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Hemodynamic responses to In-Bed Cycle Exercise in the acute phase after moderate to severe stroke: A randomized controlled trial

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Abstract

Hemodynamic responses to exercise in the acute phase after moderate to severe stroke have remained poorly investigated. The aim of this randomized controlled study, in which 52 (32 women) patients with moderate to severe stroke were randomized to three weeks of 20 minutes in-bed cycle exercise 5 days per week or to usual care, was to explore the systolic blood pressure (SBP) response to exercise and to evaluate the impact of the intervention on the resting and post-test systolic and diastolic blood pressures and heart rate, and on the systolic blood pressure response to exercise. We found that resting SBP decreased from baseline to post-intervention in both the intervention group (147.7 ± 18.1 mmHg to 125.3 ± 17.1 mmHg, $P < .001$) and in the control group (147.8 ± 23.7 mmHg to 131.4 ± 14.8 mmHg, $P < .001$) without a significant difference between the groups (interaction $P = .308$). However, there was a significant difference (interaction $P = .010$) regarding how Δ SBP (change in SBP from pre-test to post-test) changed from baseline to post-intervention. In the intervention group, Δ SBP increased from −1.0 ± 15.0 mmHg to 8.5 ± 9.4 mmHg, $P = .009$, whereas in the control group, Δ SBP decreased from 7.1 + 10.9 mmHg to 4.5 + 11.8 mmHg, $P = .395$. We conclude that patients randomized to in-bed cycle exercise seemed to normalize their blood pressure response to exercise to a larger extent than patients in the control group.

1 | INTRODUCTION

Little is known about hemodynamic responses to aerobic exercise in patients with moderate to severe stroke in the acute phase (1–7 days)[1] after stroke.[2] After a mild stroke, aerobic exercise is suggested and recommended as a safe and beneficial intervention[3-5] to improve walking ability and balance.[6,7] However, a more conservative approach to aerobic exercise has been suggested in patients with more severe stroke, due to concerns of disturbed cerebral autoregulation leading to increased blood pressure variability.[8] Disturbed cerebral autoregulation may include periods of hypotension[9] (systolic blood pressure drop ≥ 10 mmHg) after exercise, that could cause cerebral hypoperfusion.[10] Indeed, disturbed cerebral autoregulation has been associated with larger infarct size and with worse neurological outcome three months after stroke.[11]

The primary aim of this study was to explore, in normotensive and hypertensive patients with acute stroke, the systolic blood pressure response to a single bout of in-bed cycle exercise. The secondary aims of the study were to evaluate the impact of three weeks of 20 min in-bed cycle exercise 5 days per week on the resting and post-test systolic and diastolic blood pressures and heart rate, and on the systolic blood pressure response to exercise.

2 | METHODS

This was a secondary analysis of a dual-centre, parallel, prospective randomized controlled trial, comparing in-bed cycle exercise performed five days per week for three weeks (intervention) with usual care (control).[12] The study protocol (Clinical Trial Registration No: NCT04241952) was guided by the Consolidated Standards of Reporting Trials statement and has been previously described in detail together with the main results of the study.[12]

2.1 | Patients and setting

Patients were recruited consecutively from the stroke unit at Vrinnevi Hospital, Norrköping, and Höglands Hospital, Eksjö in Sweden, during Nov 2015-Nov 2018.

The subjects had to be at least 18 years old, but there was no upper age limit. All subjects had to have had a first stroke that was diagnosed by a physician prior to the request for inclusion. Subjects had to be considered able to perform aerobic exercise by the responsible physician, and to understand spoken and written instructions. Their impairments had to correspond to a National Institutes of Health Stroke Scale (NIHSS) score of 7–42.[13]

Medical or neurologic diseases that could either be a risk or make the exercise program difficult to fulfill were causes for exclusion. This judgment was made by the treating physician. Patients treated with thrombolysis were also excluded.

