Frith J, Bashir AS, Newton JL. The duration of orthostatic blood pressure drop is predictive of death. *QJM: an international journal of medicine* **2016. DOI: 10.1093/qjmed/hcv126**

DOI link to article:

Date deposited:

22/03/2016

Embargo release date:

09 July 2016

The Duration of the Orthostatic Blood Pressure Drop is Predictive of Death

James Frith PhD, Ayat S Bashir, Julia L Newton PhD

ABSTRACT

Background: Orthostatic hypotension (OH) affects 6% of community-dwelling older people. This increases to 60% when non-invasive, continuous blood pressure (BP) monitoring is used, due to identification of transient drops in BP which recover rapidly.

Aim: To determine the clinical relevance of these transient orthostatic BP drops.

Design: 5-year clinical observational study.

Methods: 103 consecutive new patients attending a Falls and Syncope Clinic in the UK from 1st February 2009 underwent continuous BP monitoring during an active stand. BP profiles were analysed to quantify all reductions in BP, measuring the duration of any drop below diagnostic criteria. Five-year follow-up data was extracted from hospital clinical records to assess clinical outcomes.

Results: Systolic BP (sBP) dropped ≥20 mmHg in 76 (74%) individuals, with 65 (63%) having ≥10 mmHg drop in diastolic BP. However, only 22 (21%) cases were diagnosed clinically with OH. A sustained reduction in BP (≥30 seconds) had a sensitivity of 0.91 and specificity of 0.88 for a clinical diagnosis of OH, being more accurate than absolute BP reduction alone. A sustained reduction in sBP was associated with greater use of vasopressors (36%, p 0.001) and an independent, significantly greater risk of death (45% at 5 years, p 0.009).

Conclusion: An orthostatic reduction in sBP lasting ≥30 seconds improves accuracy of diagnosis. Moreover, given the significant adverse outcomes with a sustained

reduction, clinicians should consider this when diagnosing and treating patients, as transient OH does not appear to be clinically significant.

Acronyms

OH – Orthostatic hypotension

BP – Blood pressure

sBP – systolic blood pressure

dBP – diastolic blood pressure

ROC – receiver operating characteristic

IQR – interquartile range

INTRODUCTION

The prevalence of orthostatic hypotension has previously been found to be as high as 6% in the community and 70% in long-term care [1, 2]. However, since the advent of non-invasive, continuous blood pressure monitoring, prevalence studies have found OH in as many as 60% of healthy, community-dwelling older people and 30% of young healthy people [3-5]. This highlights one of the dilemmas of continuous BP monitoring. Both clinicians and academics using beat-to-beat BP monitoring are regularly faced with orthostatic BP profiles that demonstrate very brief drops in BP that recover spontaneously; the significance of these being unknown [6]. Previously, international consensus produced a diagnostic criterion, setting a diagnostic threshold of a systolic drop reaching 20 mmHg and diastolic drop of 10 mm Hg upon standing [7]. While this consensus did much to standardise the diagnosis of OH, the advent of continuous BP measurement demonstrated that it is common to reach this diagnostic threshold, without having the sustained decline in BP typically seen in those with OH [3, 8].

In 2011, an update to the consensus criteria was produced [2]. The most notable update was the addition of the word *sustained* to the diagnostic criteria. However, no attempt was made to define what constitutes *sustained.* One of the difficulties in addressing the issue of transient orthostatic BP drops is that their clinical significance is unknown. A further addition was made to the 2011 update concerning initial OH. This is defined as a symptomatic, exaggerated and transient orthostatic drop in BP (40 mmHg systolic or 20 mmHg) occurring within the first 15 seconds of standing upright [2]. Because it occurs rapidly it is unlikely to be identified without the use of continuous BP monitoring.

4

There have been no follow-up or observational studies to describe the natural history of transient OH or the longer term sequelae [6]. It is unknown whether it results in similar outcomes to 'classical' OH such as falls, syncope or an increase in mortality, or whether it is a precursor to a sustained OH.

It would be of practical use for clinicians and academics to understand whether the duration of the BP drop is of additional significance to the absolute BP drop, when diagnosing OH. Moreover, the clinical outcomes based on the duration of the BP drop would be of importance while making decisions regarding diagnosis and management. This study aims to address these two clinically important, unanswered questions.

