University of Groningen

Patterns of orthostatic hypotension and the evaluation of syncope

van Wijnen, Veera Kariina

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CHAPTER 6

HEMODYNAMIC MECHANISMS UNDERLYING INITIAL ORTHOSTATIC HYPOTENSION, DELAYED RECOVERY AND ORTHOSTATIC HYPOTENSION

Veera K. van Wijnen, Dik ten hove, Ciarán Finucane, Wouter Wieling, Arie M. van Roon, Jan C. ter Maaten, Mark M.P. Harms

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ABSTRACT

Objectives Continuous noninvasive blood pressure (BP) measurement enables us to observe rapid changes in BP and to study underlying hemodynamic mechanisms. This study aimed to gain insight into the pathophysiological mechanisms underlying short term orthostatic BP recovery patterns in a real world clinical setting with (pre)syncope patients.

Setting and Participants In a prospective cohort study, the active lying-to-standing test was performed in suspected (pre)syncope patients in the emergency department with continuous noninvasive finger arterial BP measurement.

Measures Changes in systolic BP, cardiac output (CO) and systemic vascular resistance (SVR) were studied in normal BP recovery, initial orthostatic hypotension, delayed BP recovery and sustained orthostatic hypotension.

Results In normal recovery (n=47) ΔBP at nadir was -24 (23) mmHg, with a CO change of +10 (21)% and SVR of -23 (21)%. In initial orthostatic hypotension (n=7) ΔBP at nadir was -49 (17) mmHg and CO and SVR change was -5 (46)% and -29 (58)%, respectively. Delayed recovery (n=12) differed significantly from normal recovery 30 s after standing with ΔBP of -32 (19) vs. 1 (16) mmHg respectively. Delayed recovery was associated with a significant difference in SVR changes compared to normal recovery, -17 (26)% vs.+4 (20)%, respectively. There was no difference in CO changes. In sustained orthostatic hypotension (n=16) ΔBP at 180 s after standing was -39 (21) mmHg with changes in CO of -16 (31)% and SVR of -9 (20)%.

Conclusions/Implications Hemodynamic patterns following active standing are heterogeneous and differ across orthostatic BP recovery patterns, suggesting that volume status, medication use and autonomic dysfunction should all be taken into account when evaluating these patients. Moreover, results suggest that a delayed BP recovery is associated with an impaired increase in SVR in a significant proportion of individuals, implying that physicians treating older adults with hypertension should consider the possible negative effect of intensive hypertension treatment on initial orthostatic blood pressure control.

INTRODUCTION

Evaluation of blood pressure (BP) changes upon standing is an important diagnostic measure in patients with complaints of orthostatic intolerance, (pre)syncope or suspected autonomic dysfunction (1). Symptoms upon or during standing can be a debilitating condition, one that can be difficult to evaluate accurately and difficult to treat. Noninvasive measurement of continuous finger arterial pressure enables assessment of rapid changes in BP. Using this technology a spectrum of orthostatic BP recovery patterns within 180 s of standing has recently been defined i.e.: normal BP recovery, initial orthostatic hypotension, delayed BP recovery and sustained orthostatic hypotension (2-5). Initial orthostatic hypotension is common in teenagers and young adults (3). Delayed BP recovery and sustained orthostatic hypotension are increasingly prevalent in the older population, ranging between 11.3 - 43.1% in delayed BP recovery and 4.2 - 18.5% in sustained orthostatic hypotension in 50 to 80 year olds (4). Sustained orthostatic hypotension is associated with increased cardiovascular morbidity and mortality, and recent studies suggest a similar association for delayed BP recovery, pointing towards subclinical impaired physiology (6,7). However, limited data are available regarding the hemodynamic changes underlying this spectrum of orthostatic BP recovery patterns (8-11). Moreover, most studies have been performed in controlled laboratory settings with selected groups of healthy subjects or patients with neurodegenerative diseases (8,9). A better understanding of the hemodynamic mechanisms of initial orthostatic hypotension, delayed BP recovery and sustained orthostatic hypotension is an important issue given new guidelines on the treatment of hypertension in older adults (12). Intensive treatment of hypertension could do harm in older adults by leading to falls and syncope as a result of hypotension and cerebral hypoperfusion upon standing (13,14). The aim of the present investigation was therefore to gain insight into the hemodynamic mechanisms underlying the spectrum of short term orthostatic BP recovery patterns in (pre)syncope patients in a clinical setting.

METHODS

Patient selection

This study was conducted in the emergency department of a tertiary teaching hospital between January and August 2014. All consecutive patients older than 18 years attending the emergency department Monday-Friday (8am to 6pm) and suspected of (pre)syncope were included. Syncope was defined as a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous complete recovery (1). Presyncope was defined as the feeling of almost losing consciousness with similar prodromal symptoms as in syncope. Patients were excluded if they were not able to stand for 5 minutes, were hemodynamic instable (supine systolic BP <90 mmHg), in need of immediate treatment or if a cognitive disorder impaired informed consent. Continuous noninvasive orthostatic BP measurements were

performed by two trained researchers, approximately 1-2 hours after arrival at the emergency department. Patient data were derived from the medical records. The attending physicians in the emergency department work according to the syncope guideline of the European Society of Cardiology (1). The study complied with the Declaration of Helsinki, the protocol was approved by the Medical Ethics Committee and verbal informed consent was obtained from all patients.