2.2 | Procedures

Participants were recruited consecutively from the stroke units by the responsible physiotherapists. The participants received written and oral information about the study. Written informed consent was obtained from all participants. At the start of the study, 24–48 h after stroke onset (baseline/pre-intervention) and prior to randomization, a 6-minute in-bed cycle exercise test and other physical assessments were carried out in the stroke unit. The assessments were repeated after 3 weeks (post-intervention) at the stroke unit. The participants' physiotherapist and study-responsible physiotherapist were responsible for randomization. Randomization was performed by shuffling concealed envelopes after which the treating physiotherapist randomly picked an envelope. The intervention started 24–48 h after randomization.

2.3 | Blood pressure measurement

The hemodynamic response to exercise was measured at baseline and after three weeks (post-intervention). Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured by trained study personnel once before and once after the six minute in-bed cycle exercise test in the non-affected arm, which was supported at heart level with the patient in supine position. Blood pressure measurements were performed with the auscultatory method, using calibrated sphygmomanometers. Heart rate was measured before, and during the last minute of the test (Peak exercise heart rate) and after the test, using a pulse oximeter (Rad-5v, Masimo, Irvine).

2.4 | Six minute in-bed cycle exercise test

After the initial blood pressure measurement, the 6-minute in-bed cycle exercise test started with passive cycling at 20 revolutions per minute (RPM) and increased progressively to active cycling 20 RPM or more for in total 6 min cycling without resistance. Each participant was encouraged to cycle by himself/herself and the goal was to get as far as possible in 6 min. After the test, the participant was removed from the cycle while remaining supine in bed during measurement of post-test BP and heart rate approximately five minutes after the test had ended. After the test, patients were encouraged to express the intensity of the effort by the Borg rating of perceived exertion (RPE scale).[14] Since this was a trial that included patients with established vascular disease, including elderly and potentially frail participants, the exercise test protocol was adjusted individually.

2.5 | Intervention

The in-bed cycle exercise intervention began after randomization. The exercise period lasted for 3 weeks and included daily sessions five days per week, resulting in a maximum of 15 sessions. The exercise sessions were conducted in the wardroom and included 20 min of in-bed cycle exercise. The exercise sessions were led by an experienced physiotherapist. The individual exercise intensity was adapted during each session by adjusting the load or the cycling speed so that the exercise goals were achieved. If the participants did not spontaneously reach the target intensity and exercise time, the bed cycle provided active support and the physiotherapist gave verbal encouragement. Each 20-minute session was performed in bed, in supine position, with an electrical bed cycle. Each participant was encouraged to cycle by himself/herself, but otherwise the cycle was able to run passively at 20 revolutions per minute (RPM). Each participant was given 2 fitness goals for each exercise session. The first goal was to reach 20 min of cycling, active or passive. The second goal was to reach an exertion level RPE (11-13) that corresponded to ≥ 50% of the estimated maximum oxygen uptake and 60% of the maximum heart rate.[14,15]

2.6 | Outcome variables

The outcome variables in this study were SBP, DBP, and heart rate before and after exercise, and changes in these parameters from baseline to post-intervention. We also analyzed, at baseline and at 3 weeks, delta SBP (Δ SBP) which was calculated as the difference between SBP post 6-minute in-bed cycle exercise test and the resting SBP.

2.7 | Statistical analysis

The sample size calculation was based on the primary outcome measure in the randomized controlled trial, the 6-Minute Walk Test (6 MWT).[12] Using a 2-tailed test with a type I error of 0.05 and a power of 80%, a clinically significant difference between the intervention and control groups (mean improvement, 50 m, standard deviation (SD) 53 m) for the 6MWT would be detected with a minimum sample of 20 subjects per group.[16] Considering possible dropouts, the primary study goal was to include at least 100 participants. Statistical analyses were conducted using SPSS version 25. The level of significance was set at $P < .05$. Continuous variables are presented as mean (SD). Categorical data are presented as numbers and percentages. For baseline data, between-group differences were tested for statistical significance with two-sided independent t tests for numerical variables or chi-square test of Fisher´s exact test for categorical variables. For differences between variables measured at baseline and at post-intervention, paired t tests were used for numerical variables and McNemar´s test was used for categorical variables. Differences within and between groups over time were examined using a mixed design repeated-measures analysis of variance (2 groups x 2 time points).

