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Standing up slowly antagonizes initial blood pressure decrease in older adults with orthostatic hypotension

Running title: Standing up slowly in older adults.

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1 **Abstract**

2 **BACKGROUND:** Orthostatic hypotension (OH) is common in older adults and associated
3 with increased morbidity and mortality, loss of independence and high health care costs.
4 Standing up slowly is a recommended non-pharmacological intervention. However, the
5 effectiveness of this advice has not been well-studied.

6 **OBJECTIVES:** To investigate whether standing up slowly antagonizes posture related blood
7 pressure (BP) decrease in a clinically relevant population of geriatric outpatients.

8 **METHODS:** In this cross-sectional study, 24 community dwelling older adults referred to a
9 geriatric outpatient clinic and diagnosed with OH were included. BP was measured
10 continuously during three consecutive transitions from supine to standing position during
11 normal, slow and fast transition.

12 **RESULTS:** Relative BP decrease at 0-15 seconds after slow transition was significantly
13 lower compared to normal transition ($P = .003$ for both systolic BP and diastolic BP and fast
14 transition ($P = .045$ for systolic BP, diastolic BP non-significant). The relative diastolic BP
15 decrease at 60-180 seconds after normal transition was significantly lower compared with fast
16 transition ($P = .029$).

17 **CONCLUSION:** Standing up slowly antagonizes BP decrease predominantly during the first
18 15 seconds of standing up in a clinically relevant population of geriatric outpatients diagnosed
19 with OH. Results support the non-pharmacological intervention in clinical practice to
20 counteract OH.

21

22 **Introduction**

23 Orthostatic hypotension (OH) is classically defined as a drop in blood pressure (BP) of at
24 least 20 mmHg of systolic blood pressure (SBP) and/or 10 mmHg of diastolic blood pressure
25 (DBP) after standing up.[1] OH prevails in older adults, especially in those with one or more
26 chronic diseases.[2, 3] Older adults with OH are at risk for falling while standing up[4],
27 which is associated with increased morbidity, high health care costs and loss of
28 independence.[5] Especially initial OH (iOH), defined as a BP decrease within 15 seconds
29 after standing up of 40 mmHg SBP and/or 20 mmHg DBP, is associated with falls.[6]
30 Interventions counteracting OH are likely to reduce the risk for falling.[7]

31

32 The first steps in the management of OH in clinical practice are educational and non-
33 pharmacological interventions.[8] OH may be counteracted by increasing the venous return in
34 the standing position by pre-tensing lower limbs and abdominal muscles.[9] These
35 observations have led to the introduction of physical countermeasures, e.g. by advising
36 patients to bend forward, cross legs or sit down once experiencing symptoms of OH.[9]
37 Another non-pharmacological advice given in clinical practice is to stand up slowly.
38 However, the effectiveness of this recommendation has not been well-studied.[7, 10]

39

40 This study aimed to investigate whether there is evidence that standing up slowly antagonizes
41 OH in a clinically relevant population of geriatric outpatients diagnosed with OH.

42 **Materials & Methods**

43 *Study design*

44 This cross-sectional study included 24 community-dwelling older adults referred to the
45 geriatric outpatient clinic of the VU University Medical Center, Amsterdam, the Netherlands,
46 due to problems with mobility, cognition and/or general somatic health between December
47 2014 and April 2015. All patients in the study population were diagnosed with classical OH:
48 i.e. a drop of at least 20 mmHg SBP and/or 10 mmHg DBP after 15 seconds and within 3
49 minutes of standing up.[1] In addition, 13 of these patients also fulfilled the criteria for iOH,
50 i.e. a drop of at least 40 mmHg in SBP and/or 20 mmHg in DBP within the first 15 seconds
51 after standing up, OH was assessed by both intermittent and continuous BP measurements.
52 The aetiology of OH in our population was of the non-neurogenic type. Patients were
53 excluded when they were unable to perform multiple transitions from supine to standing
54 position. This study was approved by the Medical Ethics Committee of the VU university
55 medical center (Amsterdam, the Netherlands). All patients gave written informed consent.