Protocol

For continuous measurements Nexfin® (BMEYE, Edwards LifeSciences, Irvine, California, USA), a noninvasive continuous finger arterial pressure (FinAP) measurement device, was used. From the finger waveform, heart beats are detected and systolic BP, diastolic BP, mean BP and pulse rate are derived in a beat-to-beat mode. FinAP measurement has been validated extensively as a reliable method to track orthostatic changes in BP (15,16). Recent studies suggest that reconstructed BP levels lie between invasively measured BP and auscultatory pressures, with FinAP measurements remaining accurate at low pressures (16).

At the start of the measurement patients rested supine on a medical examination table. The FinAP wrist-worn unit and an appropriately sized finger cuff were affixed to the patient. The measurement hand was placed at heart level, with the height correction unit that compensates for hydrostatic pressure enabled. This height correction unit was zeroed and the automatic Physiocal® was activated, according to the manufacturer's manual. Patients were instructed to be silent during the entire measurement and to avoid any movements. After 5-10 minutes of supine rest patients were instructed to stand up as quickly as possible, preferably within 3 s. Older adults received assistance if needed. Just before standing up, the Physiocal® was disabled and after 60 s it was re-activated. The FinAP measurement was stopped after 5 minutes of standing. Subsequently patients were asked if they had experienced any symptoms like light-headedness or seeing black spots during standing.

Definitions of short term (180 s) orthostatic BP recovery patterns

The orthostatic BP recovery patterns were defined according to recent work (4,5). Normal BP recovery was defined as recovery of systolic BP to baseline values, not exceeding a decrease of more than 20 mmHg at 30 s of standing. Initial orthostatic hypotension was defined as a transient decrease of >40 mmHg in systolic BP within 15 s of active standing, with complete BP recovery within 30 s of standing. Delayed BP recovery was defined as delayed recovery of systolic BP to baseline values of more than 20 mmHg at 30 s of standing, but not meeting the criteria of sustained orthostatic hypotension. Sustained orthostatic hypotension was defined as a sustained decrease in systolic BP of ≥20 mmHg between 60-180 s of standing. With the presence of supine hypertension (supine systolic BP ≥160 mmHg) a reduction of ≥30 mmHg was used. This latter criterion was not applied to the definition of delayed BP recovery.

Hemodynamic analysis

The continuous BP measurements with Nexfin were stored on the hard disc of Nexfin for offline analysis. Using Frame Inspector (BMEYE, Amsterdam, The Netherlands) the recordings were converted to Excel files for beat-to-beat analysis. These files were used for offline inspection of the quality of the recordings, artifacts and proper position of markers and identification of the BP recovery patterns. Artifacts were detected by visual inspection and were then either removed or linearly interpolated. The marker indicating active standing up was added during the active lying-to-standing test, but the position was re-evaluated following offline inspection. Based on changes in height correction unit, BP and heart rate, the moment of standing up was adjusted, where appropriate.

For hemodynamic analysis the measured signal was digitally sampled at 200 Hz, before it was stored on the disk. Mean arterial pressure was calculated from the integral of the arterial pressure wave over one beat divided by the corresponding beat interval. Heart rate was computed as the inverse of the inter-beat interval and expressed as beats per min. Beat-to-beat left ventricular stroke volume expressed in ml was calculated by Nexfin-CO trek (Nexfin CO-trek®, BMEYE B.V., The Netherlands) by dividing the area under the systolic portion of the arterial pressure curve by the aortic input impedance, similar to the method of Wesseling et al (17). Cardiac output, expressed in l/min, was the product of stroke volume and heart rate. Total SVR, expressed in mmHg s/ml, was computed by mean arterial pressure divided by the computed CO. In conditions with regular heartbeats determination of CO by noninvasive continuous FinAP measurement with Nexfin has been validated in different settings and is not different from thermodilution CO from invasive measurement (18). Thereafter, measurements with atrial fibrillation, irregular heart beats and too many artifacts were excluded because CO estimates are not validated in these conditions. By applying these selection criteria we improved the reliability of the analysis of CO and SVR changes.

Resting supine values for CO and SVR were set at 100% (baseline), and changes were expressed in percentages from supine control. Blood pressure, heart rate, CO and SVR were compared at eight time points before and during active standing: baseline, nadir (lowest beat-to-beat value within 15 s of standing), 20, 30, 40, 60, 120 and 180 s after standing up. Baseline value was defined as the average of 60 s supine rest prior to standing. In the standing position 5 s averages (+/-2.5 s) were calculated, with exception of the nadir which was defined using beat-to-beat values.

Statistical analysis

For statistical analysis IBM SPSS statistics 22 (Version 22.0. Armonk, NY: IBM Corp.) was used. To test for normality the Shapiro-Wilk Test was used. Dichotomous variables are reported as percentages, continuous variables as median with interquartile range. The hemodynamic changes upon standing between the different orthostatic BP recovery patterns were compared with the Kruskal-Wallis test. For post-hoc analyses Mann-Whitney U tests were used and Bonferroni correction was applied. Changes in CO and SVR between groups were compared with Mann-Whitney U test. Statistical significance was set at $P < 0.05$ (2-sided).