2.8 | Ethics

The study was approved by the Regional Ethics Committee, Linköping, Sweden (DNR 2015/358-31).

3 | RESULTS

3.1 | Study participants

During a three-year period 80 stroke patients from two stroke units in Sweden were assessed for eligibility and 56 patients were included in the study.

Among these, complete data regarding resting and post-exercise blood pressure were obtained in 52 participants both at baseline and post-intervention. These 20 (38.5%) men and 32 (61.5%) women with mean age 74.7 ± 9.3 years constitute the study population for the present analysis. Their baseline characteristics are presented in Table 1. Seventy one percent of the study participants had a prior history of hypertension before baseline according to prior diagnoses retrieved from their medical records.

3.2 | Hemodynamic characteristics at baseline

Baseline tests including 6-minute in-bed cycle exercise test were made after a mean of 1.9 ± 1.7 days following stroke onset. Overall, average SBP increased from resting/pre exercise (147.8 ± 21.2 mmHg) to after 6-minute in-bed cycle exercise test (151.3 ± 21.6 mmHg), corresponding to an average Δ SBP (post-test SBP - resting SBP) of 3.5 ± 13.4 mmHg (Table 2). Delta Δ SBP did not differ significantly ($P = .308$) between the hypertension and normotension groups. At baseline, the prevalence of a hypotensive BP response, defined as a systolic blood pressure drop more than 10 mmHg after 6-minutes in-bed cycle exercise test, was 4/52 (7.7%) (not in table).

3.3 | Changes in hemodynamic characteristics from baseline to post-intervention

As shown in Table 3 and Figure 1, resting SBP decreased significantly from baseline to post-intervention both in the intervention group (147.7 ± 18.1 mmHg to 125.3 ± 17.1 mmHg, $P < .001$) and in the control group (147.8 ± 23.7 mmHg to 131.4 ± 14.8 mmHg, $P < .001$), corresponding to an average between-group difference in change from baseline to post-intervention of −6.1 (95% CI −17.9 to 5.8) mmHg. Post-test SBP also decreased significantly from baseline to post-intervention in both the intervention group (146.7 ± 18.7 mmHg to 133.7 ± 14.9 mmHg, $P < .001$) and in the control group (155.0 ± 23.4 mmHg to 135.9 ± 18.0 mmHg, $P = .014$) Table 3, Figure 1. This corresponded to an average between-group difference in change from baseline to post-intervention of 6.1 (95% CI −6.8 to 18.9) mmHg. At post-intervention the resting SBP was higher in the control group than in the intervention group but there was no statistically significant difference between groups ($P = .179$) (not in table). There was a significant difference (P for interaction = .010) regarding how Δ SBP changed from baseline to post-intervention, such that in the intervention group Δ SBP increased from −1.0 ± 15.0 mmHg to 8.5 ± 9.4 mmHg, $P = .009$, whereas in the control group, Δ SBP decreased from 7.1 ± 10.9 mmHg to 4.5 ± 11.8 mmHg, $P = .395$ (Table 3, and Figure 1). This corresponded to an average between-group difference in change from baseline to post-intervention of 12.1 (95% CI 3.0 to 21.3) mmHg. The prevalence of a hypotensive systolic blood pressure response was 3/52 (5.7%) at post-intervention. All patients with a hypotensive blood pressure response were in the control group and their average SBP drop was 15.7 ± 8.1 mmHg (range −10 to −25) (not in table). Table 4 provides additional information regarding Antihypertensive drugs used at baseline and after post-intervention in the study participants

