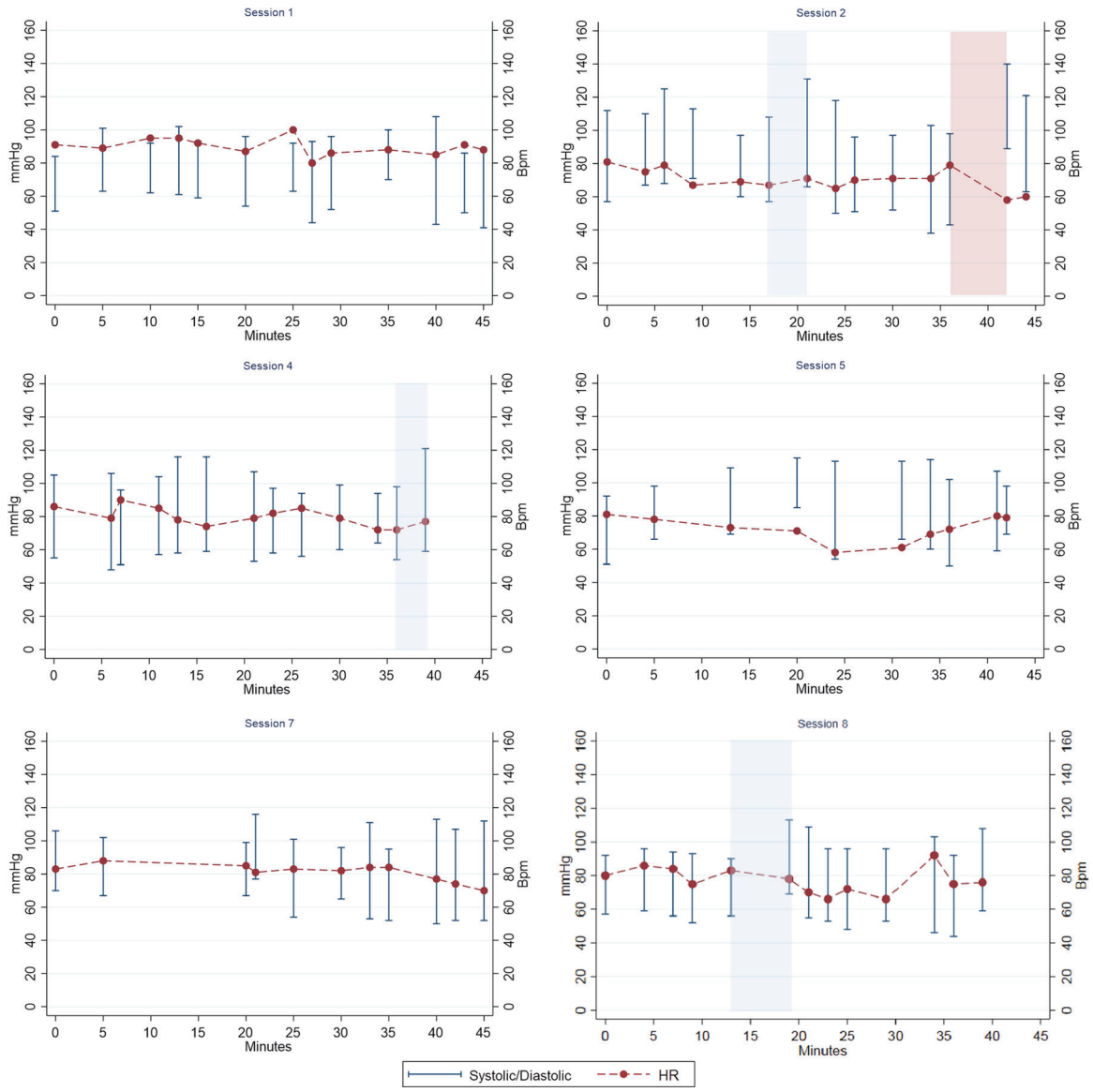

Fig. 1 Blood pressure and heart rate responses of the participant during six sessions of blood flow-restricted resistance training. SBP Systolic blood pressure, DBP Diastolic blood pressure, HR Heart rate. Blue columns represent asymptomatic AD events, red column represents the symptomatic AD event.

perform other clinical activities where he was kept under observation. Thus, the symptomatic episode that occurred during BFRE was reversed following 2 min of rest, similarly to as when AD episodes would trigger during conventional free-flow resistance training (Fig. 2). Here, the same physiotherapist would employ similar measurements and rest procedures with the participant.

A total of four cases of relatively rapid and short-lasting (4–6 min) SBP increases of 42, 23, 23 and 23 mmHg, respectively, were registered (of which one was the previously described symptomatic episode) during the duration of the study. These inherently classify as AD events according to the International Standards to Document Remaining Autonomic Function after Spinal Cord Injury (ISAFSCI) [19]. Developments of heart rate, systolic and diastolic blood pressure during training sessions with BFRE are presented in Fig. 1. Further, the reported AD events are marked in Figs. 1 and 2.

BFRE did not result in considerable changes in any biomarkers of DVT, rhabdomyolysis or vascular/nerve damage, as documented by the participant's blood profile (see Table 2).

The participant reported mild subjective pain during elbow extensors exercise, and moderate pain during elbow flexors exercise and wrist extensors exercise (see Table 3).

Two asymptomatic episodes of AD occurred in the single free-flow training session, based on ISAFSCI criterions [19] (Fig. 2).