RESULTS

Population characteristics

Orthostatic BP measurement were performed in 116 patients. Twenty-nine (25%) tracings were excluded due to: artifacts (n=6), irregular heart rhythm e.g. atrial fibrilliation (n=19) and insufficient quality of the signal (n=4). Another five patients developed reflex-mediated hypotension upon standing. Because the focus of this paper is not on reflex-mediated hypotension, these tracings were excluded. Of the remaining 82 patients, 47 (57%) had a normal BP recovery, 7 (8%) had initial orthostatic hypotension, 12 (15%) had a delayed BP recovery and 16 (19%) had sustained orthostatic hypotension. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

	Normal BP recovery (n=47)	Initial orthostatic hypotension (n=7)	Delayed BP recovery (n=12)	Sustained orthostatic hypotension (n=16)
Demographic				
Male, n (%)	21 (44.7)	3 (42.9)	7 (58.3)	9 (56.3)
Age, years	56.0 (36.0)	34.0 (45.0)	68.5 (24.0)	62.5 (32.0)
BMI, kg/m²	25.0 (5.4)	23.2 (4.2)	24.9 (5.2)	24.9 (4.5)
Medical history, n (%)				
Hypertension	11 (23.4)	1 (14.3)	7 (58.3)	3 (18.8)
Myocardial infarction	4 (8.5)	-	1 (8.3)	-
Atrial fibrillation	3 (6.4)	-	2 (16.7)	3 (18.8)
Heart failure	1 (2.1)	-	1 (8.3)	-
Peripheral vascular disease	2 (4.3)	-	1 (8.3)	-
Valvular heart disease	4 (8.5)	-	2 (16.7)	-
Diabetes Mellitus	4 (8.5)	2 (28.6)	2 (16.7)	2 (12.5)
History of (near) syncope	33 (70.2)	4 (57.1)	8 (66.7)	11 (68.8)
Medication*, n (%)				
B- Blocker	10 (21.3)	2 (28.6)	4 (33.3)	4 (25.0)
ACE-inhibitor	7 (14.9)	-	4 (33.3)	1 (6.3)
AT II Antagonist	3 (6.4)	2 (28.6)	1 (8.3)	2 (12.5)
Calcium antagonist	4 (8.5)	1 (14.3)	3 (25.0)	2 (12.5)
Diuretics	12 (25.5)	2 (28.6)	3 (25.0)	1 (6.3)
≥2 Antihypertensive	6 (12.8)	2 (28.6)	5 (41.7)	2 (12.5)
Alpha-1blocker	-	-	2 (16.7)	2 (12.5)
Admission, n (%)	5 (10.6)	-	6 (50.0)	4 (25.0)
Symptoms of OI, n (%)	15 (31.9)	2 (28.6)	2 (16.7)	9 (56.3)
Classification†, n (%)				
Reflex syncope	27 (57.4)	3 (42.9)	4 (33.3)	8 (50.0)
Cardiac syncope	3 (6.4)	-	2 (16.7)	-
Orthostatic hypotension	4 (8.5)	-	1 (8.3)	7 (43.8)
Unknown	13 (27.7)	4 (57.1)	5 (41.7)	1 (6.2)

Age and BMI is presented as median with interquartile range. OI = Orthostatic Intolerance, meaning complaints of light-headedness or presyncope during the active lying-to-standing test. BMI = body mass index. *No patients used psychoactive or anti Parkinson's medication. †Classification as made by the attending physician at the emergency department.

Baseline and nadir

There were no differences in BP or heart rate between the four groups at baseline (Figure 1, Table 2). Nadir in normal BP recovery differed significantly from initial orthostatic hypotension, delayed BP recovery and sustained orthostatic hypotension. For delta systolic BP and heart rate from baseline see Figure A1.