4 | DISCUSSION

In this study, hemodynamic responses to aerobic exercise in acute stroke patients were investigated. The principal finding was

Variables	Total group n = 52	Intervention Group n = 23	Control group n = 29
Age (years) years Mean			
Mean ± SD	74.7 ± 9.3	72.7 ± 12.0	76.3 ± 6.4
Range	50–91	50–89	61–91
Sex			
Male, n (%)	20 (38.5)	8 (34.8)	12 (41.4)
Diagnosis			
Hypertension, n (%)	37 (71.2)	16 (69.6)	21 (72.4)
Diabetes mellitus, n (%)	8 (15.4)	4 (17.4)	4 (13.8)
Type of stroke			
Ischemic, n (%)	46 (88.5)	23 (100)	23 (79.3)
Hemorrhagic, n (%)	6 (11.5)	0	6 (20.7)
Side affected by symptoms			
Right, n (%)	27 (51.9)	12 (52.2)	15 (51.7)
Left, n (%)	23 (44.2)	10 (43.5)	13 (44.8)
Unknown, n (%)	2 (3.8)	1 (4.3)	1 (3.4)
NIHSS	13.3 ± 4.3	13.4 ± 4.7	13.2 ± 4.1
mRS	4.4 ± 0.6	4.3 ± 0.7	4.6 ± 0.5
Barthel Index	12.6 ± 3.4	12.9 ± 3.9	12.5 ± 3.1
6MWT, (m)	10.8 ± 39.0	18.5 ± 56.0	4.6 ± 14.7
Stroke onset to baseline, (days)	1.9 ± 1.7	1.4 ± 1.2	2.3 ± 1.9

Abbreviations: 6MWT, 6-Minute Walk Test;mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

Values are mean ± SD (standard deviation) or n (%).

TABLE 2 Patient hemodynamic characteristics at baseline

Baseline	All patients n = 52 Mean ± SD	Resting hypertension ≥ 140 mmHg n = 37 Mean ± SD	Resting normotension < 140 mmHg n = 15 Mean ± SD	P-value
Resting SBP (mmHg)	147.8 ± 21.2	157.8 ± 14.5	123.1 ± 13.2	NA
Post-test SBP (mmHg)	151.3 ± 21.6	160.1 ± 17.1	129.6 ± 15.4	<.001
Δ SBP (mmHg)	3.5 ± 13.4	2.3 ± 14.1	6.5 ± 11.3	.308
Resting DBP (mmHg)	77.4 ± 11.7	79.6 ± 11.4	71.9 ± 10.8	.030
Post-test DBP (mmHg)	79.1 ± 11.2	81.2 ± 11.2	73.9 ± 9.7	.032
Δ DBP (mmHg)	1.7 ± 6.8	1.5 ± 7.1	1.9 ± 6.1	.852
Resting heart rate (bpm)	78.7 ± 14.6	78.1 ± 14.8	80.2 ± 14.5	.640
Post-test heart rate (bpm)	82.1 ± 16.5	80.8 ± 16.1	85.4 ± 17.8	.364
Δ Heart rate (bpm)	3.4 ± 10.9	2.7 ± 7.5	5.2 ± 16.9	.456
Peak exercise heart rate (bpm)	86.0 ± 15.4	84.3 ± 15.2	90.3 ± 15.4	.208
Change in heart rate during exercise (bpm)	7.3 ± 10.6	6.2 ± 7.0	10.1 ± 16.5	.395

Note: Values are means ± SD (standard deviation).