56

57 *Protocol*

58 Measurements were performed during the initial visit to the geriatric outpatient clinic and
59 included three separate standing up conditions, each consisting of 5 minutes in a resting state
60 in supine position, a transition period from supine to standing position, and 3 minutes in
61 standing position. The standing up conditions were performed in a fixed order with a
62 transition at subsequently normal, low and high speed, respectively called normal, slow and
63 fast transition. Transition time was recorded with a stopwatch. For normal transitions, patients
64 were instructed to stand up at the patient's usual pace. For slow transitions, patients were
65 instructed to reach a sitting position within at least 5 seconds; to remain seated during at least

66 5 seconds and to attain a standing position at low speed. The examiner coached the patients
67 by counting seconds during the transition. For fast transitions, patients were instructed to
68 stand up as fast as possible. During standing, the patient was instructed to stand unsupported
69 upright during 3 minutes with the left arm positioned on the chest in order to hold the BP
70 monitor device positioned as stable as possible. Patients were asked for OH related symptoms
71 after each of the transitions. The symptoms asked consisted of: dizziness, light headedness,
72 instability and blurred vision. Conversations were reduced to a minimum during the whole
73 protocol.

74

75 *BP measurement*

76 Continuously measured SBP and DBP were obtained with a digital photoplethysmograph
77 (Nexfin©, BM Eye, Amsterdam, The Netherlands)[11] with a cuff placed on the left middle
78 finger. Beat-to-beat BP data was analysed using Nexfin@PC software (Nexfin@PC version 2,
79 BM Eye, Amsterdam, the Netherlands). BP data were manually marked starting at the
80 moment patients attained a quiet supine position and a stable standing position respectively.
81 During each standing period, the Physiological calibrator of the Nexfin, which is automatically
82 on, was switched off to prevent missing BP data.[12] During the following supine periods, the
83 Physiological calibrator was switched on again to maintain optimal calibration.[13] BP data
84 during the transition time were excluded from analysis due to noise. Data were exported to
85 Matlab (Matlab, version R2012b, the Mathworks, Natick, MA) and beat-to-beat BP data was
86 averaged over 5 seconds intervals.[14]

87 To determine the BP profile, the following parameters were calculated for each
88 standing up condition: (i) supine BP, defined as the mean BP in supine position during 60
89 seconds prior to each transition; (ii) lowest value of the averaged BP of three time periods, i.e.

90 0-15 seconds, 15-60 seconds and 60-180 seconds during the standing period and (iii) biggest
91 BP decrease of the three time periods, determined by subtracting the lowest averaged BP of
92 each aforementioned time period from the supine BP. Relative BP decrease was defined as
93 the BP decrease after standing up in relation to the supine BP. OH₁₅₋₁₈₀ was defined according
94 to the classical OH definition between 15-180 seconds of standing up, compared with supine
95 BP. In addition, heart rate (HR) profile was determined by using the same parameters as for
96 the BP profile (parameters i-iii). HR difference was calculated by subtracting supine HR of
97 the lowest averaged HR.

98

99 *Patient characteristics*

100 Demographic and clinical data were obtained by questionnaires and from medical charts. A
101 positive history of falling was defined as one or more self-reported fall incidents in the past
102 year. Multimorbidity was defined as 2 or more of the following chronic diseases: chronic
103 obstructive pulmonary disease, diabetes mellitus, hypertension, malignancy, myocardial
104 infarction, Parkinson's disease and rheumatoid/(osteo)arthritis. For the present study we
105 defined cardiovascular disease as presence of at least one of the following: hypertension,
106 peripheral artery disease, myocardial infarction and Transient Ischemic Attack or Cerebral
107 Vascular Accident. OH provoking medication was defined as the intake of one or more
108 vasodilating, antihypertensive, anti-depressive (non SSRI) or antipsychotic drug. All
109 medication a patient used, including OH provoking medication, was continued during the
110 study. Complaints of orthostatic intolerance were defined as the presence of one or more
111 symptoms comprising lightheadedness, visual disturbances, dizziness or instability during
112 standing. To describe the patient's physical and cognitive condition the body mass index

113 (BMI), Short Physical Performance Battery (SPPB), hand grip strength in a standing position
114 and Mini Mental State Examination (MMSE) were used (15).

