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CLINICAL RESEARCH
Hypertension

Association between hypotension during 24 h ambulatory blood pressure monitoring and reflex syncope: the SynABPM 1 study

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Abstract

Aims Diagnostic criteria for ambulatory blood pressure monitoring (ABPM) in patients with suspected reflex syncope are lacking. The study hypothesis was that patients with reflex syncope have a higher prevalence of systolic blood pressure (SBP) drops on ABPM.

Methods and results ABPM data from reflex syncope patients and controls, matched by average 24 h SBP, age, sex, and hypertension were compared. Patients with constitutional hypotension, orthostatic hypotension, and predominant cardioinhibition during carotid sinus massage or prolonged electrocardiogram monitoring or competing causes of syncope were excluded. Daytime and nighttime SBP drops (<110, 100, 90, 80 mmHg) were assessed. Findings were validated in an independent sample. In the derivation sample, daytime SBP drops were significantly more common in 158 syncope patients than 329 controls. One or more daytime drops <90 mmHg achieved 91% specificity and 32% sensitivity [odds ratio (OR) 4.6, $P < 0.001$]. Two or more daytime drops <100 mmHg achieved 84% specificity and 40% sensitivity (OR 3.5, $P = 0.001$). Results were confirmed in the validation sample of 164 syncope patients and 164 controls: one or more daytime SBP drops <90 mmHg achieved 94% specificity and 29% sensitivity (OR 6.2, $P < 0.001$), while two or more daytime SBP drops <100 mmHg achieved 83% specificity and 35% sensitivity (OR 2.6, $P < 0.001$)

Conclusion SBP drops during ABPM are more common in reflex syncope patients than in controls. Cut-off values that may be applied in clinical practice are defined. This study expands the current indications for ABPM to patients with reflex syncope.

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Structured Graphical Abstract

Key Question

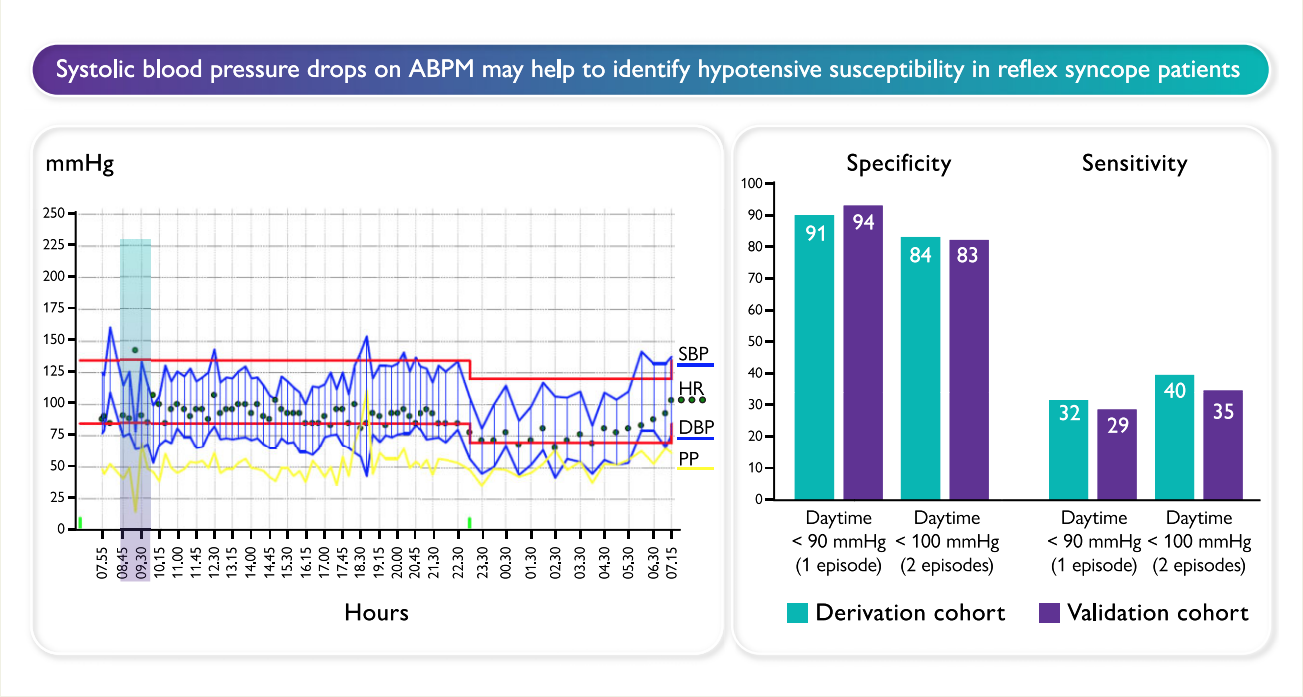
- Can systolic blood pressure (SBP) drops during ambulatory blood pressure monitoring (ABPM) detect susceptibility to reflex syncope?
- Which cut-off values allow identification of susceptibility to reflex syncope?

