Investigating the autoregulation of applied blood flow restriction training pressures in healthy, physically active adults: an intervention study evaluating acute training responses and safety

Ewoud Jacobs ,[1] Nicholas Rolnick,[2] Evi Wezenbeek ,[1] Lenka Stroobant,[3] Robbe Capelleman,[1] Nele Arnout,[3] Erik Witvrouw,[1] Joke Schuermans [1]

[1]Department of Rehabilitation Sciences, Ghent University Faculty of Medicine and Health Sciences, Ghent, Belgium
[2]The Human Performance Mechanic, Lehman College, New York City, New York, USA
[3]Department of Orthopaedics and Traumatology, Ghent University Hospital, Ghent, Belgium

Correspondence to
Ewoud Jacobs, Department of Rehabilitation Sciences, Ghent University Faculty of Medicine and Health Sciences, Gent 9000, Belgium;
ewoud.jacobs@ugent.be

Accepted 29 December 2022
Published Online First
5 January 2023

ABSTRACT

Objective To examine the effects of autoregulated (AUTO) and non-autoregulated (NAUTO) blood flow restriction (BFR) application on adverse effects, performance, cardiovascular and perceptual responses during resistance exercise.

Methods Fifty-six healthy participants underwent AUTO and NAUTO BFR resistance exercise in a randomised crossover design using a training session with fixed amount of repetitions and a training session until volitional failure. Cardiovascular parameters, rate of perceived effort (RPE), rate of perceived discomfort (RPD) and number of repetitions were investigated after training, while the presence of delayed onset muscle soreness (DOMS) was verified 24 hours post-session. Adverse events during or following training were also monitored.

Results AUTO outperformed NAUTO in the failure protocol ($p<0.001$), while AUTO scored significantly lower for DOMS 24 hours after exercise ($p<0.001$). Perceptions of effort and discomfort were significantly higher in NAUTO compared with AUTO in both fixed (RPE: $p=0.014$, RPD: $p<0.001$) and failure protocol (RPE: $p=0.028$, RPD: $p<0.001$). Sixteen adverse events (7.14%) were recorded, with a sevenfold incidence in the fixed protocol for NAUTO compared with AUTO (NAUTO: n=7 vs AUTO: n=1) and five (NAUTO) vs three (AUTO) adverse events in the failure protocol. No significant differences in cardiovascular parameters were found comparing both pressure applications.

Conclusion Autoregulation appears to enhance safety and performance in both fixed and failure BFR-training protocols. AUTO BFR training did not seem to affect cardiovascular stress differently, but was associated with lower DOMS, perceived effort and discomfort compared with NAUTO.

Trial registration number NCT04996680.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Individualised limb occlusion pressures are determined at rest and do not consider muscle contractions, thereby producing a higher-than-anticipated pressure compared with resting conditions.
⇒ With autoregulated cuffs (AUTO), this contraction-related pressure increase is taken into account, which is not the case with non-autoregulated cuffs (NAUTO).
⇒ To what extent the choice of AUTO cuffs affects the training response and safety within a fixed and until failure protocol has never been investigated before.

WHAT THIS STUDY ADDS

⇒ AUTO appears to reduce the risk for adverse events, with the OR of adverse events occurring in AUTO being almost three times lower compared with NAUTO blood flow restriction (BFR) training in physically active participants without prior BFR experience.
⇒ AUTO enables participants to perform significantly more repetitions when exercising until volitional failure with lower levels of perceived exertion and discomfort compared with NAUTO.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study supports the use of AUTO pressure applications during BFR resistance exercise, as it appears to enhance performance with less discomfort, exertion and delayed onset muscle soreness while reducing the risk for adverse events in both fixed and failure protocols.

To cite: Jacobs E, Rolnick N, Wezenbeek E, *et al*. *Br J Sports Med* 2023;**57**:914–920.

INTRODUCTION

Research from the last decades revealed the additional value of blood flow restriction (BFR) training, which has gradually been expanding into healthcare settings.[1 2] This reduced blood flow is thought to initiate localised hypoxia, leading to an increased type II muscle fibre recruitment, the accumulation of metabolites, elevated anabolic hormone secretion and muscle swelling, thereby upregulating anabolic pathways.[3–6] These physiological responses result in significant increases in both muscle mass[7] and strength,[8] improved physical function[9] and cardiorespiratory endurance capabilities,[10] in spite of the fairly low training intensities (<50% 1RM) attributed during BFR training sessions.

However, despite the growing supportive body of evidence, there is still a lack of definitive guidelines on implementation of BFR in resistance exercise.[1] For example, Patterson *et al* recommended four sets of exercise performed in a 30-15-15-15 repetition scheme be the preferred non-failure repetition

prescription, although failure exercise is often prescribed in practice.[2] While this might not be a case for concern in healthy individuals, it may compromise safety and affect training responses when applied unaccustomed or in patients with an altered perceptual, cardiovascular or haemodynamic response.[11]

To prevent potential adverse events from occurring and make this type of training accessible for a variety of individuals, personalised limb occlusion pressures (LOP) are recommended to limit excessive stress on the vascular system.[2] However, LOP is determined at rest and does not account for muscle contractions, despite previous studies already showed that blood flow during muscle contractions is reduced due to an augmented intramuscular pressure.[12 13] When combined, this might result in higher-than-anticipated pressures during exercise, compared with resting conditions. Therefore, it can be hypothesised that when not adjusted for muscular contractions, this supraocclusive amount of pressure applied to the limb during muscle contraction phases increases perceived discomfort and the level of stress put on the cardiovascular system, thereby decreasing the ability to perform more repetitions and enhancing the risk for an adverse event.