24-h-ABPM recordings from during catheterization also revealed a severe episode of AD that was likely induced by bladder distension (SBP: +101 mmHg; DBP: +85 mmHg; HR: +175 bpm (from 58 → 233 bpm), compared to the preceding record 30 min prior to catheterization).

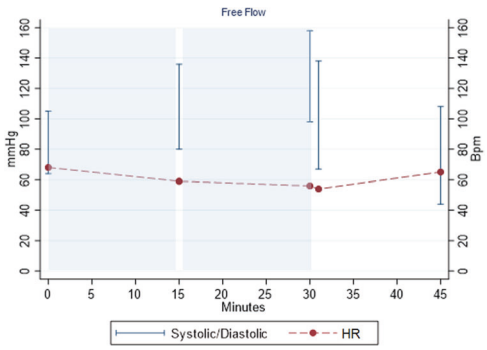

Fig. 2 Blood pressure and heart rate responses of the participant during a free-flow training session. SBP Systolic blood pressure, DBP Diastolic blood pressure, HR Heart rate. Blue columns represent asymptomatic AD events.

Discussion

In the present study, a 23-year-old tetraplegic male with autonomic dysfunction including dysreflexia successfully completed 4 weeks of BFR resistance exercise for the upper extremities. However, several episodes of AD were observed. Across eight training sessions, a single episode of symptomatic AD was registered, while three additional episodes of asymptomatic AD were registered according to the ISAFSCI definitions [19]. Correspondingly, two asymptomatic AD episodes were recorded during a single control (i.e., free-flow) training session.

BFRE did not result in any marked, acute changes in the participant's blood profile, neither following the first or the last training sessions, respectively (Table 2). Collectively evaluated, the blood sample data seemed affected by the participant's general state of health, and was potentially influenced from hip surgery procedures performed 8 weeks prior to initiation of the training study. Furthermore, we were unable to perform D-dimer analysis on blood samples obtained following the first training session, due to partial coagulation of the samples during transport to the laboratory. It may be argued, therefore, that the blood sample results are somewhat inconclusive. The participant reported mean pain levels corresponding to mild, moderate and mild pain in the classifications of the NRS [20], during the first (triceps extensions), second (biceps curls) and third (wrist extensions) exercise, respectively (Table 3). As the participant presented with impaired elbow extensor function (MMT 2+/2), normal elbow flexor function (MMT 5/5) and moderate wrist extensor function (MMT 3/3), it could be suggested that the level of reported pain is associated with the amount of motor function remaining (and hence magnitude of force production) in the respective muscle groups. In a recent study by Martin-Hernandez et al. [21], able-bodied subjects reported "strong" to "very strong" pain during six BFRE sessions of the lower limbs, while less pain has been noted when subjects gradually become accustomed to the BFRE training protocol [22]. Although the results are not readily comparable, as different rating scales and different muscle groups were employed between studies, it is interesting to note that perceptual pain during

Table 3 Mean pain scores of the SCI participant (11-point numerical rating scale) obtained before and after cuff inflation and immediately after the last set of each exercise (before deflation).

	Before inflation	After inflation	After first exercise Triceps ext.	After second exercise Biceps Curls	After third exercise Wrist ext.
Reported pain	0.1	1.1	1.4	6.4	4.9

BFRE was reported to be higher in able-bodied individuals as compared to the present participant. However, whether this is due to lower exercise intensity (load/training volume) and/or muscle volume activation, or due to SCI-induced hypoalgesia in the present participant remains unknown, and warrants further attention. A variety of noxious or non-noxious stimuli below the site of the spinal lesion can elicit AD [15]. In the present case, BFRE-induced AD is possible due to the participant not being able to register nociceptive signals from the trained limb. Both Martin-Hernandez et al. [21] and Nielsen et al. [22] reported that the mean reported pain level was lower for the last training session as compared to the first. A similar adaptive effect was not seen during the BFRE intervention period in the present case study, where the level of discomfort remained relatively stable throughout the 4-week training period. It should be noted, however, that in spite of the relatively low perceptual pain responses reported by our participant, on five occasions the cuff had to be released (deflated) following the second set of the second exercise (biceps curls, during which the reported pain was highest). The participant reported "a burning sensation in his biceps muscle". The symptoms ceased immediately following cuff deflation and rest, as also observed in able-bodied individuals [22]. Thus, it appears that the reported discomfort was naturally occurring muscle pain from the exercise performed. When asked if wishing to abort the training session (this was asked following each spontaneous deflation) the participant declined. The deflation requests did not seem to correspond with the timing of the AD events.

In conclusion, the present study participant (23-yr-old tetraplegic male with autonomic dysfunction including dysreflexia) was able to perform and tolerate 4 weeks of BFRE, although encountering four episodes of AD during the exercise sessions, of which one was symptomatic. In addition, two AD episodes were observed during a single control (conventional free-flow) resistance training session. The participant reported mild to moderate pain during the BFRE training sessions, and the discomfort ceased immediately following cuff release. Whether other types of BFRE protocols can be applied without inducing AD in SCI patients with a prior history of AD remains unknown. Future studies on BFRE in SCI individuals with injury at or above T6 should address the safety of BFRE training in this patient population, particularly in individuals with indication of AD.

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Author contributions SK, ABJ and HK are responsible for concept, design and management of the study. SK performed data analyses and wrote the initial draft of the paper. JV supervised training and collected data. KES, PA, and HK provided guidance and revised the paper. All authors have read and accepted the final version of the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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