Key Finding

- Reflex syncope patients demonstrated higher prevalence of daytime systolic blood pressure (SBP) drops compared with non-syncopal subjects.
- One or two episodes of daytime SBP <90mmHg predicted reflex syncope with high specificity.

Take Home Message

- SBP drops on ABPM identify susceptibility to reflex syncope.
- This study expands the indications for ABPM to patients with reflex syncope.
- Future research should clarify whether therapies tailored to abolish SBP drops are able to prevent syncopal recurrences.



ABPM; ambulatory blood pressure monitoring; SBP, systolic blood pressure; HR, heart rate; DBP, diastolic blood pressure; PP, pulse pressure.

Keywords Hypotension • Low blood pressure • Blood pressure cut-off values • Hypotensive episode • Ambulatory blood pressure

Introduction

Reflex syncope is the most common cause of syncope accounting for up to 60–65% of cases. Reflex syncope is highly prevalent in the general population, with approximately one in three individuals reporting at least one syncopal event in their lives.[1] Although benign in origin, reflex syncope is associated with an increased risk of adverse outcomes, including severe injuries such as head trauma and fractures.[2,3] Unfavourable consequences of syncope are even more relevant to older adults, as fall-related injuries may lead to hospitalization, reduced mobility and loss of autonomy.[4,5] Finally, recurrent syncope substantially impacts individuals' well-being and quality of life, resulting in anxiety, activity restriction, and disruption of working activities.[6,7]

Reflex syncope has two components, i.e. hypotension and bradycardia, combining between them in a variable degree among patients.[1] Knowledge of the underlying mechanism of reflex syncope is essential to prevent recurrences and related adverse events. Hypotension plays a major role in most patients with reflex syncope. A hypotensive susceptibility, that is diagnosis of likely predominant hypotensive mechanism of reflex syncope, may be revealed by tilt testing in predisposed patients.[8]

It has recently been suggested that ambulatory blood pressure monitoring (ABPM) may provide a valuable contribution to the identification of hypotension in patients with syncope, even in the absence of hypotensive symptoms.[9] The European guidelines on syncope advise using ABPM in patients with suspected orthostatic hypotension or abnormally low blood pressure (BP), particularly in the presence of autonomic failure.[1] Consistently, the European guidelines on hypertension encourage the use of ABPM to investigate hypotensive episodes in treated hypertensive patients, particularly in older frailer individuals.[10] Yet, no previous study has investigated the role of ABPM in the diagnosis of reflex syncope and the ambulatory BP profile of these patients remains currently unknown. Consequently, neither hypertension nor syncope guidelines provide more precise recommendations, and diagnostic criteria for ABPM use in this clinical context are lacking.

In our clinical experience, syncope patients undergoing ABPM frequently show systolic BP (SBP) drops to very low SBP values (Rivasi G and Fedorowski A, unpublished personal communication). An example of SBP drop is shown in *Figure 1*. Based on these premises, we hypothesized that patients with reflex syncope have a higher prevalence of ambulatory SBP drops than control subjects and we aimed to define the SBP cut-off values that better allow to identify a potential hypotensive mechanism of reflex syncope (hereinafter referred as 'hypotensive susceptibility').

Methods

We conducted a retrospective cross-sectional analysis on two samples: a derivation sample and a validation sample.

Derivation sample

The derivation sample was recruited among patients of three tertiary hospitals (two in Italy—Milan and Florence—and one in Sweden—Malmö). The study group included patients who had been referred to the local Syncope Unit during the period 2018–2020 had received a diagnosis of reflex syncope and had undergone ABPM within the following 3 months, as part of the routine work-up of syncope in use in these hospitals. In complying with European Society of Cardiology (ESC) syncope guidelines,[1] reflex syncope was diagnosed when the clinical features were consistent with a reflex mechanism and competing diagnoses had been excluded. Tilt testing was performed to confirm the diagnosis, when reflex syncope was suspected but not established after the initial assessment. Exclusion criteria were as follows: (i) syncope due to orthostatic hypotension, defined by ESC syncope guidelines;[1] (ii) dominant cardioinhibitory (asystolic) reflex syncope during carotid sinus massage or prolonged ECG monitoring; (iii) competing causes of syncope (i.e. syncope due to arrhythmias and structural cardiac diseases and non-syncopal causes of transient loss of consciousness as defined by ESC guidelines on syncope[1]); and (iv) constitutional hypotension, defined in accordance with the literature as ambulatory 24 h SBP below the lowest 5% confidence interval of the general population, i.e. SBP ≤105 mmHg for males and ≤98 mmHg for females.[11,12] Indeed, patients with constitutional hypotension are highly likely to have a predominant hypotensive component, independently of the presence of SBP drops, as recently discussed elsewhere.[9]