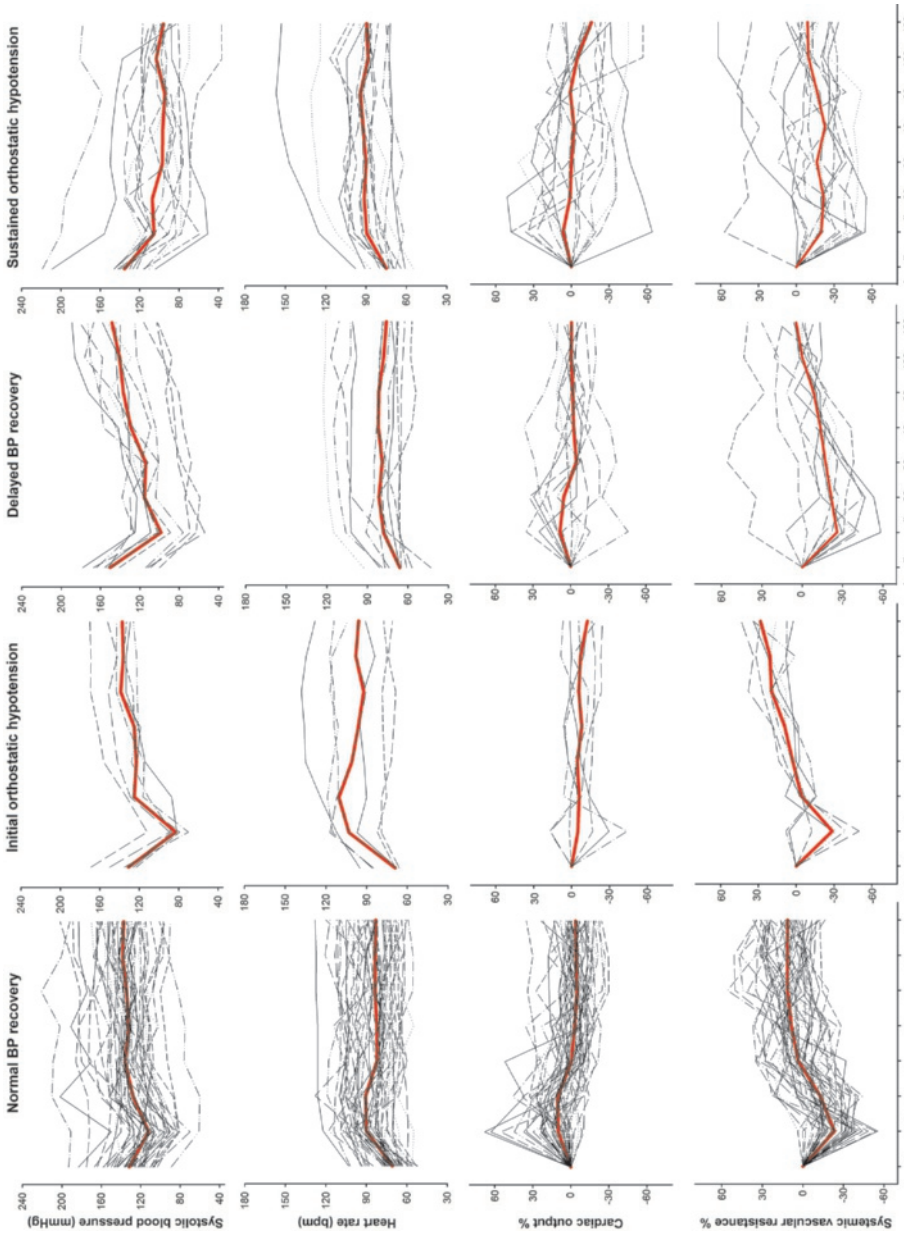

Figure 1. Individual and median systolic BP, HR, CO and SVR changes upon standing. BP, HR, CO and SVR are plotted at 8 time points. Thin lines represent individual tracings, bold red line the median. Vertically from left to right: normal BP recovery (n=47), initial orthostatic hypotension (n=7), delayed BP recovery (n=12) and sustained orthostatic hypotension (n=16). BP = blood pressure, CO = cardiac output, HR = heart rate, SVR = systemic vascular resistance.

Table 2. Hemodynamic changes in the spectrum of short term orthostatic BP recovery patterns

	Normal BP recovery N= 47	Initial orthostatic hypotension N= 7	Delayed BP recovery N= 12	Sustained orthostatic hypotension N= 16	Overall P-value
Systolic BP *(mmHg)*					
Baseline	132 (27)	131 (23)	150 (50)	136 (27)	.662
Nadir	112 (34)†	83 (10)†	99 (50)	106 (35)	**.020**
Delta	-24 (23)†‡§	-49 (17)†	-48 (18)‡	-34 (31)§	**.000**
20 s	128 (33)	125 (18)	115 (40)	107 (53)	.065
30 s	136 (26)‡§	123 (27)	114 (43)‡	97 (49)§	**.001**
40 s	132 (25)§	125 (27)	129 (49)	97 (47)§	**.004**
60 s	134 (28)§	139 (25)ll	137 (60)	95 (34)§ll	**.001**
120 s	138 (31)§	136 (10)ll	141 (63)	103 (29)§ll	**.001**
180 s	137 (34)§	137 (23)ll	148 (53)#	96 (22)§ll#	**.000**
Heart rate *(bpm)*					
Baseline	71 (12)	69 (18)	66 (17)	75 (11)	.459
Nadir	90 (18)	103 (33)	78 (31)	90 (26)	.112
Delta	19 (15)	29 (19)	12 (17)	15 (18)	.147
20 s	91 (25)	111 (40)	81 (31)	91 (24)	.362
30 s	82 (24)	101 (38)	79 (36)	90 (23)	.351
40 s	82 (27)	96 (36)	82 (36)	92 (16)	.291
60 s	84 (21)	92 (38)	82 (38)	94 (20)	.139
120 s	83 (25)	98 (42)	78 (33)	88 (26)	.122
180 s	83 (26)	96 (37)	76 (35)	90 (16)	.241
Cardiac output %					
Baseline	100	100	100	100	-
Nadir	10 (21)	-5 (46)	9 (27)	6 (50)	.103
20 s	11 (24)†	-6 (14)†	5 (35)	1 (37)	**.039**
30 s	0 (18)	-5 (13)	-5 (18)	0 (40)	.713
40 s	-3 (13)	-8 (21)	-2 (18)	-2 (39)	.833
60 s	-5 (16)	-6 (19)	-2 (21)	1 (31)	.670
120 s	-4 (15)	-7 (19)	-1 (7)	-5 (26)	.402
180 s	-4 (15)	-12 (21)	-1 (14)	-16 (31)	**.033***
Systemic vascular resistance %					
Baseline	100	100	100	100	-
Nadir	-23 (21)	-29 (58)	-26 (32)	-20 (32)	.985
20 s	-13 (26)	-4 (13)	-22 (28)	-22 (37)	.109
30 s	4 (20)‡	3 (12)	-17 (26)‡	-16 (43)	**.003**
40 s	9 (24)§	9 (18)	-13 (21)	-23 (34)§	**.003**
60 s	11 (22)‡§	20 (19)	-9 (23)‡	-16 (37)§	**.000**
120 s	12 (27)§	21 (24)	0 (21)	-10 (19)§	**.000**
180 s	11 (21)§	28 (27)ll	5 (19)	-9 (20)§ll	**.001**

Systolic BP, heart rate, cardiac output and systemic vascular resistance are expressed in median with interquartile range or in median % change from baseline with interquartile range. *indicates a significant overall difference, but no difference after post hoc analysis and Bonferroni correction. BP = blood pressure.
† a significant difference between normal recovery vs initial orthostatic hypotension.
‡ a significant difference between normal recovery vs delayed recovery.
§ a significant difference between normal recovery vs sustained orthostatic hypotension.
ll a significant difference between initial orthostatic hypotension vs sustained orthostatic hypotension.
a significant difference between delayed recovery vs sustained orthostatic hypotension.