Abbreviations: bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; Δ: Post-test variable-Resting variable.

that resting SBP decreased significantly from baseline to post-intervention to a similar extent in both the intervention and control groups. The finding that SBP decreased from the acute phase is in line with other studies[17-19] and is also likely to have been influenced by goal-directed medical treatment titration during this time period. We also found that there was a significant difference between the intervention and control groups regarding how Δ SBP changed from baseline to post-intervention, which suggests that in-bed cycle

TABLE 3 Changes in hemodynamic characteristics at resting and post-test an in-bed cycle exercise test performed at baseline and after 3 weeks (post-intervention) in 52 patients in acute and subacute phase after a stroke, stratified according to randomization

Variable	Intervention Group n = 23			Control Group n = 29			P for interac-tion between time and group
	Baseline Mean ± SD	Post-intervention Mean ± SD	P-value	Baseline Mean ± SD	Post-intervention Mean ± SD	P-value	
Resting SBP, mmHg	147.7 ± 18.1	125.3 ± 17.1	<.001	147.8 ± 23.7	131.4 ± 14.8	<.001	.308
Post-test SBP, mmHg	146.7 ± 18.7	133.7 ± 14.9	<.001	155.0 ± 23.4	135.9 ± 18.0	.014	.348
Δ SBP, mmHg	−1.0 ± 15.0	8.5 ± 9.4	.009	7.1 ± 10.9	4.5 ± 11.8	.395	.010
Resting DBP, mmHg	77.4 ± 11.9	71.2 ± 8.8	.738	77.5 ± 11.8	70.9 ± 9.8	.047	.886
Post-test DBP, mmHg	80.6. ± 12.1	72.6 ± 10.2	.807	77.8 ± 10.5	70.6 ± 11.4	.367	.835
Δ DBP, mmHg	3.3 ± 7.4	1.4 ± 7.5	.343	0.4 ± 6.0	−0.3 ± 6.8	.664	.642
Resting heart rate, bpm	77.3 ± 15.5	72.6 ± 10.5	.050	79.8 ± 14.0	78.1 ± 11.9	.120	.480
Post-test heart rate, bpm	82.5 ± 18.4	79.5 ± 10.5	.405	81.8 ± 15.2	80.4 ± 12.5	.657	.721
Δ Heart rate, bpm	5.2 ± 15.4	6.9 ± 7.8	.603	2.0 ± 5.3	2.3 ± 8.7	.826	.684
Change in heart rate during exercise, bpm	8.2 ± 14.5	15.6 ± 11.2	.085	6.7 ± 6.2	7.3 ± 8.9	.724	.120

Note: Values are means ± SD (standard deviation). P values denote pairwise comparisons between baseline and post-intervention values within randomization strata.

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; Δ: Post-test variable-Resting variable.

TABLE 4 Antihypertensive drugs used at baseline and after post-intervention in 52 patients in the subacute phase after a stroke

|	Total group n = 52			Intervention Group n = 23			Control Group n = 29		
	Baseline	Post-intervention	P-value	Baseline	Post-intervention	P-value	Baseline	Post-intervention	P-value
β-Blocker, n (%)	21 (40.4)	22 (42.3)	1.000	9 (39.1)	9 (39.1)	1.000	12 (41.4)	13 (44.8)	1.000
Calcium channel blocker, n (%)	16 (30.8)	15 (28.8)	1.000	8 (34.8)	7 (30.4)	1.000	8 (27.6)	8 (27.6)	1.000
Angiotensin converting enzyme inhibitor, n (%)	6 (11.5)	9 (17.3)	.250	2 (8.7)	4 (17.4)	.500	4 (13.8)	5 (17.2)	1.000
Angiotensin receptor blocker, n (%)	16 (30.8)	17 (32.7)	1.000	7 (30.4)	5 (21.7)	.754	9 (31.0)	12 (41.4)	.453
Spironolactone, n	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Diuretic, n (%)	6 (11.5)	8 (15.4)	.727	3 (13.0)	3 (13.0)	1.000	3 (13.0)	5 (13.0)	.500

Note: Values are expressed as numbers (percentages).