With autoregulated (AUTO) devices, this increase in pressure is considered by releasing air during each muscle contraction, whereas extra air is pumped into the cuffs in between contractions,[11] keeping the total pressure applied to the vasculature relatively constant. This has been previously investigated by Hughes *et al* who attempted to provide some context to discussion of this feature by comparing the cuff-limb pressure (ie, set pressure applied by the practitioner vs the pressure actually applied to the limb) between an AUTO BFR device and non-autoregulating devices. The results showed the AUTO device was better able to maintain cuff-limb pressure while exhibiting lower perceptual and haemodynamic responses compared with the other devices. However, despite standardising the cuffs to a similar LOP, each cuff had different widths that may influence perceptual and/or haemodynamics during exercise.[14] Striking, to what extent the choice of AUTO cuffs affects safety and training responses has never been investigated before.

Therefore, this is the first study to examine the acute differences between autoregulation (AUTO) and non-autoregulation (NAUTO) of applied pressures during BFR training considering adverse effects, performance, cardiovascular and perceptual responses during a training protocol with a fixed number of repetitions and another until volitional failure.

METHODS

Participants

Eighty-seven healthy, physically active participants were recruited via a QR Code on a flyer handed out within the Ghent University network. Participants filled out a preliminary questionnaire that included anthropometric questions, current level of physical activity—expressed as weekly hours of physical activity participation—along with assessment of inclusion/exclusion criteria to check study eligibility. If a candidate was found eligible for participation (18–60 years old, no prior BFR experience, absence of cardiovascular, metabolic and neuromuscular diseases or injuries impacting lower limb, chronically high (>160/100 mm Hg) or low (<90/60 mm Hg) blood pressure (BP) or pregnancy), the first session was scheduled, and an informed consent was signed in accordance with the Declaration of Helsinki.

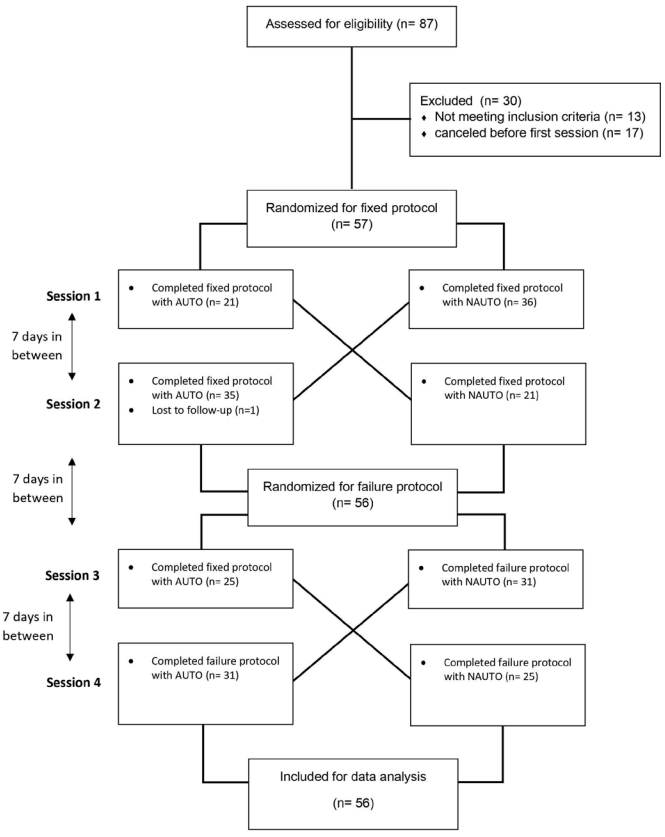

Figure 1 CONSORT statement—flow chart participants. AUTO, autoregulated; CONSORT, Consolidated Standards of Reporting Trials; NAUTO, non-autoregulated.

Study design

This intervention study intended to assess differences in AUTO and NAUTO applied pressures during BFR resistance exercise in terms of performance and cardiovascular capacity, perceptual exercise responses and the prevalence of adverse events (if any). This was done by means of a fixed and until-failure training protocol in a sample of healthy, active participants. This study was a randomised, cross-over design in which participants attended four training sessions, subdivided into two training protocols. These four sessions were preceded by a familiarisation session. The sequence for AUTO or NAUTO BFR application was determined using randomisation software (www.random/org/lists) prior to the fixed and the failure protocol (figures 1 and 2).

Each visit was separated by 7 days to avoid any influence from a previous session.[15] Participants were instructed to attend each session at the same time (±1 hour) to minimise diurnal variations

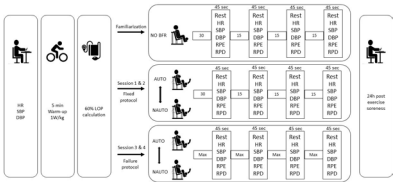

Figure 2 Experimental design. AUTO, autoregulated; BFR, blood flow restriction; DBP, diastolic blood pressure; HR, heart rate; LOP, limb occlusion pressures; NAUTO, non-autoregulated; RPD, rate of perceived discomfort; RPE, rate of perceived effort; SBP, systolic BP.

and were asked to avoid excessive alcohol and caffeine consumption 24 hours prior to each session.

Patient and public involvement

No participants were directly involved in designing the research question or in conducting the research. However, participants were asked for advice on interpretation of the adverse events experienced. All participants were informed regarding the conclusions of this study.

Equity, diversity and inclusion statement

The author group is gender balanced and consists of physiotherapists, orthopaedic surgeons, predoctoral and postdoctoral researchers from Europe and North-America. The study included 31 males and 25 females between the ages of 20 and 55, thereby covering a wide spectrum of ages and possible differences in socioeconomic statuses. However, while variables such as age, sex, level of physical activity participation were taken into account, we acknowledge we did not focus on the effects of race/ethnicity or socioeconomic status.