Cardiac Output and Systemic Vascular Resistance (Figure 1&2, Table 2).

In normal BP recovery the changes in CO and SVR during nadir had a large variance. An immediate median increase in CO of +10 (21)% during nadir was seen with a simultaneous fall in SVR of -23 (21)%. At 30 s after standing SVR had increased to +4 (20)% and CO decreased to -1 (18)%. In initial orthostatic hypotension both CO and SVR decreased during nadir with -5 (46)% and -29 (58)%, respectively. Noteworthy is the large fall in CO of >15% in 3 patients, which did not occur in normal BP recovery. In delayed BP recovery the median CO and SVR changes during nadir were similar to normal BP recovery, but individual differences were large (+9 (27)% and -26 (32)%, respectively) (Figure 2). The difference between normal BP recovery and delayed BP recovery was clearly shown by the significant slower increase in SVR in delayed BP recovery. At 30 s of standing, SVR was -17 (26)% in delayed BP recovery vs. +4 (20)% in normal BP recovery and remained significantly lower up to 60 s of standing (-9 (23)% vs. +11 (22)%), respectively.

In sustained orthostatic hypotension the hemodynamic response was scattered. At 180 s of standing CO was -16 (31)% and SVR -9 (20)%. SVR changes differed significantly between 40 and 180 s of standing from normal BP recovery.

There were two outliers in the group with sustained orthostatic hypotension, i.e. both had an exaggerated fall in CO, with a high increase in heart rate and a corresponding large increase in SVR. Detailed study of the patient data, history, complaints and medication use did not provide a cause for this response, i.e. no indication for presumed hypovolemia. In general, based on the available patient data, the presumed causes in delayed BP recovery and sustained orthostatic hypotension were: dehydration (n=3, n=3), medication (n=4, n=4), suspected autonomic dysfunction (n=3, n=3), hormonal (n=1 in sustained orthostatic hypotension) and unknown (n=2, n=5).

DISCUSSION

The aim of this study was to describe the CO and SVR changes underlying normal BP recovery, initial orthostatic hypotension, delayed BP recovery and sustained orthostatic hypotension in (pre) syncope patients in the emergency department. The main finding is that an impaired increase in SVR was the main determinant of a delayed BP recovery, suggesting that both the use of vasodilators and impaired sympathetic vasoconstrictor function should be considered as a cause of delayed BP recovery.

Normal BP recovery

From previous studies, we know that the transient BP fall upon standing is based on a supply-demand mismatch between increasing CO and a pronounced fall in SVR (8,9,19). In short, during active standing leg and abdominal muscles compress the venous vessels in the legs and abdomen, causing an immediate shift of blood towards the heart resulting in an increase in right atrial pressure. The increase of ventricular filling together with an increase in heart rate, results in an increase in CO in the first seconds upon standing. The simultanous drop in BP is caused by a