The control group included patients who had undergone ABPM with different clinical indications from syncope (e.g. suspected hypertension, antihypertensive treatment monitoring, abnormal office BP values, evaluation of BP in the context of cardiovascular risk assessment) or from a general population study (Malmö Offspring Study[13]), selected to achieve 2:1 individual matching with syncope patients by average 24 h SBP, age, and sex. Individual matching was carried out separately in each centre applying the same matching strategy, with tolerance margins set at 3 mmHg for average 24 h SBP and 3 years for age.

Validation sample

Subsequently, an analysis aimed at verifying generalizability of results was carried out on an independent validation sample including syncope cases and non-syncopal controls. Syncope patients complied with the inclusion criteria of the derivation sample and included subjects evaluated at the Syncope Unit of Milan and Florence (after the recruitment period of the derivation sample) and at the Syncope Unit of Dublin, Ireland. Validation controls were selected from an epidemiological study of the general outpatient population of Malmö, Sweden (Malmö Offspring Study[13]) and from a database of patients of a tertiary hospital in Milan, Italy, who had undergone ABPM with clinical indications different from syncope. Controls were frequency matched to cases to guarantee the same average 24 h SBP and age and the same proportion of females and use of antihypertensive medications.

Ambulatory blood pressure monitoring

ABPM was performed using validated oscillometric devices (TM-2430, A&D, Tokyo, Japan, and Spacelabs Healthcare, model 90207, Snoqualmie, WA, USA) with the most appropriate cuff for arm size (small, medium, or large). Readings were obtained automatically at 15 min intervals between 7 a.m. and 11 p.m. and at 30 min intervals between 11 p.m. and 7 a.m. ABPM recordings were checked for quality, and artefacts were automatically excluded before data collection using the standard criteria incorporated in the analysis software. ABPM recordings including <50 valid measurements during the 24 h course and/or <10 valid measurements during the night-time and/or <70% of expected valid readings were excluded, thus fulfilling the European Society of Hypertension recommendations.[14]

Daytime and night-time SBP drops consisting of ≥1 or ≥2 single SBP measures <110, <100, <90 and <80 mmHg were recorded. For the purposes of this analysis, in order to exclude errors due to inter-individual differences in the actual sleep time, we used the 'narrow-fixed' approach[15] defining daytime as the period between 10:00 am and 10:00 pm and night-time as the period between 12:00 pm and 6:00 am.

Ethics

The study protocol was approved by the internal review board of Istituto Auxologico Italiano, Milan, Italy. According to European law, use of retrospective anonymized data collected exclusively for patient care, as is the case in this study, does not require individual informed consent nor evaluation by medical ethics committees.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were shown as absolute and relative frequencies. We considered 16