Testing protocol

Seven days before the start of the actual testing protocol, a familiarisation session was given to get participants accustomed to the protocol and cuff pressure and to determine the participants' estimated 1RM via the Holten Curve,[16 17] which was remeasured prior to each session. Both fixed and failure training protocols consisted of the unilateral leg extension exercise. This was executed on a leg extension machine using the dominant leg only, at a cadence allowing 2 s for both the concentric and eccentric phase (4 s each repetition). The range of motion was 90° (going from 90° to 0° of knee flexion).

Fixed protocol

The fixed protocol consisted of 75 repetitions (reps) (set 1: 30 reps, set 2–4: 15 reps with 45 s of interset rest) at 20% 1RM. Prior to this fixed protocol, participants were given a 10 min rest period to mitigate influence from any previous activities, after which baseline measures were taken and the patient was instructed to perform a 5 min warm-up on a stationary bicycle (Ergofit Cycle 400). Next, the 60% LOP was determined in a seated position using the Smartcuffs PRO (cuff width 10.16 cm). This validated device was used for all sessions. It enables determination of the LOP via a pulse pressor sensor and has a feature that allows for autoregulation.[18] Besides autoregulation, the Smartcuffs PRO also allow NAUTO BFR training, since the valve can be detached from the unit after which the originally installed pressure is kept constant. Recently, Abbas *et al* revealed that no significant difference was found between the build in pressor sensor and the current gold standard of manual Doppler ultrasound.

Failure protocol

This protocol started with a similar 10 min rest period, followed by baseline measures and a 5 min warm-up. Next, four unilateral leg extension sets until volitional failure at 20% 1RM with 60% LOP were performed, investigating the same outcome measures within the 45 s rest period after each set. Each set was terminated when participants verbally expressed the desire to stop or when they could not keep up with the cadence of the exercise or the desired range of motion. A verbal warning was given for the first violation of cadence, whereas the exercise was stopped the second time it occurred.[19]

Outcome measures

Cardiovascular

Both heart rate (HR) and BP were captured after the 10 min rest period to obtain baseline measures. These measurements were repeated after each set, in which the HR and BP were measured at the dominant arm using the Omron 3 Comfort.[20] The mean arterial pressure (MAP) was calculated from the diastolic BP (DBP) and pulse pressure (PP), taking into account HR by using the formula: MAP=DBP + (0.01* EXP(4.14–40.74/HR)*(PP)).[21]

Perceptual

For the perceptual response, rate of perceived exertion (RPE) and rate of perceived discomfort (RPD) were obtained after every set using a visual Borg scale (with scores ranging between 6 and 20) and a scale for discomfort (with scores ranging from 0 to 11).[22] Participants were asked if they felt any soreness prior to each session on a scale from 0 to 10 after palpating the Quadriceps and move from 90° knee flexion to full extension, with 0 meaning 'no soreness at all, and 10 being 'never been so sore'.[23 24] After 24 hours, the participants were asked to repeat this procedure to score the level of perceived soreness (DOMS) on the same 10-point scale.

Performance

Performance was evaluated by means of the amount of full range leg extension repetitions one was able to perform within each of the four sets until reaching volitional failure during the failure protocol only.[19]

Adverse events

Adverse events were defined as unintended or detrimental effects from a treatment during or after the exercise, prohibiting participants to continue with the exercise.[25] Additionally, participants were asked for a detailed description to map out the adverse event.

Statistical analysis

A priori sample size calculation based on the systolic BP (SBP) collected from results of previous literature[11 26] revealed a sample size of 56 individuals was required, taking into account an estimated 10% drop-out and aspiring α-level and β-level set at 0.05 and 0.1 (90% power), respectively. Baseline characteristics were compared using linear mixed models analysis, which was also used to investigate the effects of each set and conditions (AUTO/NAUTO categorisation) on the outcome measures of interest: number of repetitions, cardiovascular (HR, SBP, DBP and MAP) and perceptual responses (RPE and RPD). Respective analyses were performed using 'participant ID' as random factor with set and randomisation as fixed predictors. Post hoc analyses in which differences in mean response (for HR, SBP, DBP, RPE and RP) between sets and conditions were performed using Bonferroni corrections. This correction was also performed in quantifying the mean difference in response for DOMS and adverse events when comparing between conditions. All reported values are expressed in mean±SD. Cross-tabulation was used to visualise the relationship between pressure application and adverse event for both protocols and a general estimation equation model with a binomial distribution and a logit link function was used to quantify the risk difference between training conditions.

Table 1 Participant characteristics and pre-session measures of 56 participants who completed all sessions

Participant characteristics			Mean (SD)		
Age (years)			27.7 (9.7)		
Gender (male/female)			31/25		
Height (cm)			176.2 (10.3)		
Weight (kg)			70.5 (11.1)		
Body mass index (kg/m²)			22.6 (2.3)		
Physical activity participation (hour/week)			5.4 (3.5)		
Presession level of soreness (0–10)			1.4 (1.7)		
Outcome measures	**Pre-session 1 Mean (SD)**	**Pre-session 2 Mean (SD)**	**Pre-session 3 Mean (SD)**	**Pre-session 4 Mean (SD)**	**P value**
Systolic blood pressure (mm Hg)	131 (16)	131 (17)	131 (17)	129 (16)	0.750
Diastolic blood pressure (mm Hg)	79 (11)	78 (9)	78 (10)	78 (9)	0.797
Heart rate (bpm)	72 (16)	75 (15)	73 (15)	72 (13)	0.813
Mean arterial pressure (mm Hg)	97 (13)	97 (11)	97 (11)	96 (10)	0.216
Limb occlusion pressure	219 (26)	219 (26)	218 (23)	226 (22)	0.273

Within this model, an exchangeable correlation matrix structure for repeated measurements over time (over the four sessions) was attributed. Statistical analysis was done with the statistical package of the Social Sciences (SPSS V.28, IBM). The level of significance was set at $\alpha=0.05$.