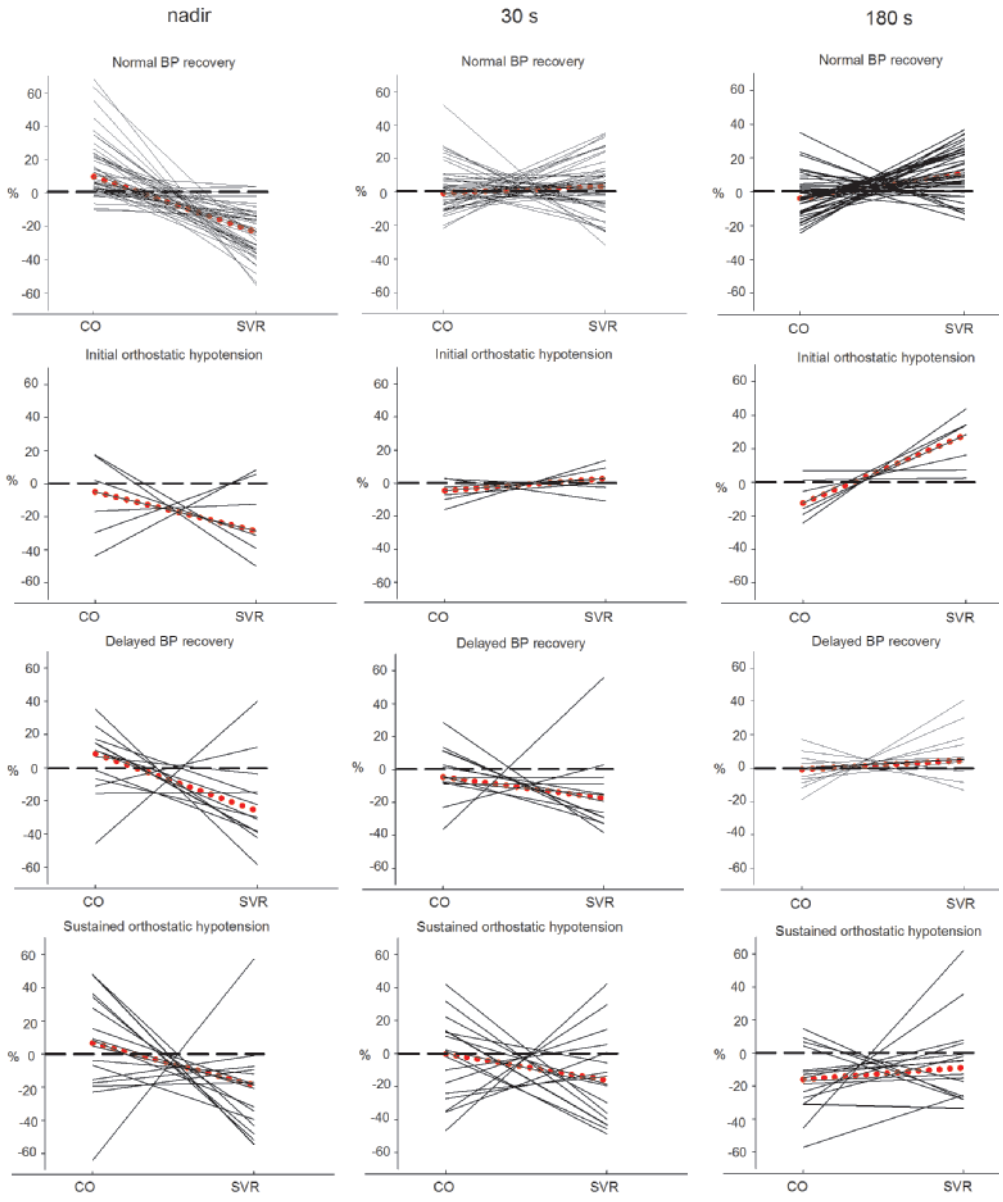

Figure 2. CO and SVR changes during nadir, 30 s and 180 s after active standing up.
Continuous noninvasive orthostatic BP measurement. The hemodynamic changes in CO and SVR during nadir, at 30 s and 180s (5-s averages) were analysed, with baseline (supine control) set as 100% and change given as % change. Thin lines represent individual tracings, red bold dotted line is the median change. BP = blood pressure, CO = cardiac output, SVR = systemic vascular resistance.

pronounced fall in SVR. Because this transient BP fall does not occur, or is far less pronounced, in passive change of posture (i.e. during head-up-tilt testing), it is suggested that the pronounced fall in SVR during active standing is a reflection of the muscular effort of standing, causing rapid vasodilatation. A second mechanism underlying the fall in SVR is a transient increase of the A-V pressure gradient (mechanical effect), which is also present during passive change of posture (3).

Compared to this study the changes in CO and SVR within the first 15 s upon standing were much more pronounced in previous studies with young and older healthy patients in laboratory settings (mean CO between +24% and +43% vs. 10% in this study and mean SVR between -36% and -58% vs. -23%) (8,9,19). Of note, 2 out of 3 previous studies used the maximum and minimum value of CO and SVR within the first 15 s of standing, while we used the CO and SVR value concurrent with the lowest systolic BP value within 15 s.

At 2-3 minutes after standing the SVR increase and CO decrease were 2-5 fold more pronounced in the previous studies. The most likely explanation for these differences is the difference in study population. The previous studies consisted of healthy young adult and older subjects, while this study population consisted of patients with (pre)syncope, a cardiovascular history and/or vasoactive medication use (21.3% used b-blockers). For the purpose of this study, the normal BP recovery group served as a good reference for the abnormal orthostatic BP recovery patterns. It also corresponds better to recent large population studies in middle-aged subjects and community dwelling older adults (4). In general, reference values for normal CO and SVR changes upon standing should be based on the smaller studies in selective groups of healthy young and older adults in laboratory settings (8,9,19).

Initial orthostatic hypotension

The hemodynamic findings in our study are very similar to a recent study, performed in young adults referred to a syncope unit and diagnosed with initial orthostatic hypotension (11). Changes in CO during nadir were -8% (range -37 to +27%) and in SVR -31% (range -46 to +10%), which is conspicuously similar to this study. This study showed that 3/7 patients had a decrease in CO of >15% during nadir, which did not occur in normal BP recovery. Thus CO seems to be the main determinant in the pronounced BP fall upon standing in initial orthostatic hypotension, although median CO did not differ from CO in normal BP recovery.

Delayed BP recovery

Delayed BP recovery is increasingly recognised as risk factor for (unexplained) falls, cognitive decline and cardiovascular mortality (5-7) , and is prevalent in the older population. The prevalence of delayed BP recovery in this study (14.6%) was similar to a large population study (17.9%) (4). To the best of our knowledge this is one of the first studies that studied the underlying hemodynamic mechanisms in delayed BP recovery. It showed that at 30 s of standing the SVR increase was significantly lower than in normal BP recovery, while changes in CO were not different. These findings indicate that delayed BP recovery is associated with an impaired SVR response, which can point towards impaired sympathetic vasoconstrictor function or the use of vasodilators.

A similar hypothesis was suggested by a previous study in older falls clinic patients, that found an association between delayed BP recovery and increased mortality (6). In this study, only the use of calcium channel blockers was significantly different between normal recovery and delayed BP recovery, and therefore the authors hypothesized that a delayed BP recovery is a physical sign, reflecting a final common pathway of various forms of subclinical impaired physiology. In addition, a similar pattern of delayed BP recovery has been seen in patients after bilateral carotid body tumor resection, implying dysfunction of the arterial baroreceptorreflex (5).