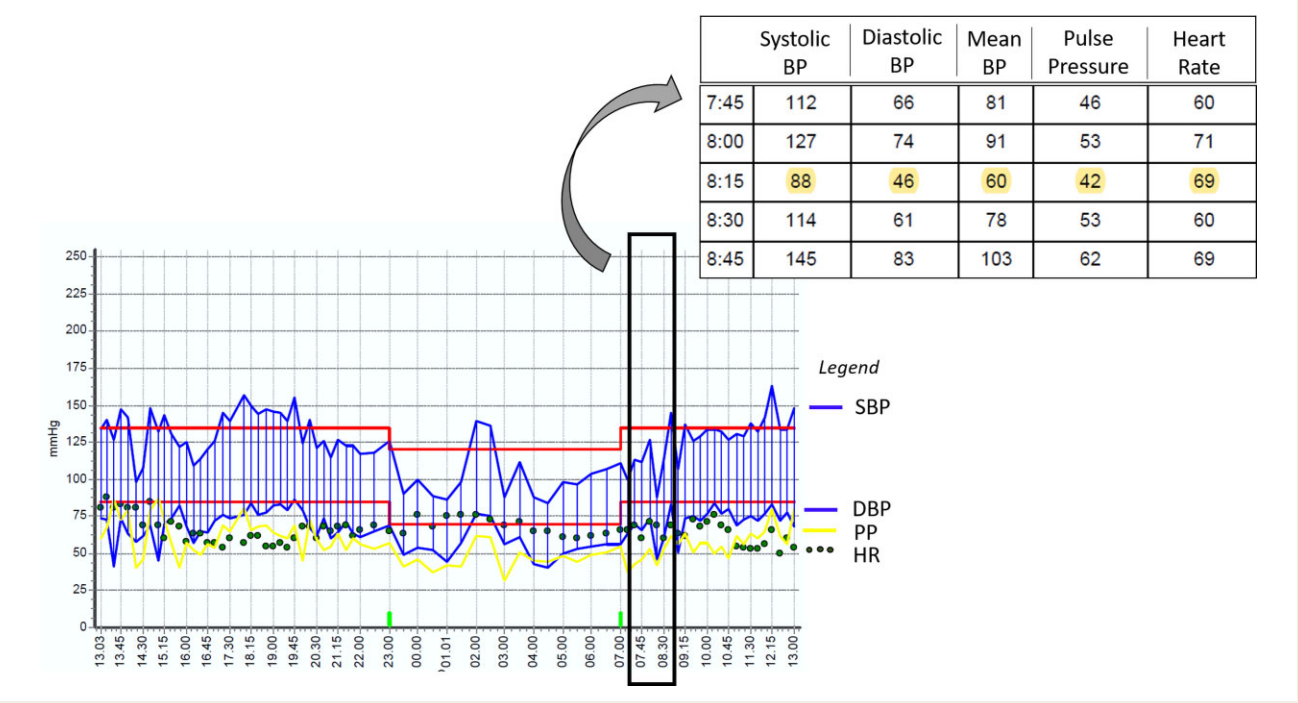


Figure 1 Twenty-four hour ambulatory blood pressure monitoring report of a patient with reflex syncope, showing a systolic blood pressure drop (88/46 mmHg) at 8.15 am. Case report from the Hypertension Clinic of Careggi Hospital, Florence, Italy. DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure.

Table 1 Characteristics of the study groups after matching procedure

	Derivation sample		Validation sample	
	Syncope (*N* = 158)	**Controls (*N* = 329)**	**Syncope (*N* = 164)**	**Controls (*N* = 164)**
Age, years, median (IQR)	62 (48–75)	58 (48–69)	66 (51–76)	62 (53–68)
Female sex, *n* (%)	95 (60)	192 (58)	91 (55)	89 (54)
ABPM, mmHg, median (IQR)	—	—	—	—
24 h SBP	123 (113–132)	124 (118–132)	129 (116–140)	129 (117–138)
Daytime SBP	127 (117–136)	130 (121–138)	132 (119–145)	134 (123–142)
Night-time SBP	112 (102–124)	114 (106–124)	118 (103–131)	114 (101–125)
MBP	89 (84–96)	92 (86–98)	93 (85–100)	93 (80–100)
Antihypertensive therapy, *n* (%)	64 (41)	282 (86)	87 (53)	78 (48)
Positive tilt testing response/total performed, *n* (%)	79/125 (63)	—	75/108 (69)	—
mixed or vasodepressor form	68	—	71	—
cardioinhibitory form	11	—	4	—

ABPM, ambulatory blood pressure monitoring; IQR, interquartile range; MBP, mean blood pressure; SBP, systolic blood pressure; —, not applicable.

potential scenarios defined from the combination of BP cut-off values (<110, <100, <90 and <80 mmHg), time of occurrence (daytime and night-time) and number of episodes (≥1 or ≥2). For each scenario, we estimated the proportion of SBP drops in syncope patients and controls and corresponding 95% confidence intervals (95% CIs) following the Wilson method. Moreover, the odds ratios and the corresponding *P*-values were reported. Cut-off values with the highest sensitivity among those with a specificity >90% were considered to provide a diagnosis of likely predominant hypotensive mechanism of reflex syncope ('hypotensive

susceptibility'), achieving an acceptably low rate of false positive diagnoses. Diagnosis of hypotensive susceptibility was still deemed possible for cut-off values achieving the highest sensitivity among those showing specificity between 80 and 90%.

High specificity was considered to take priority over high sensitivity, as false-positive cases may lead to misdiagnosis of hypotensive reflex syncope and underdiagnosis of different syncope mechanisms and may, for example, inappropriately encourage antihypertensive therapy reduction in hypertensive patients who may instead tolerate a more intensive BP control.