exercise intervention does affect these patients BP. This may indicate that this kind of intervention may positively influence a normalization of blood pressure variability during exercise, which may be a marker of improved autonomic regulation. Moreover, the immediate reaction after 3 weeks in-bed cycle exercise was similar to healthy persons reactions to aerobic exercise.[20] One possible explanation may be that Δ SBP changed more in the intervention group than in the control group as a response to an increased requirement of perfusion in peripheral tissues. Such a change might counterbalance the decreased physical performance commonly seen after a stroke.[21,22] We also found that hypotension response at baseline was not common after a single bout of aerobic exercise. None of participants who were randomized to 3 weeks of in-bed cycle exercise did exhibit a systolic blood pressure drop after 6-minute in-bed cycle exercise test at post-intervention. To our knowledge, only one study has

evaluated the effects of exercise in the acute phase after stroke.[23] However, they did not report hemodynamic responses. From this study, we can tell that patients randomized to in-bed cycle exercise seemed to be heading toward normalized BP reactions compared with the control group.

4.1 | Study strengths and limitations

A strength of this study is that it represents, to the best of our knowledge, the first randomized trial which characterizes the blood pressure responses to in-bed cycle exercise in the acute phase after a moderate to severe stroke. However, some limitations should be acknowledged. First, the present analysis represents a post hoc analysis of a previously performed randomized clinical trial, which was not specifically
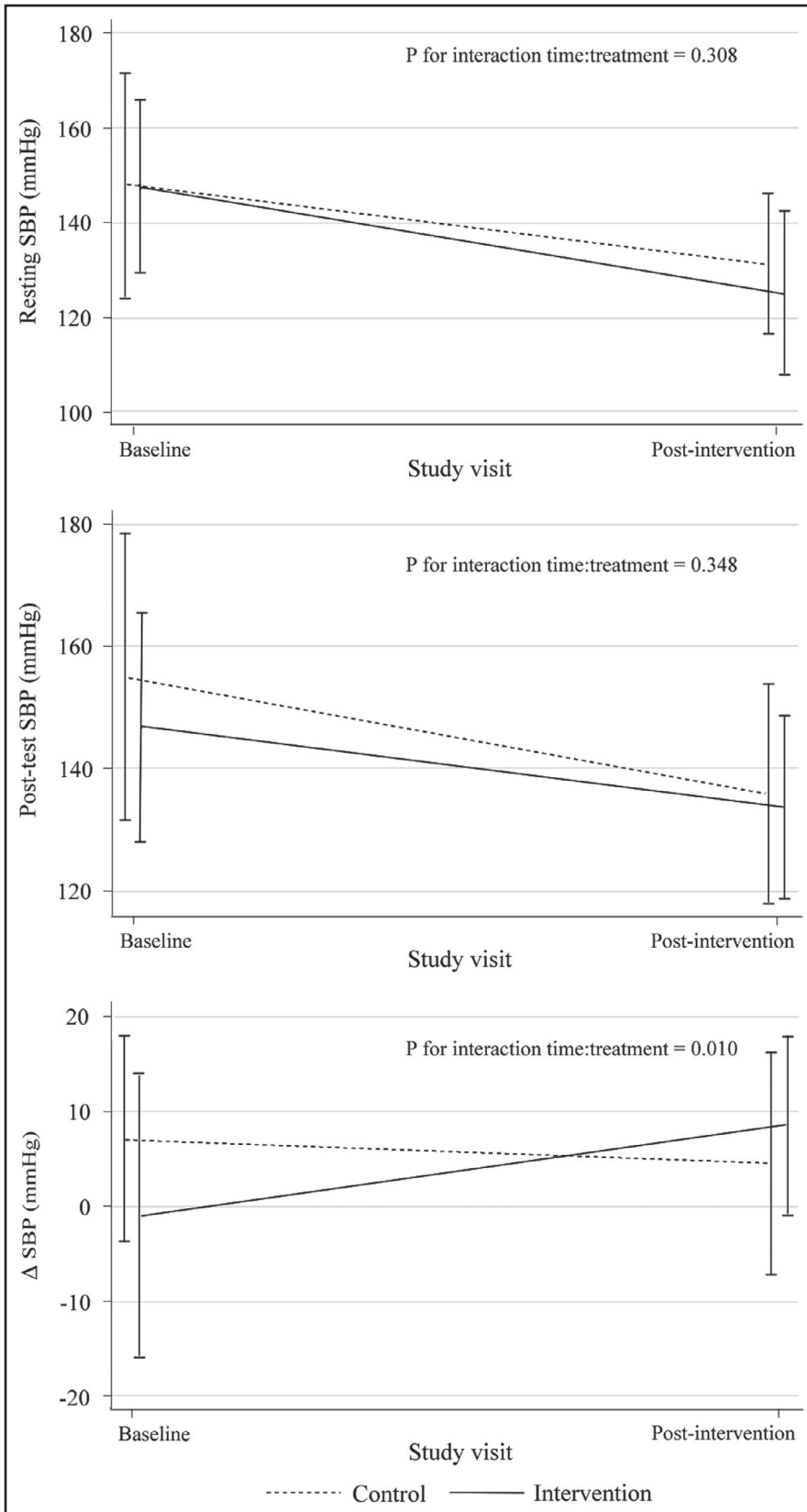
FIGURE 1 Changes in Resting (pre-) and post-test systolic blood pressure (SBP) and ΔSBP between baseline and post-intervention by randomization groups. Upper figure: Resting SBP changes from baseline to post-intervention. Center figure: Post exercise SBP changes from baseline to post-intervention. Lower figure: ΔSBP changes from baseline to post-intervention Δ = Post-test SBP – Resting SBP.