115

116 *Statistical analysis*

117 The sample size was calculated based on an α of 0.05, a β of 0.2, using a mean value of the
118 drop of SBP after transition of 25 mmHg, an expected mean value in the intervention group
119 ‘slow transition’ of 15 mmHg SBP and a standard deviation of 15 mmHg as reported in
120 Pasma et al., resulting in N=20 patients. [15] Continuous variables with a normal distribution
121 were presented as mean and standard deviation (SD). Values with a skewed distribution (non-
122 Gaussian) were presented as median and interquartile range (IQR). Paired-samples t tests
123 were used to test for significant differences in supine BP before transition, duration of
124 transition and mean BP decrease per time interval of each standing up condition. Patients
125 were excluded from the analysis if >30% of the BP values in each time interval were
126 randomly missing due to technical errors of the BP device. Statistical analysis was performed
127 using the Statistical Package for the Social Sciences (SPSS version 22, Chicago, IL). P-values
128 below 0.05 were considered statistically significant.

129 **Results**

130 *Patient characteristics*

131 Table 1 shows the patient characteristics and appearance of symptoms after normal, fast and
132 slow transition. The mean age was 79.3 years (SD 7.7). All patients had OH and thirteen out
133 of 24 patients also had iOH. Sixteen out of 24 patients had a history of falling, 18 patients
134 used OH provoking medication and 13 patients had complaints of orthostatic intolerance after
135 normal transition during standing.

136

137 *Standing up conditions*

138 Table 2 shows transition times, absolute blood pressure and heart rate per standing up
139 condition.

140

141 *Comparison of transition time and the supine BP*

142 Table 3 depicts the mean differences of transition times and supine SBP and DBPs. The
143 transition times differed significantly, with slow transition being on average 12.1 seconds
144 longer ($P < .001$) than normal transition and on average 16.6 seconds longer than fast
145 transition ($P < .001$).

146 Supine SBP and DBP were significantly higher preceding slow transition ($P < .001$ and
147 $P = .001$) and fast transition ($P < .001$ and $P = .007$) compared with the supine SBP and DBP
148 preceding normal transition.

149

150 | *Comparison of the relative BP and HR response*

151 Table 4 depicts the mean differences of the relative BP change for all patients and the ones
152 with iOH and the HR response. A maximum of data of 5 patients were missing per time
153 period.

154 The relative BP decrease at 0-15 seconds was significantly lower after slow transition
155 compared to normal transition (OH: $P = .003$ for both SBP and DBP; iOH: $P = .020$ and P
156 $= .047$ for systolic and diastolic BP respectively) and fast transition ($P = .045$ for SBP, non-
157 significantly for DBP). In the group of patients with iOH, the relative DBP decrease at 0-15
158 seconds was significantly higher after normal transition compared to fast transition ($P = .014$).

159 BP decrease at 15-60 seconds was not dependent on transition. At 60-180 seconds, the
160 relative diastolic BP decrease was significantly lower after normal transition compared to fast
161 transition ($P = .029$), other transition conditions did not reach significance.

162 Four out of 24 patients did no longer meet the criteria of OH while standing up after
163 slow transition compared to normal transition.

164 HR response did not significantly differ between standing up conditions. Eight out of
165 24 patients used beta blockers. Although these patients were less able to increase the HR in
166 response to standing up in comparison with patients not using beta blockers, four of these
167 patients showed a less severe BP decrease after slow transition compared to normal transition.

