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<u>**Vascular adaptations during hybrid- or handcycling**</u>

Key words: *Spinal cord injury, Functional electrical stimulation, Exercise, Vascular adaptations, Intima media thickness, Flow mediated dilatation*

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Vascular adaptations in non-stimulated areas during hybrid cycling or handcycling in people with a spinal cord injury: a pilot study of 10 cases

Abstract

Study Design Sub-study of a randomized controlled trial

Objectives To examine if hybrid cycling (cycling with the legs via electrical stimulation combined with voluntary handcycling) compared to handcycling leads to different systemic vascular adaptations in individuals with a long-term spinal cord injury (SCI) .

Setting Two rehabilitation centers in the Netherlands.

Methods Ten individuals with a SCI trained on a hybrid bicycle (N=5) or a handcycle (N=5) for 16 weeks twice a week. Prior to and following the training the intima media thickness (IMT) of the common coronary artery (CCA) and superficial femoral artery (SFA) were measured and the flow-mediated dilation (FMD) of the brachial artery (BA) was analyzed.

Results Before training, there were no significant differences in any of the outcome measures between the groups. We found no change in CCA-IMT (pre: 0.616mm, post: 0.586mm), or in SFA (pre: 0.512mm, post: 0.520mm) after hybrid cycling. We also found no change in FMD % of BA after hybrid cycling (pre: 9.040%, post: 9.220%). There were no changes in CCA-IMT, SFA-IMT and FMD% after handcycling either.

Conclusions It appears that 16 weeks of twice weekly training of up to 30 min on a hybrid bicycle or handcycle does not lead to systemic vascular adaptations. A larger sample size and training protocol with more frequent and higher intensity training (which might involve a home-based setting and an adapted period prior to the training) might show different results.

Introduction

Provision of interventions that improve vascular adaptation are highly relevant given the high mortality and morbidity of cardiovascular disease (CVD) and cerebrovascular disease, particularly among individuals with spinal cord injury (SCI). The prevalence of cardiovascular disease is 17% in people with a SCI compared to 5% in individuals without a SCI (1) (2) (3). It is known that exercise plays an important and relevant role in vascular adaptations.

One way to measure vascular adaptations is through the intima media thickness (IMT), another is through flow mediated dilation (FMD) with cuff inflation and deflation. In the case of able-bodied people with increased cardiovascular risk or disease demonstrating a priori impaired FMD, exercise training leads to improvement in FMD. In healthy able-bodied people a temporary increase in FMD with normalization is expected after a period of training. Existing research recognizes the critical role played by exercise in able-bodied people on activated and non-activated regions (9) (10). Exercise three times a week of 30 minutes of cycling for 8 weeks resulted in a decrease of wall thickness and Wall-to-Lumen ratio in the superficial femoral artery and the carotid artery (11). A study focusing on training for the marathon (4 times a week for a period of 16 weeks) showed a decrease in brachial and popliteal total wall thickness and increase in lumen diameters (12). A six-month training program consisting of either full body resistance training or endurance training showed a decrease in carotid artery intima media thickness (IMT)(13).

In people with SCI, hybrid cycling, which includes cycling with the legs via electrical stimulation (ES) combined with voluntary handcycling, is the approach with the most potential for improving the endothelial function in the activated limbs of people with a SCI (6). In people with SCI, despite the increased cardiovascular risk, FMD is higher than in healthy people but FMD decreases in the stimulated areas following a period of exercise training (4)(5) (17). Previous studies in people with SCI (7) (14) (15) (8) have only shown local vascular adaptations after a period of ES exercise, but not in the non-stimulated areas. Thijssen et al. (8) found that local vascular adaptations (diameter) occurred in the ES- stimulated areas, but not in the non-stimulated areas (calf and forearm) (diameter and FMD), in individuals with a SCI after 4 weeks of hybrid cycling (3 times a week for 30 minutes). Measurements on the forearm, however, were biased by the fact that the arms were highly developed as a result of regular wheelchair exercise. In addition to that, this study was limited to a period of 4 weeks of hybrid cycling, which was probably not sufficient for vascular adaptations in the non-stimulated areas. It has previously been observed that the systemic effects of hybrid cycling result in increased cardiorespiratory fitness in people with a SCI . It was also demonstrated that hybrid cycling resulted in a higher metabolic rate and cardiorespiratory response than handcycling (16).