RESULTS

Participants

Fifty-six participants completed all four BFR sessions (figure 1). One participant was lost to follow-up unrelated to BFR intervention. No baseline differences were found for SBP (p=0.750), DBP (p=0.797), MAP (p=0.813), HR (p=0.216) and LOP (p=0.273) between the four training sessions (table 1).

Cardiovascular response

For SBP, no significant differences were found over time or when comparing AUTO and NAUTO in either of the training protocols (fixed (p=0.147) and failure (p=0.052)) (tables 2 and 3). For DBP (p=0.018) and MAP (p=0.047), the only significant difference was found for set 2 of the failure protocol, with lower values for AUTO compared with NAUTO (table 3). For HR, a significant increase over time was found for both conditions (p=0.003), although no significance was found between AUTO and NAUTO (table 3).

Perceptual response

For RPE, a statistically significant difference over time was found in both the fixed (p=0.014) and failure (p=0.028) protocols when comparing AUTO and NAUTO, with lower scores for AUTO (tables 2 and 3). In both fixed and failure protocol, no significant differences were found for RPE after each set when comparing between AUTO and NAUTO conditions.

Similar to RPE, AUTO provided lower scores for RPD compared with NAUTO (p<0.001) in the fixed protocol (p<0.001) as well as in the failure protocol (p<0.001) (tables 2 and 3). When evaluating discomfort after each set, RPD was higher after set 3 in the failure protocol, favouring AUTO over NAUTO (p=0.022).

Performance

All 56 participants were able to complete the fixed protocol with both pressure applications, except for one participant who could not pursue after the first set with NAUTO.

In the failure protocol, a statistically significant difference in number of repetitions between conditions was found over time (p<0.001), with participants performing more repetitions each set in the AUTO protocol compared with the NAUTO protocol (table 3).

Table 2 Fixed protocol outcome measures of 56 participants who completed all sessions

Fixed protocol	Pressure application	Preset Mean (SD)	Set 1 Mean (SD)	Set 2 Mean (SD)	Set 3 Mean (SD)	Set 4 Mean (SD)	P values from linear mixed models		
							Time	Condition	Interaction
Systolic blood pressure (mm Hg)	AUTO	132 (18)	133 (19)	134 (18)	136 (18)	135 (16)	0.396	0.147	0.955
	NAUTO	130 (16)	135 (19)	136 (18)	137 (19)	136 (19)			
Diastolic blood pressure (mm Hg)	AUTO	79 (11)	86 (10)	88 (12)	87 (15)	86 (11)	0.448	0.384	0.248
	NAUTO	78 (9)	87 (10)	86 (12)	89 (12)	88 (11)			
Heart rate (bpm)	AUTO	75 (16)	84 (16)	84 (16)	85 (16)	85 (16)	0.148	0.667	0.855
	NAUTO	73 (15)	84 (17)	84 (17)	87 (17)	85 (17)			
Mean arterial pressure (mm Hg)	AUTO	98 (13)	104 (13)	106 (13)	106 (14)	105 (12)	0.221	0.225	0.653
	NAUTO	96 (11)	105 (12)	105 (13)	108 (15)	106 (12)			
Rate of perceived exertion (6–20)	AUTO		13.4 (2)	14.1 (2)	15.0 (2)	15.5 (20	<0.001	0.014	0.876
	NAUTO		13.7 (2)	14.7 (2)	15.3 (2)	15.7 (2)			
Rate of perceived discomfort (0–11)	AUTO		5.2 (2)	5.9 (1)	6.5 (1)	6.8 (2)	<0.001	<0.001	0.632
	NAUTO		5.4 (2)	6.3 (2)	6.9 (1)	7.3 (1)			

AUTO, autoregulated; NAUTO, non-autoregulated.

Table 3 Until failure protocol outcome measures of 56 participants who completed all sessions

Until failure protocol	Pressure application	Pre-set Mean (SD)	Set 1 Mean (SD)	Set 2 Mean (SD)	Set 3 Mean (SD)	Set 4 Mean (SD)	P values from linear mixed models		
							Time	Condition	Interaction
Systolic blood pressure (mm Hg)	AUTO	130 (16)	138 (17)	139 (20)	139 (20)	137 (19)	0.391	0.052	0.978
	NAUTO	131 (16)	140 (18)	140 (21)	141 (19)	138 (23)			
Diastolic blood pressure (mm Hg)	AUTO	78 (9)	90 (11)	87 (8)	89 (10)	89 (10)	0.755	0.051	0.420
	NAUTO	78 (9)	89 (13)	91 (11)*	91 (12)	90 (14)			
Heart rate (bpm)	AUTO	73 (14)	87 (16)	89 (19)	91 (19)	93 (19)	0.003	0.217	0.840
	NAUTO	73 (14)	89 (17)	91 (20)	93 (21)	92 (22)			
Mean arterial pressure (mm Hg)	AUTO	96 (10)	108 (12)	107 (11)	109 (12)	108 (12)	0.697	0.015	0.839
	NAUTO	97 (11)	109 (13)	110 (14)*	111 (14)	109 (16)			
Rate of perceived exertion (6–20)	AUTO		15.1 (2)	16.2 (2)	16.7 (2)	17.2 (2)	<0.001	0.028	0.236
	NAUTO		15.1 (3)	16.3 (2)	17.1 (2)	17.7 (2)			
Rate of perceived discomfort (0–11)	AUTO		6.6 (2)	7.5 (1)	7.7 (1)	8.1 (1)	<0.001	<0.001	0.452
	NAUTO		6.7 (2)	7.8 (1)	8.2 (1)*	8.5 (1)			
Repetitions	AUTO		73 (34)	43 (29)	39 (29)	44 (37)	<0.001	<0.001	0.374
	NAUTO		69 (32)	34 (21)*	28 (18)*	30 (22)*			

*Significant difference between AUTO and NAUTO with p<0.05.
AUTO, autoregulated; NAUTO, non-autoregulated.