168

169 **Discussion**

170 This study showed that standing up slowly antagonizes posture related BP decrease.
171 Furthermore, the effect of standing up slowly is more strongly seen in patients with iOH, and
172 a proportion of 4 patients with iOH did no longer meet the criteria for iOH after standing up
173 slowly.

174

175 *Speed of standing up*

176 Standing up slowly was beneficial in counteracting the relative BP during the first 15 seconds
177 after standing up, when compared with standing up at normal speed. It could be hypothesized
178 that during and directly after slow transition, the use of the skeletal muscle pump is more
179 effective due to the longer time period of transition compared with normal transition. The
180 prolonged activation of the muscles during standing up at low speed, but also the vigorous
181 activation of the muscles during standing up at high speed could both be beneficial. The
182 skeletal muscle pump increases the intramuscular pressure and reduces venous blood pooling
183 associated with OH. [16] After 15 seconds of standing up, the positive effect of standing up
184 slowly on relative BP decrease disappeared. This could be explained by the fact that during
185 the prolonged period of quiet standing the continued pooling of blood in the abdominal
186 region, the biggest reservoir during orthostatic shifts[17], overrules the initial positive effect
187 of the skeletal muscle pump.

188 iOH has a different pathophysiology than classical OH. The initial orthostatic
189 response is constituted by a direct neural response with increase in heart rate as a direct
190 effector. It could be hypothesized that during slow transition, the heart rate increases in
191 concordance with or as a reaction of the more effective use of the muscle pump. After this
192 first orthostatic response, the effects caused by the volume shift become more important.

193 Postural seated hypotension[18], a prevalent condition, should also be taken into
194 account during the short period of time that patients remained in sitting position during slow
195 transition.

196 Although the response rate of standing up slowly is only 4 out of 24 patients who no
197 longer meet the criteria for iOH, it should be put into perspective by the fact that it is a
198 relatively safe intervention without side-effects and considerably easy to perform by patients
199 in their daily lives.

200

201 *Order of transitions*

202 The protocol was designed as a fixed order of standing up conditions with three different
203 transition speeds after which a period of standing up followed. Supine BP increased after
204 three periods of standing up without being compensated by the 5 minutes in supine rest,
205 whereas communication and interaction with the patient was reduced to a minimum. We
206 hypothesize that the supine BP rises after each standing up condition due to physical strain on
207 the body and that 5 minutes rest in supine position is, although reported in literature[15], not
208 sufficient in this group of patients. To the best of our knowledge, this effect has not been
209 previously reported in literature. Calculation of relative BP decreases compensated for this
210 effect in the statistical analyses. Future studies should explore this effect and take the increase
211 in BP during postural transitions into account. For clinical practice this could imply that a
212 period of rest before measuring OH should be longer than 5 minutes.

213

214 *Continuously vs. intermittently measured BP*

215 These results underline the importance of the use of continuous measuring BP devices, which
216 are the only means to assess iOH and are of great importance to a clinician to analyse the

217 continuous BP response to orthostatic stress.[6, 14, 15, 19] Patients with iOH are likely to
218 have complaints of orthostatic intolerance and a higher risk of falling.[6] The importance of
219 iOH, as a clinically relevant parameter of orthostatic intolerance, can be explained by the
220 large SBP decrease and therewith loss of cerebral blood flow (CBF), when the SBP is not able
221 to recover to at least 80% of baseline BP within 30 seconds after this BP decrease.[6, 20]
222 Hypothetically, the BP response in the first 15 seconds and the ability to recover from this BP
223 decrease is an important hallmark of BP regulation and occurrence of orthostatic intolerance
224 during the rest of the standing period, which cannot be detected using sphygmomanometer
225 measurements.[20] Future studies are necessary to identify phenotypes of BP regulation and
226 recovery.