It is established that exercise in people with a SCI induces vascular adaptation in the stimulated area. The influence of exercise on the non-stimulated areas, however, remains unclear. To date no study has investigated the effect of exercise for periods longer than 4 weeks on the non-stimulated areas in persons with a SCI.

The aim of this pilot study was to explore whether vascular adaptations occur in the non-activated areas after a relatively long training period either with hybrid cycling or handcycling. The IMT and diameter at the common coronary artery (CCA) and superficial femoral artery (SFA) were used to measure non-stimulated areas. FMD at the brachial artery (BA) was a measure for non-stimulated areas in de hybrid group with the consideration of local muscle activity during hand and hybrid cycling. It was expected that training would reduce the intima media thickness (IMT) in the CCA and SFA. It was also expected that the difference in mainly the CCA and SFA would be larger with hybrid cycling compared to handcycling, due to the larger muscle mass involved.

Methods

This study is part of a larger study, which was described by Bakkum et al.(18) in 2013. Briefly, a 16-week Randomized Controlled Trial was performed in two Dutch rehabilitation centers (Amsterdam and Nijmegen) between November 2011 and November 2013. Participants were randomly assigned to either the experimental group (hybrid cycle training group) or the control group (handcycle training group). Participants in Nijmegen also provided vascular measurements as part of the present study in order to study vascular adaptations in non-stimulated areas during hybrid cycling as opposed to handcycling.

Participants

Ten man with a long-standing SCI of at least 8 years, aged between 28 and65, wheelchair dependent and inactive (lower than the 75th percentile in the Physical Activities Scale for Individuals with Physical Disabilities (PASIPD)(19) of a Dutch cohort study population) were recruited from the database of the rehabilitation center in Nijmegen. Each received an information letter and signed an informed consent indicating voluntary participation in the study. The study was completed in accordance with the Medical Ethics Committee of the VU University Medical Centre Amsterdam. After screening by a rehabilitation physiatrist, patients with pressure sores, cardiovascular problems, severe musculoskeletal complaints or psychiatric problems were excluded.

The handcycle

The handcycle (Speedy-Bike, Reha-Technik GmbH, Delbrück, Germany) was equipped with a wide synchronous bull-horn crank, and with 8 gears that can be changed manually. The handcycle was placed on a Tacx Flow ergotrainer (Tacx Flow, Technische Industrie, Tacx B.V., Wassenaar, The Netherlands).

The hybrid cycle

The BerkelBike Pro (Berkelbike BV, Sint-Michielsgestel, the Netherlands) with a similar handbike and also placed on the Tacx Flow ergotrainer was used for hybrid cycling, combining synchronous handcycling with asynchronous ES-induced leg cycling. A 6-channel stimulator (NeuroPro, Berkelbike) provided ES via self-adhesive 50 x 90 mm surface electrodes placed bilaterally over the quadriceps, hamstrings, and gluteal muscles. The pulse duration was 400 µs and maximum current amplitude was 150mA.

Training protocol

One week before the first training session, participants carried out a graded peak exercise test in their own handrim-propelled wheelchair and had their maximal exercise response measured. Participants performed 32 training sessions within a continuous period of 16 weeks. Each training session started with a warm-up, followed by a training session of between 18 and 32 minutes (rate of perceived exertion of 4-7 on the Borg's 10 point scale and 65-75% heart rate reserve response during training). For the detailed training program see Bakkum et al. (18).

Outcome measurement

The primary outcomes were intima media thickness (IMT) at the carotid artery and FMD at the brachial artery. Secondary outcomes were IMT and FMD at the femoral artery.
At baseline (pre-test) we collected patient characteristics: age, gender, lesion level and completeness with the AIS scale, medical history, intoxication history, spasticity, body mass, height, body mass index (BMI) and PASIPD score (Physical Activities Scale for Individuals with Physical Disabilities) (19). The IMT and diameter were measured at CCA, BA and SFA and FMD at BA was measured. During the training we collected training time,

stimulation (amplitude) of the ES, Borg scale and if there was any discomfort or pain. After the training program (post-test) IMT, diameter and FMD were measured again as soon as possible.