Sustained orthostatic hypotension

Sustained orthostatic hypotension was three times more prevalent in (pre)syncope patients in this study than it is prevalent in the general population (4). Sustained orthostatic hypotension has widely been associated with increased all-cause mortality, late life depression and is a known cause for falls and (pre)syncope, hence detection is important (20-22). The presumed causes in this study were diverse and this is reflected in the wide range of CO and SVR changes resulting in sustained orthostatic hypotension. In general, a global distinction can be made between neurogenic orthostatic hypotension and non-neurogenic orthostatic hypotension (10,23,24). The first is characterised by sympathetic noradrenergic failure, resulting in an inadequate SVR increase upon standing. The latter is a result of intravascular hypovolemia and consequent decreased CO and is usually accompanied by compensatory tachycardia. In addition, vasoactive and psychoactive drugs can influence both CO and SVR. Differentiating between different underlying mechanisms of sustained orthostatic hypotension is important, because it has different implications for treatment, additional tests, follow-up and prognosis (23). The active lying-to-standing test with FinAP can guide the clinician in whether patients need further autonomic testing because of presumed neurogenic orthostatic hypotension or whether intravascular hypovolemia is the more likely diagnosis and treatment of the underlying cause is the first step.

Limitations

The presented study has a number of limitations. Firstly, the measurements were performed in the emergency department: e.g. there was no control for intake of caffeine or food prior to the orthostatic BP measurement and the setting was a busy, noisy environment. Secondly, the patients were not selected at random. Patients were selected during workdays and most vulnerable patients were excluded. Despite this, a large proportion of the recruited patients had an abnormal orthostatic BP pattern. Thirdly, additional information, such as an extensive history about the (pre-) syncope episode and a follow-up period, was not part of the research protocol. Therefore the clinical relevance and short and long term implications of abnormal orthostatic BP patterns in (pre)syncope patients could not be studied.

CONCLUSIONS/RELEVANCE

The underlying hemodynamic patterns of cardiac output and systemic vascular resistance following active standing are heterogeneous, differ across orthostatic BP recovery patterns and are time dependent. Our results suggest that a delayed BP recovery is associated with an impaired increase in SVR in a significant proportion of individuals. Factors that alter SVR e.g. the use of vasodilators and impaired arterial baroreflex mediated function may therefore play a role in the etiology of a delayed BP recovery and warrant future research.

These findings are important in the light of recent discussions on the treatment of hypertension in older adults (13,14). Physicians should be aware of delayed orthostatic BP recovery during standing and consider individualizing the application of intensive anti-hypertension treatments to mitigate their possible negative impact on initial orthostatic blood pressure control and related morbidity.

Conflicts of Interest

The authors have nothing to disclose.

REFERENCES

(1) Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA), Heart Rhythm Society (HRS), Moya A, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009 Nov;30 (21):2631-2671.

(2) Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011 Apr;21 (2):69-72.

(3) Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME. Initial orthostatic hypotension: review of a forgotten condition. Clin Sci (Lond) 2007 Feb;112 (3):157-165.

(4) Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, et al. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). Circulation 2014 Nov 11;130 (20):1780-1789.

(5) van Wijnen VK, Finucane C, Harms MPM, Nolan H, Freeman RL, Westerhof BE, et al. Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages. J Intern Med 2017 Dec;282 (6):468-483.

(6) Lagro J, Schoon Y, Heerts I, Meel-van den Abeelen AS, Schalk B, Wieling W, et al. Impaired systolic blood pressure recovery directly after standing predicts mortality in older falls clinic patients. J Gerontol A Biol Sci Med Sci 2014 Apr;69 (4):471-478.

(7) Finucane C, O'Connell MD, Donoghue O, Richardson K, Savva GM, Kenny RA. Impaired Orthostatic Blood Pressure Recovery Is Associated with Unexplained and Injurious Falls. J Am Geriatr Soc 2017 Mar;65 (3):474-482.

(8) Sprangers RL, Wesseling KH, Imholz AL, Imholz BP, Wieling W. Initial blood pressure fall on stand up and exercise explained by changes in total peripheral resistance. J Appl Physiol (1985) 1991 Feb;70 (2):523-530.

(9) Wieling W, Veerman DP, Dambrink JH, Imholz BP. Disparities in circulatory adjustment to standing between young and elderly subjects explained by pulse contour analysis. Clin Sci (Lond) 1992 Aug;83 (2):149-155.

(10) Deegan BM, O'Connor M, Donnelly T, Carew S, Costelloe A, Sheehy T, et al. Orthostatic hypotension: a new classification system. Europace 2007 Oct;9 (10):937-941.

(11) van Wijnen VK, Harms MP, Go-Schon IK, Westerhof BE, Krediet CT, Stewart J, et al. Initial orthostatic hypotension in teenagers and young adults. Clin Auton Res 2016 Dec;26 (6):441-449.

(12) Messerli FH, Rimoldi SF, Bangalore S. Changing definition of hypertension in guidelines: how innocent a number game? Eur Heart J 2018 Jan 9.

(13) Sexton DJ, Canney M, O'Connell MDL, Moore P, Little MA, O'Seaghdha CM, et al. Injurious Falls and Syncope in Older Community-Dwelling Adults Meeting Inclusion Criteria for SPRINT. JAMA Intern Med 2017 Sep 1;177 (9):1385-1387.

(14) van Wijnen VK, Harms MPM, Wieling W. Orthostatic Hypotension in the First Minute After Standing Up: What Is the Clinical Relevance and Do Symptoms Matter? Hypertension 2018 May;71 (5):816-818.

(15) Martina JR, Westerhof BE, van Goudoever J, de Beaumont EM, Truijen J, Kim YS, et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin (R). Anesthesiology 2012 May;116 (5):1092-1103.