227

228 *Strengths & Limitations*

229 This is the first study performed to provide evidence for the validity of advice to stand up
230 slowly presented to older adults with OH. Strengths of the study are the use of continuously
231 measured BP and the use of a well-characterized cohort of older patients visiting a geriatric
232 outpatient clinic, providing a clinically relevant study population. In retrospect, limitations of
233 the study are the use of fixed order in transitions because of the resulting increase in supine
234 BP per transition period.

235

236 *Conclusion*

237 Standing up slowly antagonizes BP decrease during the first 15 seconds of standing up in
238 older patients with OH. The results underpin the use of non-pharmacological interventions in
239 clinical practice.

240 **Acknowledgements**

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242 patient recruitment and Roel Jongejan for helping with the data analysis in Matlab.

243

244 **Conflict of Interest**

245 The authors have declared no conflicts of interests.

246

247 **Author Contributions**

248 ESB, EMR, MCT, OJV, CGM and ABM designed the study. ESB performed the data
249 analysis and drafted the manuscript. All authors revised the manuscript and approved the final
250 version of the manuscript.

251

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Table 1. Patient characteristics.

Characteristic	All (n=24)
Socio-demographics	
Age in years, mean (SD)	79.3 (7.7)
Female	14
Living at home	21
Health status	
Use of walking aid	8
History of falling	16
Multimorbidity	17
Cardiovascular disease	18
Number of medication, median [IQR]	7 [5-11]
BMI in kg/m ² , mean (SD)	25.9 (4.1)
MMSE, median [IQR]	27 [24-29]
Physical performance	
Handgrip strength in kg, mean (SD)	26.5 (9.6)
SPPB, median [IQR]	9 [7-11]
Orthostatic hypotension	
iOH ^a	13
OH ₁₅₋₁₈₀ ^b	24
OH provoking medication	18
Complaints of OH after normal transition	13
Complaints of OH after slow transition	10
Complaints of OH after fast transition	18

All variables are presented as n, unless indicated otherwise. MMSE= Mini Mental State Examination, SPPB= Short Physical Performance Battery, BP= blood pressure, SBP= systolic BP, DBP= diastolic BP, OH= orthostatic hypotension, iOH= initial orthostatic hypotension.

^a iOH was defined as a decrease of at least 40 mmHg SBP and/or 20 mmHg DBP during the first 15 seconds after standing up compared to supine BP.

^b OH₁₅₋₁₈₀ was defined as a decrease of at least 20 mmHg SBP and 10 mmHg DBP during 15 to 180 seconds after standing up compared to supine BP, after transition at normal speed.

Table 2. Transition times, absolute blood pressure and heart rate of different standing up conditions.

Characteristic	Normal	Slow	Fast
Transition times in seconds (s)	11.5 (6.12)	23.7 (5.72)	7.05 (3.69)
Supine BP before transition in mmHg			
SBP	144.5 (27.5)	154.2 (30.9)	156.2 (30.0)
DBP	71.5 (13.2)	74.9 (14.3)	75.0 (14.5)
BP 0-15 s. in mmHg			
SBP	102.3 (25.8)	116.6 (24.9)	116.0 (33.3)
DBP	52.8 (14.6)	57.6 (13.4)	60.0 (22.7)
BP 15-60 s. in mmHg			
SBP	99.3 (26.9)	102.1 (25.2)	104.5 (27.1)
DBP	58.4 (15.7)	58.0 (12.3)	58.7 (12.1)
BP 60-180 s. in mmHg			
SBP	108.4 (24.9)	115.3 (28.1)	113.8 (27.7)
DBP	61.8 (11.6)	63.9 (11.2)	62.5 (12.1)
Supine HR before transition in bpm			
HR 0-15 s. in bpm	69.8 (24.1)	76.4 (12.9)	80.4 (22.1)
HR 15-60 s. in bpm	73.5 (18.5)	76.6 (12.8)	72.8 (20.7)
HR 60-180 s. in bpm	71.9 (19.1)	75.3 (12.8)	73.5 (14.5)

All data are presented as mean (SD). BP= blood pressure, SBP= systolic BP, DBP= diastolic BP, HR= heart rate, bpm= beats per minute.