Intima media thickness (IMT) and diameter were measured under standardized conditions using high resolution ultrasound (T3000, Terason, Burlington, MA) across arteries in the neck (common carotid artery) and leg (superficial femoral artery). With the AVI converter the files were converted to Dicom files. Those files were analyzed in IMT software version 3.0. The program visualized the upper and lower lumen intima and the media adventitia (figure 1). Frames that were taken when the ultrasound was moved, frames were no media adventitia was found, and part of the frames were no media adventitia was found or placed wrong, were excluded. Then the program made a calculation of the mean, minimum, maximum, and standard deviation of the IMT and Diameter. The analysis was done by a different person than who performed the ultrasound measurement and was blinded for the training group. To gain experience with the computer program all 10 analyses were done once without adding those results into the study result. When all measurements were done a second time, the analyses were viewed together with an expert and after receiving advice the analyses were done a third time. Those results were used in the study results.

Flow mediated dilatation and nitroglycerine mediated dilatation were measured under standardized conditions using high resolution ultrasound across arteries in the arm (brachial artery) and leg (superficial femoral artery). The video was analyzed in Dicom encoder and FMD/blood flow analysis program version 3.0. The region of interest in the Doppler signal and in the artery were selected. The video was played while the artery and Doppler signal were visualized. The program transfers this into graphs; one with time on the x-as and diameter on the y-as, one with peak blow flow on the x-as and one with shear rate on the y-as. The peak blood flow graph is to inform when the constriction and dilatation took place. Irregularities of the signal were selected and the video of that part was shown again. If at that moment the ultrasound was moved, those areas were excluded. In FMD settings the baseline area and dilatation area were selected and subsequently the program calculated baseline diameter, FMD peak diameter, FMD peak diameter percentage. The same was done with glyceryl trinitrate (GTN) mediated dilatation with GTN settings, where baseline, GTN peak, GTN peak percentage were measured. Again to gain experience all measurements were done three times and viewed with an expert, where only the third results were used for further analysis.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software package version 23. The repeated measures ANOVA analysis was used and effect size (Cohen's d) to examine the effect of 16 weeks exercise either with hybrid cycling or handcycling on IMT and FMD of the different arteries. The handcycle and hybrid cycle training group were equally analyzed. For Cohen's d 0.2 is a small effect, 0.5 medium and 0.8 large (20). To analyze the individual effects, graphs were made with the pre-test outcomes of IMT, diameter and FMD plotted against the post-test outcomes.

Results

Participants

Characteristics of the participants are shown in Table 1. Participants 5, 9 and 10 were smokers and participants 3, 4 and 5 had mild spasticity. All 10 participants finished the study but participant 8 missed one training session, participant 7 missed two sessions and participant 10 missed five sessions due to holidays. With participant 1 some measurements were incorrect. Participant 6 was too hypotensive post-test to complete the measurements. Half the participants (participants 3,6,7,8 and 10) were measured more than one week after the last training session.

Vascular adaptations

In the whole test group (hybrid and/or handcycle) thirty-two handcycle or hybrid cycle training sessions did not result in significant changes in IMT in the CCA and in the SFA. No changes in diameter and FMD of the BA (table 2 and figure 2) were found. When viewing the plots in which the individual pre- and post-test outcomes are visualized, group differences are not clearly shown and contradictory results between the individual participants appeared.

Discussion

The study showed that 16 weeks (twice a week for 18-30 minutes) of hybrid cycling or handcycling did not result in vascular changes at non-stimulated areas. Our hypothesis was that after hybrid cycling or handcycling IMT at the non-stimulated area's would get smaller but neither on a group level, nor on an individual level were vascular changes found.

Pre-test results showed that the diameters of SFA and CCA were comparable to those previously reported (5) but the pre-test FMD was slightly higher (4)(21). People with SCI use their arms more intensively than able-bodied people, which might show a local trained effect of the arm. Pre-test results of the 3 participants who smoke, were the same as the rest of the group, even though it is known that there is an inverse relationship between the intensity of tobacco smoke and FMD (2). Pre-test results of the 3 participants with mild spasticity were the same as the rest of the group even though spasticity can simulate a small exercise effect. Two people with a cervical lesion (participant 3 and 5) were included, which could have influenced their FMD in the brachial artery with a larger pre-test FMD (due to atrophy of the arm muscles). They did, however, not show different values in their pre-test FMD (perhaps because one had a motor incomplete lesion and both had spasticity).