Delayed onset muscle soreness

In the failure protocol, a significant difference for soreness after 24 hours was found in favour of AUTO compared with NAUTO (3±2.2 vs 4±2.6, p<0.001, 95% CI 0.554 to 1.022) whereas no difference was found in the fixed protocol between both BFR applications (AUTO: 2±2.1 vs NAUTO: 2±2.2, p=0.358, 95% CI −0.267 to 0.201).

Adverse events

Taking both AUTO and NAUTO training conditions into account over all 4 BFR sessions, 16 adverse events were reported, corresponding to 7.14% of all sessions. The NAUTO condition induced a higher overall incidence of adverse events in absolute number[12] and percentage (10.6%) compared with the AUTO condition, in which only four adverse events (3.6%) were observed, and these were all 'presyncopal symptoms' (table 4). Statistical analysis revealed that the odds of occurrence of adverse events in the NAUTO condition were 11%, where this was only 4% in the AUTO condition, with a risk difference of 7% between both conditions (95% CI −1% to 14%; p=0.07). Taking into account fixed and failure protocol features as well, the odds of adverse event occurrence appeared to be 12% and 9% in the fixed and failure protocols of the NAUTO condition, respectively. The odds of adverse event occurrence in the AUTO condition were 2% for the fixed protocol and 6% for the failure protocol. The adverse event risk difference in between four training conditions was only statistically significant between the AUTO and NAUTO conditions of the fixed protocol, with a risk difference of 11% (95% CI 1% to 20%; p=0.028). This was only 3% (95% CI −5% to 12%; p=0.451) for the failure protocol, were the adverse event occurrence rate was slightly higher performing the AUTO protocol as well (figure 3).

Of the 16 adverse events experienced, 13 were described as 'presyncopal symptoms', 2 as 'exercise intolerance' and 1 as 'numbness', all of these prohibiting the participants to continue/finish the exercise. Presyncopal symptoms caused 10 participants to stop exercising due to 'lightheadedness' as if they were going to faint, combined with pallor and increased sweating. Three of these 10 individuals experienced these presyncopal symptoms twice. Furthermore, two participants experienced 'exercise intolerance', as both experienced severe discomfort, causing them to stop the exercise as they were unable to lift their leg at the start of next set. Lastly, one participant complained of 'numbness', with a loss of sensation distal to the cuff which made it unfeasible to continue the exercise. Overall, three adverse events were related to set 1, seven to set 2, two to set 3, whereas four to set 4.

Table 4 Adverse events within 56 participants who completed all sessions

	Study-related adverse events	
Event	NAUTO	AUTO
Presyncopal symptoms	9	4
Numbness in leg	1	/
Exercise intolerance	2	/
Events in fixed protocol n=8	7	1
Events in failure protocol n=8	5	3
Total adverse events n=16	12	4
Total sessions n=224	113	111
Percentage (7.14%)	10.6%	3.6%

AUTO, autoregulated; NAUTO, non-AUTO.

DISCUSSION

This is the first study to examine the acute differences between AUTO and NAUTO training conditions considering adverse events, performance, cardiovascular and perceptual responses in healthy, physically active adults. The main findings are that although no major cardiovascular differences were found between both pressure applications, compared with NAUTO, AUTO(1) appears to reduce the risk for adverse events,(2) enables participants to perform significantly more repetitions

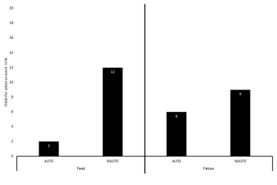

Figure 3 Odds of adverse event occurrence in each condition. AUTO, autoregulated; NAUTO, non-autoregulated.

when exercising until volitional failure, (3) reduces muscle soreness after 24 hours and (4) is perceived to be significantly less uncomfortable.

Performance and perception

The AUTO condition was associated with a significantly higher number of repetitions compared with NAUTO when performing until failure. It is noteworthy that this was not accompanied with significant differences in the cardiovascular system between AUTO and NAUTO. Participants also indicated significantly less discomfort and exertion when the cuff pressure was adjusted during muscle contractions (AUTO) compared with the NAUTO. This finding seems logical since it can be hypothesised that because NAUTO cuffs do not mitigate the effect of muscle contractions, and therefore, apply a higher-than anticipated pressure compared with autoregulation, discomfort and fatigue rapidly increases, leading to less repetitions compared with AUTO. This is an interesting finding as mitigating exercise-induced increments in the perceptual experience of BFR training has been labelled as a perceived barrier to successful BFR implementation.[27] Therefore, the difference in perception found between AUTO and NAUTO in this healthy population could be of great additional value to reduce the perceptual demands of BFR exercise, thereby fostering long term compliance to the modality without compromising possible training effects.

In addition to this increase in performance, the difference between both pressure applications on possible delayed onset muscle soreness (DOMS) was investigated as an indirect marker of exercise induced muscle damage. Although some previous studies found no significantly higher levels of DOMS following BFR after 24 hours or compared with free flow conditions,[28 29] it has been reported as a very common side effect of BFR training in other studies,[15 30] especially within individuals who are not accustomed to the high metabolic stress associated with BFR, particularly when performing until volitional failure. Indeed, our study demonstrated a significant difference in favour of AUTO in the failure protocol, which is interesting taking into account the extra number of repetitions participants were able to perform in the AUTO condition. A possible reason for the difference observed in DOMS is that BFR-training involves a high degree of metabolic accumulation largely determined by the amount of pressure applied.[4 31] As with AUTO application, the total amount of pressure imposed will not further increase the intramuscular pressure, thereby producing less hypoxia and metabolic accumulation compared with NAUTO conditions. However, more invasive measures of metabolic stress (eg, lactate sampling) are warranted to support or refute this hypothesis.