METHODS

Setting

The Newcastle upon Tyne Hospitals NHS Foundation Trust's Falls and Syncope Service

in the UK is a specialist clinical service for people who fall, have syncope or have

dizziness, gait or balance abnormalities. The service covers a wide geographical area

over much of Northern England, covering urban and rural communities.

Participants

All patients who attend the service undergo a comprehensive medical assessment,

including an Active Stand to detect orthostatic hypotension. The Active Stand is

performed in accordance with international consensus methodology [2]. This test is

performed in all new patients attending the clinic, regardless of reason for referral. All

new patients attending the service over a six-week period (beginning 1st February

2009) who were aged over 18 years and who consented to allow their clinical data to be

used were included.

Data

All consecutive new patient encounters were recorded and reviewed. Continuous, beat-

to-beat BP was measured and recorded using digital photoplethysmography, with the

CNSystems Taskforce Monitor. The beat-to-beat BP data, which was stored

electronically, was exported into individual data files so each BP profile could be

visually inspected to extract the degree of BP drop and the duration of such drops.

Patients wore the equipment while resting in the supine position for 10 minutes and

were then assisted into the standing position where they remained for 3 minutes. Five-

year follow-up data was reviewed in March 2014 for the 103 cases who had had an

active stand in the study period. This follow-up data was retrieved from the hospital's electronic record, focussing on hospital admission due to falls/syncope/dizziness, requiring vasopressor treatment (fludrocortisone/midodrine/pyridostigmine/clonidine) and all cause mortality.

Diagnosis of Orthostatic Hypotension

A diagnosis of OH is made by a specialist physician within the Falls and Syncope Service. This is based on the international consensus statement on the definition of OH (a drop of 20 mmHg systolic, or 10 mmHg diastolic within 3 minutes of standing, or a drop of 40 mmHg systolic or 20 mmHg diastolic within 15 seconds of standing) [2]. The use of continuous BP monitoring is associated with false positive drops in BP [3, 5, 6]; the physician identifies a false positive as the presence of a drop in BP (as described above) in the absence of symptoms (fall, syncope, dizziness, weakness, cognitive disturbance, blurred vision, tremulousness, vertigo, pallor, anxiety, palpitations, clammy feeling and nausea [9]).

Ethical Permissions

All patients whose data are included in this study, provided written consent for their clinical data to be used for audit and research. The NHS Foundation Trust reviewed and approved the methods of gaining written consent and performing the data collection.

Data Analysis

Normally distributed data are presented as mean with standard deviation, with non-parametric being summarised as the median with the range. Student's t-test was used to compare parametric data between two groups and the Kolmogorov-Smirnov Z test

was used in preference to the Mann-Whitney U when comparing 2 non-parametric data sets with numbers less than 25 per group. Relationships between 2 categorical variables were assessed by performing the chi-square test; on review of expected frequencies, Fisher's exact test was not required. Where logistic regression was performed, assumptions which were verified were multicollinearity of the independent variables and linearity of the continuous independent variables with the natural log of the dependent variable. Independent variables violating these assumptions were excluded from the model. The goodness of fit of the model is described with Cox's R2, the associated $\chi 2$ statistic and significance value. The regression coefficient (b), standard error (SE) the significance level (p), the odds ratio (OR) and the 95% confidence intervals are tabulated. A predefined significance level was set at 0.05.

RESULTS

Of 114 eligible patient data files, one patient declined consent, four were repeat tests and six contained a poor unusable data signal. One hundred and three eligible continuous BP profiles were included in the analysis. The resulting cohort had a median age of 73 [range 22-94, interquartile range (IQR) 60-80], with a median of 3 comorbidities (range 0-10, IQR 1-5), with 43% taking vasoactive (including anti-hypertensive and anti-anginal) medication.

Diagnosis

An orthostatic drop in systolic BP occurred, to some degree, in 100 of the 103 cases. Of those 100 cases with a systolic drop, 76 cases met the diagnostic threshold, decreasing by 20 mmHg or more on standing. However, despite meeting this threshold, only 22 were given a clinical diagnosis of OH (29% of those who crossed the diagnostic threshold); meaning 54 orthostatic BP drops were not considered as clinically significant. Similarly, 94 cases demonstrated a diastolic BP drop on standing, with 65 reaching the diagnostic threshold. Table 1 compares the characteristics of those who were diagnosed with OH with those who reached the diagnosed threshold, but who were not considered to have OH. Those with a clinical diagnosis of OH had significantly greater number of comorbidities and had significantly greater drop in systolic and diastolic BP, with the drops below diagnostic threshold lasting for significantly longer.