designed to evaluate hemodynamic responses to in-bed cycle exercise. Even if measurements of BP were recorded according to conventional clinical routines by experienced caring personnel, there is a tendency toward digit preference concerning SBP values, that is, BP values were often rounded to the nearest 5 or 10 mmHg rather than to the nearest 2 mmHg as recommended in current hypertension guidelines, and resting blood pressures were not measured in duplicate. Furthermore, according to patient's severe stroke BPs were measured

in supine position and not sitting as recommended. Furthermore, BPs at submaximal workloads were not measured in this study. Although there seemed to be no major changes in the proportions of patients who used any specific antihypertensive drug class within the entire cohort, or in the number of antihypertensive drugs that were used in either of the randomization groups, we have no data concerning the doses used and we cannot exclude that treatment changes or dose titrations made during the trial affected the BP outcome parameters. Since this is a secondary analysis, the sample size requirement may not match that of the primary end point. Confirmation of our study results in a larger trial may be necessary before any firm conclusion can be drawn. Finally, the time period from the end of the in-bed cycle exercise session to the measurement of the post-test BP was not standardized and may have differed between patients.

5 | CONCLUSION

The resting SBP decreased spontaneously during the first weeks after stroke, and this change did not differ significantly between the intervention and control groups. There was a significant difference regarding how Δ SBP changed from baseline to post-intervention, such that in the intervention group Δ SBP increased whereas in the control group, Δ SBP decreased. Also, none of the participants who were randomized to 3 weeks of in-bed cycle exercise exhibited a systolic blood pressure drop after 6-minute in-bed cycle exercise test at post-intervention. We conclude that patients randomized to aerobic in-bed cycle exercise seemed to normalize their blood pressure response to exercise to a larger extent than patients in the control group.

5.1 | Suppliers

Sphygmomanometers Boso.
   Pulse oximeter (Rad-5v, Masimo, Irvine).
   MotoMed Letto2; RECK-Technic GmbH & CO KG.
   SPSS Version 25; IBM.

AUTHOR CONTRIBUTION
Sandberg, Kleist, Enthoven, and Wijkman: conceptualized and designed the study. Sandberg and Kleist: acquired the data. Sandberg, Kleist, Enthoven, and Wijkman: analyzed and interpreted the data. Sandberg, Kleist, Enthoven, and Wijkman: drafted the manuscript. Sandberg, Kleist, Enthoven, and Wijkman: involved in critical revision.

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