Furthermore, BFR training is commonly performed in a fixed repetition scheme with four sets exercise performed in a 30-15-15-15 repetition scheme which Patterson *et al* recommended to be the preferred non-failure repetition prescription. However, exercise until volitional failure is often prescribed in practice,[2] thereby elevating the perceptual and acute cardiovascular response compared with non-failure exercise.[32] Although the dose–response relationship between volume and adaptation needs more clarification, previous research showed exercise until failure may not even be necessary to elicit positive musculoskeletal benefits of BFR training and likely carries an additional risk of adverse events, especially during initial sessions.[33 34]

While the results of this study show an increase in training volume with AUTO compared with NAUTO BFR-training without additional cardiovascular stress, our study design does not permit extrapolation to longitudinal training (and long-term training responses). Notwithstanding mechanical tension and volume playing an important role in resistance training, previous research showed metabolic stress to have at least an equally important role, if not more.[3] Furthermore, it can be argued that lower metabolic stress arises with AUTO due to the air-release during muscle contractions, thereby negating the benefit of additional repetitions in terms of hypertrophy and strength. Nevertheless, in line with the rationale of applying individualised LOPs and based on the current study findings, we recommend to apply the chosen occlusion percentage in a relaxed muscle, thereby anticipating for muscle contractions as well as this affects the participants' safety and perception too, besides the increase in repetitions.

Safety

In this study, out of 224 BFR-sessions, no 'rare' adverse events were reported (eg, deep venous thrombosis, rhabdomyolysis); whereas 'common' (eg, presyncopal symptoms, numbness and exercise intolerance) occurred 7.14% of the time.[25] Out of the 16 adverse events that occurred, 12 events were reported in NAUTO conditions (10.6%) and 4 in AUTO-application (3.6%).

The number of adverse events occurring in this study with NAUTO appears to be in line with previous literature where adverse events are reported between 11% and 15%.[1 35–37] In contrast to these relatively high incidences with NAUTO, only 4 out of 111 BFR sessions (3.6%) occurred with AUTO application (1 adverse event in the fixed protocol (1.8%) and 3 (5.5%) in the failure protocol). Statistical analysis revealed an adverse event risk difference of 11% between AUTO and NAUTO conditions in the fixed protocol. This risk difference was 3% and non-significant, but nonetheless clinically relevant, when comparing AUTO and NAUTO conditions in the failure protocol. This is a key finding in this study as it is very valuable for BFR recommendations in daily training and clinical practice.

It can be hypothesised that cuffs mitigate the risk for an adverse event as this pressure application is able to keep the total pressure on the vasculature constant, compared with the NAUTO cuffs, which allow for a higher-than-anticipated pressure during each muscle contraction, despite using individualised %LOPs. Because of these pressure fluctuations and particularly high local occlusion levels during muscle contraction, the higher prevalence of adverse events (most commonly presyncopal symptoms, for example, lightheadedness, pallor and sweating) could be at least partially explained by higher levels of vascular occlusion using NAUTO BFR, potentially inducing more blood pooling in the exercising limb.[38] The associated decrease in venous return would lead to a decline in stroke volume that might contribute to adverse events related to an imbalance in autonomic function. In addition, this might be enhanced by a Valsalva-manoeuvre which is frequently observed when performing heavy resistance exercises or when exercising until volitional failure, resulting in an increase in intrathoracic pressures, thereby further reducing the venous return and subsequent cardiac preload.[39] In their paper discussing exercise-related syncope in young athletes, O'Connor *et al* described that decrement in stroke volume, exercise-induced circulating catecholamines and forceful ventricular contractions against a diminished ventricular volume could stimulate ventricular mechanoreceptors excessively. Afferent vagal C-fibres would subsequently transmit these signals to the central nervous system with efferent reflexes, resulting in vasodilation and bradycardia, inducing hypotension and syncope. In addition, it could be assumed that the overall higher pressure with NAUTO might lead to a higher arterial compression and increased shear stress of the endothelium, thereby downregulating autonomic sympathetic

activity and induce shear-dependent vasodilatation.[40] This mismatch in vasomotor tone (due to the external cuff pressure, which is theoretically increased with NAUTO compared with AUTO) could enhance the risk for (pre)syncopal episodes. In addition, the overall higher compression imposed on participants submitted to NAUTO BFR training could also explain the numbness distal to the cuff and exercise intolerance—defined by very intense discomfort by the cuff pressure and lack of strength causing participants to stop the exercise—observed in this study and in previous research.[25 41]

While this rationale provides a theoretical explanation for the higher incidence in adverse events in NAUTO compared with AUTO, it is noteworthy that the incidence of adverse events within the NAUTO application was higher in the fixed protocol compared with the more intense failure protocol. While this finding is counterintuitive and might suggest more complex mechanisms behind the occurrence of adverse events (eg, the level of stress, nervousness and discomfort, as these are also known to elicit a vasodepressor syncope, which is accompanied with prodromal symptoms including, eg pallor, sweating, nausea[42]), it could be explained to some extent by a certain 'repeated bout' effect in which participants were able to get accustomed to BFR, as prior research showed an increased risk for adverse events when no prior BFR experience.[27] Furthermore, despite being commonly applied, we recommend the fixed protocol (30/15/15/15 reps) to be preceded by a familiarisation session with less volume or applied pressure to get patients accustomed to BFR-training as this might mitigate the risk for adverse events.[27 33]

Nevertheless, more research is necessary to better understand the mechanism behind these adverse events, as the difference in incidence is likely not related to the cardiovascular response to BFR. Results in this study revealed that in the fixed protocol, no significant effects in cardiovascular parameters between AUTO and NAUTO were found. In the failure protocol, only a significantly lower MAP ($p=0.015$) was found favouring AUTO over NAUTO.