A regression analysis was performed to identify which blood pressure parameters were independently associated with a clinical diagnosis of OH, whilst controlling for the number of comorbidities (Table 2). All 103 cases were included in the model to capture all sizes of BP drops. The regression model demonstrates that it is the time below the

systolic diagnostic threshold that is the most predictive parameter for a clinical diagnosis of OH. The systolic nadir is also significantly associated with the diagnosis, although less so, but perhaps more interestingly, the degree to which the systolic and diastolic BP decreases during orthostasis is not independently associated with the diagnosis.

With the results of this regression in mind, a receiver operating characteristic (ROC) with curve coordinates was created to compare the sensitivity and specificity of the blood pressure drop compared to the duration of the BP drop below the diagnostic threshold. For systolic BP, a duration of 30 seconds resulted in the greatest sensitivity and specificity, while it was 10 seconds for the diastolic BP. The area under the curve of the ROC is presented in Figure 1 alongside the specificity and sensitivity. The consensus criteria were used as diagnostic criteria (systolic drop greater than 20 mmHg and diastolic BP drop greater than 10 mmHg) and are compared to the length of time below the diagnostic threshold derived from the ROC analysis. The figure demonstrates that by incorporating the duration of the BP drop the specificity increases greatly and sensitivity reduces slightly. However, using a diagnostic criterion of systolic BP drop greater than 20mmHg with a sustained duration of at least 30 seconds yields a sensitivity of 0.91, specificity of 0.88 and an area under the curve of 0.956.

Clinical Outcomes

The five-year outcomes for a transient, a sustained or no drop in orthostatic BP are summarised in Figure 2. A significantly higher proportion of those with a sustained drop in BP was on vasopressor medication at 5 years or had died (p <0.001 for each

outcome). No significant difference was noted in hospital admissions over the 5-year follow up.

Mortality

Given that 45% of those with a sustained diagnostic drop in BP had died by 5 years follow up, a logistic regression model was created to control for age and comorbidity. The regression model, which is displayed in Table 3 demonstrates that a systolic drop in BP that lasts over 30 seconds below the 20 mmHg threshold, is independently associated with death, even when controlling for age and comorbidity (Table 3). In contrast, a drop in systolic BP lasting less than 30 seconds, is not independently associated with death, nor is age or comorbidity.

DISCUSSION

Since the advent of non-invasive BP measurement in the 1970s the relevance of transient drops in BP upon standing upright have been uncertain [6]. This study is the first to report longitudinal, follow up data of these transient BP drops. The findings reported here demonstrate that these short-lived orthostatic drops in BP are common in a specialist falls and syncope clinic setting, and at five years follow-up, it is the duration of the BP drop which is associated with a clinical diagnosis of OH, with a duration of at least 30 seconds being associated with adverse clinical outcomes.

These findings will be of interest to clinicians and academics alike. While continuous BP measurement produces a high rate of false positives, it has not been known if these transient drops are false positives, a natural precursor to OH or a normal response to standing. Indeed in 2011, the consensus criteria were updated and the addition of the word *sustained* was added to their diagnostic criteria to remove some of the uncertainty

of these brief drops [2]. However, no attempt was made to quantify what was meant by the term sustained. The results presented here suggest that a duration of at least 30 seconds for the systolic BP below 20 mmHg from baseline would be an appropriate length of time, excluding those with a transient drop in BP.

Incorporating the duration of the BP drop, with a cut-off value of 30 seconds is reasonable, given the high value sensitivity and specificity presented here. It may not be too surprising that the length of time below the diagnostic threshold is independently associated with a clinical diagnosis of OH, because time below threshold takes into account the consensus diagnostic threshold itself. However, incorporating a cut off value of 30 seconds greatly improves upon the specificity of the consensus cut-off values alone, while reducing the sensitivity only slightly.