The 16 weeks, twice a week, up to 30 minutes, hybrid or handcycle training program did not result in any vascular adaptations of non-stimulated areas in people with a SCI. All except one participant finished their exercise schedule. Results contrast with several training studies (including able-bodied people) in which the training frequency was at least 3 times a week resulting in vascular changes in non-trained areas (13)(22).

Thijssen et al. (8) did not measure any change in vascular adaptation in the brachial artery in patients with SCI after 4 weeks of twice weekly hybrid cycling for 25 minutes. Four weeks of hybrid cycling, and 16 weeks of twice a week 30 min training might, therefore, not have been long and/or frequent enough for vascular adaptation. To train for a 3 month period 3x/week for 60 minutes will be a challenge for this group. If people with a SCI want to achieve the benefits, lifelong training will probably be necessary to reduce their increased risk of cardiovascular diseases. It is a challenge to arrange frequent long-term training in a rehabilitation centre with enough motivated sedentary participants. Training at home with a handcycle and Compex electrical stimulation might be an acceptable alternative.

The training intensity in our study was between 4-7 on the Borg's 10 point perceived exertion scale and/or 65-75% heart rate reserve response during training. In our study the time and intensity were gradually increased, whilst all the studies with able-bodied participants immediately started with training at least 3 times a week. People with a SCI need to gradually increase the intensity to adapt to hybrid cycling. It is known that exercise intensity is an important factor in remodelling endothelial function in healthy, obese and heart failure patients

(23) (24)(25). Training at a higher intensity might have been more effective in people with SCI. To achieve a higher intensity, one may increase the resistance with handcycling. However starting on a high intensity is prone for overuse injuries. Especially in case of spinal cord injured people, who are limited in which muscles they can use . Adding more resistance might make the exercise more prone to overuse injuries in the arms, which can be a significant handicap for wheelchair users with SCI (29). The balance between exercise with high intensity and low risk of overuse is important. It might be necessary to separate the adapting period from the intervention period and to start the actual intervention after the adapting period, resulting in a longer period of exercise with a high intensity.

The limitations of our study include the small sample size and the heterogeneity within the sample. We were aware that it would be difficult to get significant results with such a small sample size in this pilot study, but we hoped to see a trend, which could be explored in a future study. Our recommendation for a future study would be more frequent training (>3 times a week) with a higher intensity in a home-based setting with an adaptation period prior to training.

Conclusion

Sixteen weeks of hybrid cycling or handcycling did not result in vascular adaptation in non-stimulated areas (such as brachial, coronary artery and femoral superficialis artery). We cannot conclude that this does not happen either with a more intense and frequent training protocol with a larger sample size. This pilot study had its limitations, particularly the small sample size. To analyse if hybrid cycling or handcycling has an effect on the non-stimulated areas, a study design with more frequent training and higher intensity is needed, which might involve home-based training and an adaption period prior to training.

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Conflict of interest

All authors have nothing to disclose.

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Table 1. Patient information
* ASIA grade is used to classify the completeness of the lesion: A, sensory and motor complete; B, sensory incomplete but motor complete; C, sensory and motor incomplete but no functional motor activity.
BMI = Body Mass Index, HB = handcycling, HC = hybrid cycling

Table 2. Pre and post 16-week training values for the total group as well as hybrid cycle group and handcycle group, are provided for all outcome measures. For all outcome measures, no significant effects were found.

CCA: common coronary artery; IMT: intima media thickness; SFA: superficial femoral artery; FMD: flow mediated dilatation; BA: brachial artery; GTN: glyceryl trinitrate

Figure 1: The carotid artery where the lumen intima (yellow) and media adventitia (red) are marked.

Figure 2. A) scatter plot of the IMT at CCA, B) scatter plot of the diameter at CCA, C) scatter plot of IMT at SFA, D) scatter plot of diameter at SFA, E) scatter plot of FMD peak at BA and F) scatter plot of the percentage of FMD of the baseline at BA.