(16) Imholz BP, Wieling W, van Montfrans GA, Wesseling KH. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. Cardiovasc Res 1998 Jun;38 (3):605-616.

(17) Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol (1985) 1993 May;74 (5):2566-2573.

(18) Truijen J, van Lieshout JJ, Wesselink WA, Westerhof BE. Noninvasive continuous hemodynamic monitoring. J Clin Monit Comput 2012 Aug;26 (4):267-278.

(19) Tanaka H, Sjoberg BJ, Thulesius O. Cardiac output and blood pressure during active and passive standing. Clin Physiol 1996 Mar;16 (2):157-170.

(20) Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). Eur Heart J 2010 Jan;31 (1):85-91.

(21) Briggs R, Kenny RA, Kennelly SP. Systematic Review: The Association between Late Life Depression and Hypotension. J Am Med Dir Assoc 2016 Dec 1;17 (12):1076-1088.

(22) Shaw BH, Loughin TM, Robinovitch SN, Claydon VE. Cardiovascular responses to orthostasis and their association with falls in older adults. BMC Geriatr 2015 Dec 24;15 (1):174-015-0168-z.

(23) Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: a pathophysiological approach. Circulation 2009 Jan 6;119 (1):139-146.

(24) Cheshire WP,Jr. Clinical classification of orthostatic hypotensions. Clin Auton Res 2017 Jun;27 (3):133-135.

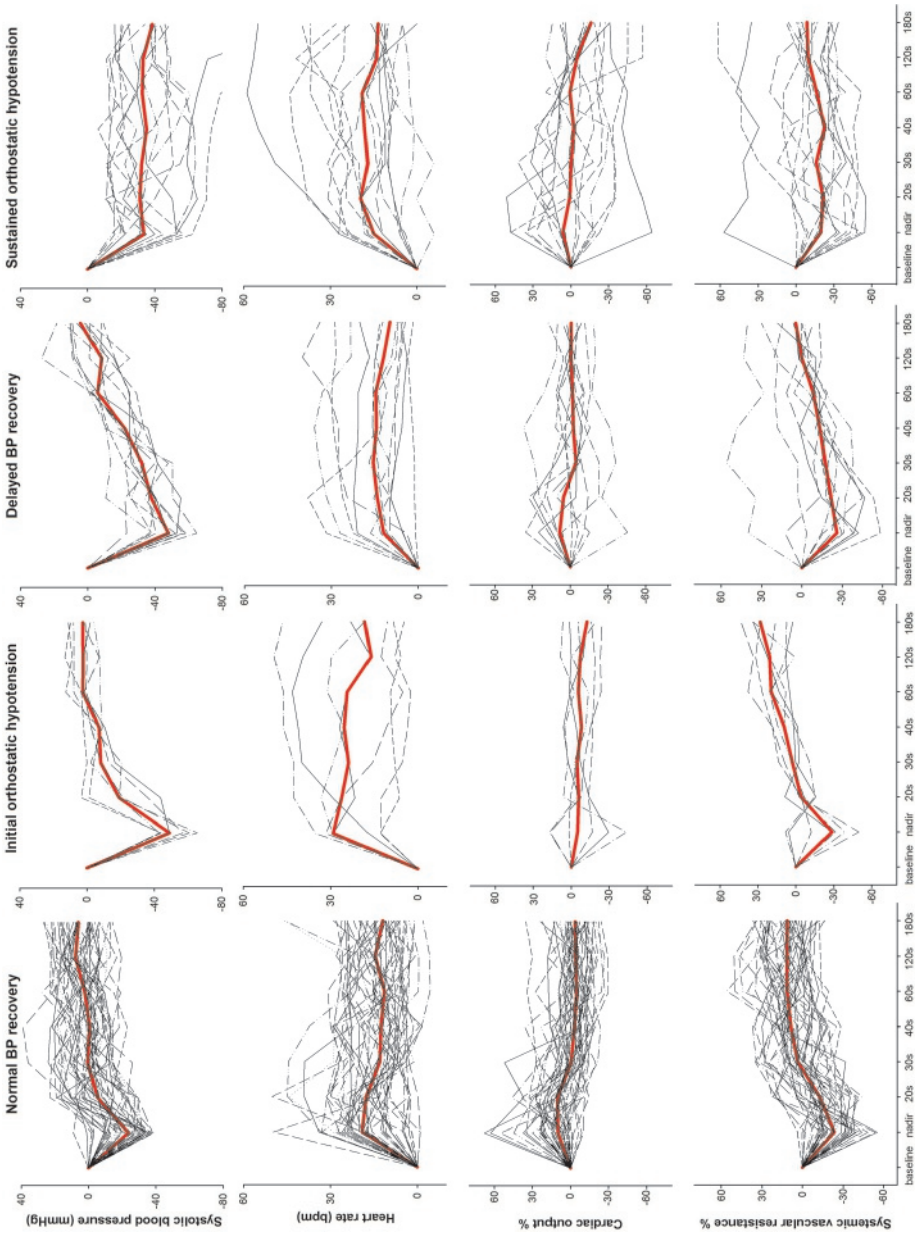

Figure A1. Individual and median systolic BP, HR, CO and SVR changes upon standing. BP, HR, CO and SVR are plotted at 8 time points using delta changes from baseline. Thin lines represent individual tracings, bold red line the median. Vertically from left to right: normal BP recovery (n=47), initial orthostatic hypotension (n=7), delayed BP recovery (n=12) and sustained orthostatic hypotension (n=16). BP = blood pressure, CO = cardiac output, HR = heart rate, SVR = systemic vascular resistance.