One of the most important findings demonstrated in this 5-year follow-up study is the significantly higher prevalence of adverse outcomes in those with a sustained diagnostic BP drop. The hospital-derived follow-up data demonstrates that progression to pharmacotherapy, death and combined outcomes are all significantly more prevalent in those who have a systolic BP drop lasting over 30 seconds. This has important implications for clinicians who are uncertain about how to diagnose and treat people who have transient drops in their orthostatic BP. Indeed, on regression analysis, for diagnostic drop in BP lasting for greater than 30 seconds there is an independent and significant increased risk of death, even while controlling for age and comorbidity. The lack of an association between age, comorbidity and mortality in the regression model may be explained by demographics of the cohort. The regression model is derived from all patients who attended the specialist unit. The cohort is relatively old and frail and by

nature of a specialist clinic does not include the more straightforward cases. The result

is that the association between age, comorbidity and mortality may have been diluted

out of the model.

Clinical outcomes in this study were limited to hospital data only. This may skew the

results, such that only the most serious outcomes are reported. For example, it is not

known how common unreported falls were during the follow-up, nor do we know

whether quality of life is affected by the duration of the orthostatic BP drop. Because

the 5-year mortality data were derived from hospital records rather than death

certificates and registers it does limit the overall impact of mortality data.

All patients who participated in this study were attending a secondary care Falls and

Syncope Service and therefore may represent the more complex or severe cases than

are found in the general population. This may explain why there were no significant

differences in the 5-year hospital admission outcomes, as all cases, whether they

suffered from OH or not, were at risk of falls or syncope. Ideally, the significant

association with mortality would have been explored further with Cox regression

analysis, but due to the cohort size, a time-based analysis was precluded. In order to

confirm these results, it will be necessary to validate them in a prospective study, which

would ideally be placed in a non-specialist setting and capture a wider range of

outcomes.

It is expected that these results will have an increasing relevance in the context of the

rapidly ageing population. Given that there remains a great deal of uncertainty and lack

of evidence for the treatment of OH in older people, these results may help clinicians

make decisions regarding treatments based on the duration of orthostatic BP drop [6, 10, 11]. In fact, this study provides evidence which compliments the international consensus, using a duration of 30 seconds to quantify the recent addition of *sustained* to the diagnostic criteria.

Conflict of Interest Disclosures:

None

Author Contributions:

JF: Study concept, design, data collection, data analysis and manuscript preparation.

JLN: Study design and manuscript preparation.

REFERENCES

1. 1.	Shibao C, Grijalva CG, Raj SR, Biaggioni I and Griffin MR. Orthostatic hypotension-related hospitalizations in the United States. *Am J Med*. 2007;120:975-80.
2.	Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz I, Schondorff R, Stewart JM and van Dijk JG. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res*. 2011;21:69-72.
3.	Cooke J, Carew S, Quinn C, O'Connor M, Curtin J, O'Connor C, Saunders J, Humphreys E, Deburca S, Clinch D and Lyons D. The prevalence and pathological correlates of orthostatic hypotension and its subtypes when measured using beat-to-beat technology in a sample of older adults living in the community. *Age Ageing*. 2013;42:709-14.
4.	Romero-Ortuno R, Cogan L, Foran T, Kenny RA and Fan CW. Continuous noninvasive orthostatic blood pressure measurements and their relationship with orthostatic intolerance, falls, and frailty in older people. *J Am Geriatr Soc*. 2011;59:655-65.
5.	Boddaert J, Magula D and Belmin J. Diagnosis of orthostatic hypotension. *Lancet*. 1998;352:1705-6.
6.	Frith J, Newton JL and Parry SW. Measuring and defining orthostatic hypotension in the older person. *Age Ageing*. 2014;43:168-70.
7.	Anonymous. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology*. 1996;46:1470.
8.	Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, Cronin H and Kenny RA. 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;130:1780-9.
9.	Low PA, Opfer-Gehrking TL, McPhee BR, Fealey RD, Benarroch EE, Willner CL, Suarez GA, Proper CJ, Felten JA and Huck CA. Prospective evaluation of clinical characteristics of orthostatic hypotension. *Mayo Clin Proc*. 1995;70:617-22.
10.	Frith J and Newton JL. Lower limb and abdominal compression in the management of orthostatic hypotension--not supported by the evidence. *J Am Geriatr Soc*. 2014;62:781-2.
11.	Logan IC and Witham MD. Efficacy of treatments for orthostatic hypotension: a systematic review. *Age Ageing*. 2012;41:587-594.