Nonetheless, the percentage of individuals experiencing 'presyncopal symptoms' during the exercising conditions in both groups are something to consider when administering BFR training as this appears to be a common adverse event in unaccustomed, healthy, physically active participants.

Limitations

This was the first study evaluating the difference between the use of AUTO or NAUTO cuffs during fixed and failure resistance exercise protocols looking at performance and acute haemodynamic and perceptual responses to training, but it is not without limitations. Due to the equipment used for leg extensions, we were unable to determine an exact 1RM value for 22 male participants. We elected to use the Holten Curve[16 17] to produce an estimate 1RM value based on sub-maximal leg extension exercise. Nonetheless, while this may alter 1RM estimates in these participants (likely <20% 1 RM), the within-subject design mitigates the differences in training load between participants, as the participant's measured responses to the exercise protocols are using a similar percentage of 1RM in either condition (NAUTO/AUTO). In addition, assessment of a 1RM in clinical populations is largely unfeasible due to injury or post-surgical precautions, so this load determination approach fits in well in clinical settings. Surprisingly, no previous literature described the occurrence of similar adverse events in traditional strength training, thereby prohibiting any direct comparison. Lastly, as this study was performed on a healthy, physically active population between 18 and 60 years old, extrapolation to clinical populations warrants caution.

Clinical implications

As clinicians look to incorporate BFR into their practice, understanding of the different ways that it can be applied is essential to improve outcomes and/or reduce incidence of adverse events. Our study supports the use of autoregulation of applied pressure as it appears to enhance performance and safety during training. Although these AUTO devices may be more expensive, the safety of the individuals using BFR remains primordial and therefore justifies the higher economic cost of these devices. During AUTO conditions participants were able to perform more repetitions with less discomfort and exertion and without increasing stress on the cardiovascular system compared with NAUTO, while mitigating DOMS after 24 hours. Of great value is the finding in this study that autoregulation appears to reduce the risk for adverse events with the odds of adverse event occurrence being 11% in the NAUTO vs 4% in the AUTO training protocols.

Twitter Ewoud Jacobs @Ewoud Jacobs, Nicholas Rolnick @thebfrpros and Evi Wezenbeek @WezenbeekEvi

Contributors First author EJ is responsible for the overal content as guarantor. NR conceived of the study. EJ and NR designed the exercise protocol. EJ performed all data collection, statistical analyses and designed the tables with the help of EW and JS. LS was the responsible physician during data collection. EJ and NR drafted the first version of the manuscript. EJ, NR, EW, RC, NA and JS critically revised the manuscript and approved its final form.

Funding This research was funded by the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (FWO).

Competing interests NR is the founder of The BFR PROS and teaches BFR training workshops to fitness and rehabilitation practitioners using a variety of BFR training devices.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by Ethics Committee of the Ghent University Hospital (number of approval: BC-11035). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data are available upon reasonable request. Requests for data sharing from appropriate researchers and entities will be considered on a case-by-case basis. Interested parties should contact EJ (ewoud.jacobs@ugent.be).

ORCID iDs
Ewoud Jacobs http://orcid.org/0000-0002-4658-0552
Evi Wezenbeek http://orcid.org/0000-0001-9303-6915
Joke Schuermans http://orcid.org/0000-0001-6631-4334

REFERENCES

1 Patterson SD, Brandner CR. The role of blood flow restriction training for applied practitioners: a questionnaire-based survey. *J Sports Sci* 2018;36:123–30.
2 Patterson SD, Hughes L, Warmington S, *et al*. Blood flow restriction exercise: considerations of methodology, application, and safety. *Front Physiol* 2019;10:533.
3 Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Medicine* 2015;45:187–200.
4 Takarada Y, Nakamura Y, Aruga S, *et al*. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J Appl Physiol* 2000;88:61–5.
5 Fujita S, Abe T, Drummond MJ, *et al*. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J Appl Physiol* 2007;103:903–10.
6 Nakajima T, Yasuda T, Koide S, *et al*. Repetitive restriction of muscle blood flow enhances mTOR signaling pathways in a rat model. *Heart Vessels* 2016;31:1685–95.
7 Lixandrão ME, Ugrinowitsch C, Berton R, *et al*. Magnitude of muscle strength and mass adaptations between high-load resistance training versus low-load resistance