Table 1

Participant	Age at time of inclusion (years)	Gender	Lesion level	ASIA Grade *	Time since injury (years)	BMI (kg/m2)	PASIPD score (METS)	Group
1	64	M	T4	A	18	26.5	2.8	HC
2	30	M	T4	A	12	24.4	16.7	HB
3	47	M	C6	C	13	26.5	1.0	HB
4	45	M	T5	A	16	24.8	14.8	HB

5	38	M	C5	B	13	24.9	1.8	HC
6	49	M	T1	A	28	19.4	20.9	HC
7	31	M	T10	A	14	24.6	6.0	HC
8	58	M	T8	A	25	28.1	8.2	HC
9	45	M	T11	A	16	16.8	7.4	HB
10	38	M	T9	A	10	20.2	23.2	HB

Table 2

	Total group					Hybrid cycling					Handcycling					Ptime	Ptime x group
	N	pre	post	Δ (SD)	d	N	pre	post	Δ (SD)	d	N	pre	post	Δ (SD)	d		
		Mean (SD	Mean (SD)				Mean (SD)	Mean (SD)				Mean (SD)	Mean (SD)				
CCA IMT (mm)	8	0.62 (0.13)	0.58 (0.08)	0.03 (0.15)	0.211	3	0.613 (0.11)	0.59 (0.05)	0.03 (0.10)	0.261	5	0.62 (0.16)	0.58 (0.11)	0.03 (0.18)	0.187	0.622	0.951

CCA diameter (mm)	9	6.8 (0.5)	6.7 (0.6)	0.07 (0.5)	0.139	4	6.9 (0.6)	6.5 (0.6)	0.34 (0.5)	0.066	5	6.7 (0.4)	6.9 (0.5)	-0.16 (0.30)	-0.513	0.524	0.113
SFA IMT (mm)	8	0.54 (0.09)	0.56 (0.1)	-0.02 (-0.05)	-0.477	4	0.54 (0.09)	0.61 (0.09)	-0.03 (0.05)	-0.628	4	0.51 (0.06)	0.52 (0.09)	-0.013 (0.05)	-0.276	0.250	0.640
SFA diameter (mm)	9	5.8 (0.6)	6.0 (0.8)	-0.13 (0.63)	-0.200	4	5.7 (0.8)	5.5 (0.7)	0.10 (0.08)	1.278	5	5.9 (0.4)	6.3 (0.7)	-0.38 (0.77)	-0.492	0.650	0.192
Baseline prior to FMD measurement (mm)	9	3.99 (0.64)	4.11 (0.75)			4	4.14 (0.89)	4.11 (0.91)			5	3.87 (0.44)	4.11 (0.70)				
FMD peak BA (mm)	8	4.44 (0.66)	4.57 (0.70)	-0.13 (0.88)	-0.147	3	4.81 (0.67)	4.73 (0.80)	0.07 (0.22)	0.325	5	4.24 (0.61)	4.46 (0.07)	-0.25 (0.10)	-0.219	0.802	0.657
FMD % BA	8	8.94 (4.72)	8.88 (3.60)	0.07 (2.25)	0.029	3	9.5 (6.8)	9.2 (5.7)	0.23 (1.32)	0.175	5	8.6 (3.9)	8.7 (2.6)	-0.03 (2.83)	-0.011	0.915	0.887
GTN peak (mm)	8	4.96 (0.82)	4.96 (0.63)	0.001 (0.78)	-0.002	3	0.54 (0.08)	0.53 (0.08)	0.01 (0.2)	0.732	5	0.47 (0.07)	0.48 (0.05)	-0.007 (0.10)	0.071	0.944	0.767
GTN %	8	22.1 (7.36)	22.9 (8.29)	-0.73 (5.10)	0.141	3	24.3 (7.8)	24.5 (10.4)	-0.21 (5.21)	-0.040	5	20.9 (7.7)	21.9 (7.9)	-1.05 (5.62)	-0.187	0.764	0.841