TABLE 1. Demographic and blood pressure characteristics of those with a clinical diagnosis of OH, and those who had blood pressure drops that reached the diagnostic threshold but were not considered to be clinically significant (IQR – interquartile range).

	Orthostatic drop in systolic or diastolic BP meeting diagnostic criteria		
	Not diagnosed with OH (59)	Clinical diagnosis of OH (22)	*p*
Age	71 (range 23-94, IQR 56-81)	75 (range 34-88, IQR 73-78)	0.065
Comorbidities	2 (range 0-9, IQR 1-5)	4 (range 0-7, IQR 3-5)	0.024
Prescribed vasodepressor	24 (41%)	9 (41%)	1.0
Resting systolic BP	130 (105-229)	138 (106-198)	0.264
Resting diastolic BP	81 (13)	83 (18)	0.459
Nadir systolic BP during standing	103 (23)	78 (21)	<0.001
Nadir diastolic BP during standing	66 (14)	53(14)	0.001
Systolic BP drop	30 (11-77)	55 (27-113)	<0.001
Diastolic BP drop	14 (1-39)	29 (11-66)	0.001
Time below systolic threshold	5 (0-150)	153 (6-180)	<0.001

Time below diastolic threshold	3 (0-180)	68 (0-180)	0.001

TABLE 2. The regression model demonstrates which BP characteristics are associated with a clinical diagnosis of OH. Time below the diagnostic sBP threshold is independently associated with the clinical diagnosis, more so than the absolute drop in sBP itself (SE=standard error, OR=odds ratio).

	B	S.E.	OR	95% Confidence Interval		P
				Lower	Upper	
Comorbidities	0.338	0.242	1.402	0.873	2.252	0.162
Systolic nadir	-0.059	0.029	0.943	0.891	0.997	0.039
Systolic drop from baseline	-0.037	0.048	0.964	0.878	1.058	0.441
Time below systolic threshold	0.093	0.027	1.097	1.04	1.157	0.001
Diastolic nadir	0.058	0.046	1.06	0.968	1.159	0.207
Diastolic drop from baseline	0.043	0.085	1.044	0.884	1.233	0.613
Time below diastolic threshold	-0.051	0.025	0.95	0.904	0.998	0.042
Constant	-2.716	3.39	0.066			0.423
Cox r^2 0.506, Homer & Lemeshow 4.938 (8), p 0.783						

TABLE 3. The regression model, with death as the dependent variable. It demonstrates that sustained (≥30 seconds) drops in sBP, which remain below a 20 mmHg reduction in BP on standing, are independently and significantly associated with death at 5 years (Where transient is considered as duration below 30 seconds. SE=standard error, OR=odds ratio).

	B	SE	OR	95% Confidence interval		p
				Lower	Upper	
Constant	-6.301	2.064	0.002			0.002
Age	0.038	0.025	1.039	0.989	1.091	0.126
Comorbidities	0.105	0.136	1.11	0.85	1.451	0.442
Systolic BP group						0.005
Transient systolic BP drop	1.491	1.117	4.442	0.497	39.68	0.182
Sustained systolic BP drop	2.904	1.106	18.244	2.087	159.468	0.009
Cox r^2 0.188, Homer & Lemeshow 5.732 (8), p 0.677						

20

FIGURE LEGENDS

FIGURE 1. The sensitivity and specificity of each of the four criteria to diagnose OH. The size of the bubble represents the area under the curve of the receiver-operating characteristic, with the value displayed. A=diastolic BP drop below diagnostic threshold lasting over 10 seconds, B=systolic BP drop below diagnostic threshold for over 30 seconds, C=any diastolic BP drop below diagnostic threshold, D=any systolic BP drop below diagnostic threshold.

FIGURE 2. A comparison of the clinical outcomes of the three diagnostic

categories (No significant BP drop, systolic BP drop lasting less than 30 seconds

and a sustained systolic BP drop lasting over 30 seconds. The combined

outcomes do not include symptoms, as these were recorded at time of Active

Stand rather than during follow-up).