training associated with blood-flow restriction: a systematic review and meta-analysis. *Sports Med* 2018;48:361–78.
8 Grønfeldt BM, Lindberg Nielsen J, Mieritz RM, *et al*. Effect of blood-flow restricted vs heavy-load strength training on muscle strength: systematic review and meta-analysis. *Scand J Med Sci Sports* 2020;30:837–48.
9 Abe T, Sakamaki M, Fujita S, *et al*. Effects of low-intensity walk training with restricted leg blood flow on muscle strength and aerobic capacity in older adults. *J Geriatr Phys Ther* 2010;33:34–40.
10 Held S, Behringer M, Donath L. Low intensity rowing with blood flow restriction over 5 weeks increases VO_2max in elite rowers: a randomized controlled trial. *J Sci Med Sport* 2020;23:304–8.
11 Hughes L, Rosenblatt B, Gissane C, *et al*. Interface pressure, perceptual, and mean arterial pressure responses to different blood flow restriction systems. *Scand J Med Sci Sports* 2018;28:1757–65.
12 Lutjemeier BJ, Miura A, Scheuermann BW, *et al*. Muscle contraction-blood flow interactions during upright knee extension exercise in humans. *J Appl Physiol* 2005;98:1575–83.
13 Hoelting BD, Scheuermann BW, Barstow TJ. Effect of contraction frequency on leg blood flow during knee extension exercise in humans. *J Appl Physiol* 2001;91:671–9.
14 Spitz RW, Chatakondi RN, Bell ZW, *et al*. Blood flow restriction exercise: effects of sex, cuff width, and cuff pressure on perceived lower body discomfort. *Percept Mot Skills* 2021;128:353–74.
15 Sieljacks P, Matzon A, Wernbom M, *et al*. Muscle damage and repeated bout effect following blood flow restricted exercise. *Eur J Appl Physiol* 2016;116:513–25.
16 De Ridder E, Danneels L, Vleeming A, *et al*. Trunk extension exercises: how is trunk extensor muscle recruitment related to the exercise dosage? *J Electromyogr Kinesiol* 2015;25:681–8.
17 Van Roie E, Bautmans I, Boonen S, *et al*. Impact of external resistance and maximal effort on force-velocity characteristics of the knee extensors during strengthening exercise: a randomized controlled experiment. *J Strength Cond Res* 2013;27:1118–27.
18 Abbas MJ, Dancy ME, Marigi EM, *et al*. An automated technique for the measurement of limb occlusion pressure during blood flow restriction therapy is equivalent to previous gold standard. *Arthrosc Sports Med Rehabil* 2022;4:e1127–32.
19 Stanford DM, Park J, Jones R, *et al*. Acute cardiovascular response to unilateral, bilateral, and alternating resistance exercise with blood flow restriction. *Eur J Appl Physiol* 2020;120:1921–30.
20 Topouchian J, Hakobyan Z, Asmar J, *et al*. Clinical accuracy of the omron M3 comfort® and the omron evolv® for self-blood pressure measurements in pregnancy and pre-eclampsia - validation according to the Universal Standard Protocol. *Vasc Health Risk Manag* 2018;14:189–97.
21 Moran D, Epstein Y, Keren G, *et al*. Calculation of mean arterial pressure during exercise as a function of heart rate. *Applied Human Science* 1995;14:293–5.
22 Borg G. *Borg's perceived exertion and pain scales, 30*. Human Kinetics, 1998: 1.
23 Umbel JD, Hoffman RL, Dearth DJ, *et al*. Delayed-onset muscle soreness induced by low-load blood flow-restricted exercise. *Eur J Appl Physiol* 2009;107:687–95.
24 Brandner CR, Warmington SA. Delayed onset muscle soreness and perceived exertion after blood flow restriction exercise. *J Strength Cond Res* 2017;31:3101–8.
25 Minniti MC, Statkevich AP, Kelly RL, *et al*. The safety of blood flow restriction training as a therapeutic intervention for patients with musculoskeletal disorders: a systematic review. *Am J Sports Med* 2020;48:1773–85.
26 Lemes Ítalo Ribeiro, Ferreira PH, Linares SN, *et al*. Resistance training reduces systolic blood pressure in metabolic syndrome: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* 2016;50:1438–42.
27 Rolnick N, Kimbrell K, Cerqueira MS, *et al*. Perceived barriers to blood flow restriction training. *Front Rehabil Sci* 2021;2:697082.
28 Wernbom M, Augustsson J, Thomeé R. Effects of vascular occlusion on muscular endurance in dynamic knee extension exercise at different submaximal loads. *J Strength Cond Res* 2006;20:372–7.
29 Thiebaud R, Loenneke JP, Fahs CA, *et al*. Muscle damage after low-intensity eccentric contractions with blood flow restriction. *Acta Physiol Hung* 2014;101:150–7.
30 de Queiros VS, Dantas M, Neto GR, *et al*. Application and side effects of blood flow restriction technique: a cross-sectional questionnaire survey of professionals. *Medicine* 2021;100:e25794.
31 Suga T, Okita K, Morita N, *et al*. Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol* 2010;108:1563–7.
32 Sieljacks P, Degn R, Hollaender K, *et al*. Non-failure blood flow restricted exercise induces similar muscle adaptations and less discomfort than failure protocols. *Scand J Med Sci Sports* 2019;29:336–47.
33 Wernbom M, Schoenfeld BJ, Paulsen G, *et al*. Commentary: can blood flow restricted exercise cause muscle damage? Commentary on blood flow restriction exercise: considerations of methodology, application, and safety. *Front Physiol* 2020;11:243.
34 Bjørnsen T, Wernbom M, Paulsen G, *et al*. Frequent blood flow restricted training not to failure and to failure induces similar gains in myonuclei and muscle mass. *Scand J Med Sci Sports* 2021;31:1420–39.
35 Martín-Hernández J, Santos-Lozano A, Foster C, *et al*. Syncope episodes and blood flow restriction training. *Clin J Sport Med* 2018;28:e89–91.
36 Nakajima T, Iida H, Kurano M, *et al*. Hemodynamic responses to simulated weightlessness of 24-h head-down bed rest and KAATSU blood flow restriction. *Eur J Appl Physiol* 2008;104:727–37.
37 Prue J, Roman DP, Giampetruzzi NG, *et al*. Side effects and patient tolerance with the use of blood flow restriction training after ACL reconstruction in adolescents: a pilot study. *Int J Sports Phys Ther* 2022;17:347–54.
38 O'Connor FG, Oriscello RG, Levine BD. Exercise-related syncope in the young athlete: reassurance, restriction or referral? *Am Fam Physician* 1999;60:2001–8.
39 Hackett DA, Chow C-M. The Valsalva maneuver: its effect on intra-abdominal pressure and safety issues during resistance exercise. *J Strength Cond Res* 2013;27:2338–45.
40 Lu X, Kassab GS. Integrins mediate mechanical compression-induced endothelium-dependent vasodilation through endothelial nitric oxide pathway. *J Gen Physiol* 2015;146:221–32.
41 Mendonca GV, Mouro M, Vila-Chã C, *et al*. Nerve conduction during acute blood-flow restriction with and without low-intensity exercise nerve conduction and blood-flow restriction. *Sci Rep* 2020;10:7380.
42 Kapoor WN. Syncope. In: Walker HK, Hall WD, Hurst JW, eds. *Clinical methods: the history, physical, and laboratory examinations*. Boston, 1990.