Figure 1

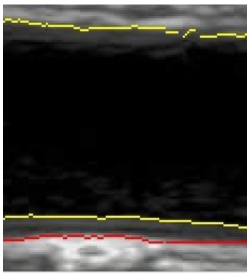
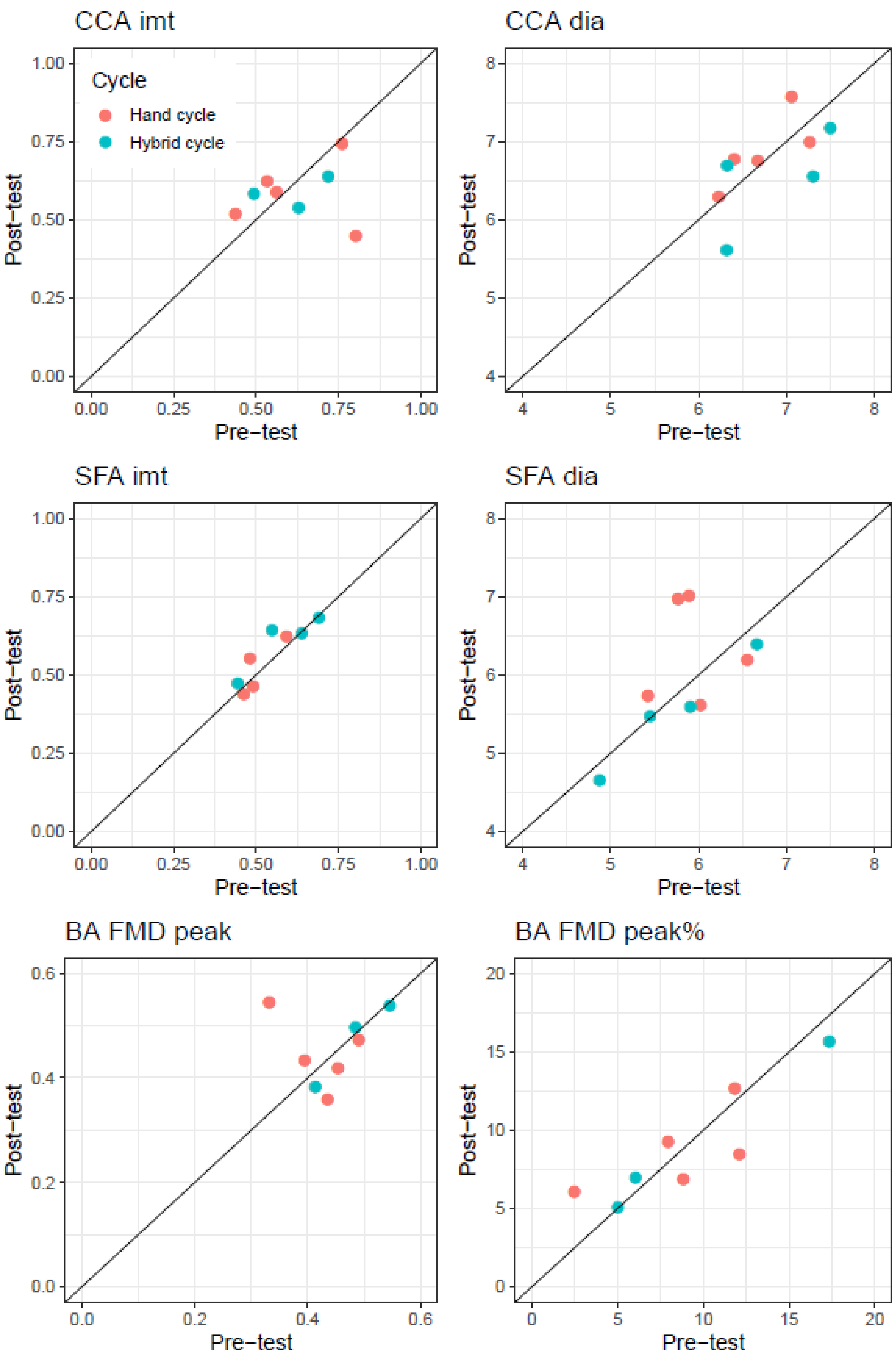


Figure 2


CCA imt
CCA dia
SFA imt
SFA dia
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BA FMD peak%
Cycle
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Post−test
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0.00
0.25
0.50
0.75
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4
5
6
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