Table 3. Comparison of transition times and supine systolic and diastolic blood pressure of different standing up conditions.

	n	Slow vs Normal		n	Normal vs Fast		n	Slow vs Fast	
		MD (SD)	p-value		MD (SD)	p-value		MD (SD)	p-value
Transition time and BP									
Transition time in s.	24	12.1 (4.1)	<.001	24	4.5 (4.4)	<.001	24	16.6 (3.7)	<.001
Supine SBP (mmHg)	24	9.6 (8.3)	<.001	24	-11.6 (11.5)	<.001	24	-2.0 (7.7)	.219
Supine DBP (mmHg)	24	3.4 (4.6)	.001	24	-3.5 (5.8)	.007	24	-0.1 (3.0)	.892

N= number, MD= mean difference, SD= standard deviation, s.= seconds, BP= blood pressure, SBP= systolic BP, DBP= diastolic BP.

P-values (p) <.05 are considered statistically significant and are presented in bold.

Interpretation: the mean supine systolic BP before slow transition was 9.6 mmHg higher compared with the mean supine systolic BP before normal transition.

Table 4. Comparison of the relative blood pressure change and heart rate of different standing up conditions.

	n	Slow vs Normal		n	Normal vs Fast		n	Slow vs Fast	
		MD (SD)	p		MD (SD)	p		MD (SD)	p
Relative BP decrease									
<i>All patients</i>									
SBP 0-15 s. in mmHG, %	20	- 5.9 (7.7)	.003	19	1.0 (8.7)	.615	22	-4.7 (10.4)	.045
DBP 0-15 s. in mmHG, %	20	-7.1 (9.3)	.003	19	6.1 (13.4)	.061	22	-1.1 (12.1)	.664
SBP 15-60 s. in mmHG, %	20	-0.3 (9.2)	.889	20	- 0.9 (8.7)	.667	22	-0.7 (6.2)	.582
DBP 15-60 s. in mmHG, %	20	1.5 (8.5)	.438	20	-2.2 (6.3)	.143	22	-0.4 (6.8)	.787
SBP 60-180 s. in mmHG, %	22	0.0 (5.5)	.973	21	-1.8 (6.3)	.199	22	-2.0 (4.9)	.072
DBP 60-180 s. in mmHG, %	22	1.0 (5.2)	.400	21	-2.8 (5.4)	.029	22	-1.7 (4.8)	.113
<i>Patients with iOH</i>									
SBP 0-15 s. in mmHG, %	10	-7.4 (8.3)	.020	10	4.5 (7.5)	.092	12	-1.8 (12.3)	.615
DBP 0-15 s. in mmHG, %	10	-6.6 (9.1)	.047	10	10.8 (11.2)	.014	12	3.6 (10.7)	.267
HR decrease									
<i>All patients</i>									

HR 0-15 s. in bpm	22	1.0 (5.4)	.391	22	-5.4 (18.7)	.194	24	-3.9 (16.6)	.258
HR 15-60 s. in bpm	24	3.5 (14.9)	.261	23	-3.5 (13.3)	.228	23	0.2 (8.1)	.929
HR 60-180 s. in bpm	24	3.8 (12.3)	.146	24	-1.9 (13.1)	.477	24	1.7 (5.2)	.095

N= number, MD= mean difference, SD= standard deviation, BP=blood pressure, SBP= systolic, DIA= diastolic, s.= seconds, HR= heart rate.

Relative BP decrease is defined as percentage of BP drop compared to supine BP.

P-values <.05 are considered statistically significant and are presented in bold.

Interpretation relative BP: in the 0-15 second interval of standing up, patients after slow transition had 5.9% less relative SBP decrease, compared with patients after normal transition.

Interpretation HR: in the 0-15 second interval of standing up, patients after slow transition had an average heart rate of 1.01 beats per minute higher, compared with patients after normal transition.