Further, a sensitivity analysis was performed to verify the impact of syncope status misclassification and individual mean 24 h SBP on the selected test. In brief, we applied a logistic regression model using the cut-off of SBP drop as dependent variable and real status and 24 h SBP on ABPM as independent variables.[16] Diagnostic test model-based sensitivity and specificity were calculated varying 24 h SBP values. These measures were corrected following Brenner's approach assuming a misclassification rate of 25% in both cases and controls groups and a prevalence rate of reflex syncope of 32%.[17] All tests were two-sided, and a significant level of 0.05 was considered. Analyses were conducted using Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Derivation sample

At outset, the syncope group included 169 patients who met inclusion criteria. Among these, 11 patients (mean age 36 ± 22 years, 7 females) had constitutional hypotension on ABPM (mean 24 h SBP 97 ± 5 mmHg, mean office SBP 113 ± 17 mmHg) and were excluded from analysis. The final analysis thus included 158 syncope patients and 329 matched controls. Although the two groups were matched for age, sex, and mean ambulatory BP values, antihypertensive treatment was more common among controls (*Table 1*).

Daytime SBP drops were significantly more common in syncope patients compared with controls, regardless of the cut-off value considered (*Table 2*). Among these, one or more daytime SBP drops <90 mmHg achieved 91% specificity (95% CI, 87–94) and 32% sensitivity (95% CI, 25–39), corresponding to an odds ratio of 4.6 ($P < 0.001$) (*Table 2*, *Figure 2A*). The positive and negative predictive values were 62% (95% CI, 52–72) and 73% (95% CI, 69–78), respectively. Two or more daytime SBP drops <100 mmHg achieved 84% specificity (95% CI 81–87) and 40% sensitivity (95% CI, 33–48), achieving an odds ratio of 3.5 ($P < 0.001$) (*Table 2*, *Figure 2B*). The positive and negative predictive values were 54% (95% CI, 45–63) and 74% (95% CI, 70–79), respectively. Lower cut-offs had higher specificity but lower sensitivity. Night-time SBP drops <90 and <100 mmHg were significantly more frequent among syncope patients than controls but showed less diagnostic yield (*Figure 2*, *Table 2*) and were not used for subsequent analyses (below).

Twenty-four hour average SBP influenced sensitivity and specificity of SBP drops, as specificity decreased in patients with lower average SBP values. In particular, one or more daytime SBP drops <90 mmHg provided a specificity >90% only in patients with average 24 h SBP ≥125 mmHg. Specificity varied between 80 and 90% in patients with lower 24 h systolic values (*Figure 3A* and Supplementary material online, *Table S1*). Two or more daytime SBP drops <90 mmHg were needed in order to achieve higher specificity in patients with average 24 h SBP <125 mmHg (*Figure 3B* and Supplementary material online, *Table S2*).

Table 3 reports the best parameters to achieve a likely diagnosis (specificity >90%) and a possible diagnosis (specificity 80–90%) of hypotensive susceptibility in the overall sample and in two subgroups according to average 24 h SBP ≥125 or <125 mmHg.

Validation sample

The analysis was performed on 164 syncope patients and 164 controls (*Table 1*). The analysis of the Validation sample confirmed a significantly higher proportion of daytime SBP drops in syncope patients compared with controls, regardless of the cut-off value considered (*Table 2*). Consistently with data from the derivation sample, one or more daytime SBP drops <90 mmHg identified syncope patients with 94% specificity (95% CI, 89–97) and 29% (95% CI, 22–36) sensitivity, corresponding to an odds ratio of 6.2 ($P < 0.001$) (*Table 2*). Two or more daytime SBP drops <100 mmHg identified syncope patients with 83% specificity (95% CI 76–88) and 35% sensitivity (95% CI, 28–42), achieving an odds ratio of 2.6 ($P < 0.001$) (*Table 2*). Night-time SBP drops showed limited diagnostic value also in the validation sample (*Table 2*).

When the analysis was stratified by average 24 h SBP, similar results were reported in patients with average 24 h SBP ≥125 mmHg (see Supplementary material online, *Table S3*). In patients with average 24 h SBP <125 mmHg, two or more daytime SBP drops <90 mmHg provided higher specificity (100%, 95% CI 98–100; 22% sensitivity, 95% CI 16–29) (see Supplementary material online, *Table S4*). SBP cut-off values achieving the best diagnostic yield in the validation sample are summarized in *Table 3*.

Discussion

In this study, we have shown that 24 h ABPM may offer a useful instrument for the detection of hypotensive susceptibility in reflex syncope. First, we documented that patients with reflex syncope have a higher frequency of SBP drops on ABPM than BP-matched controls. Second, one episode of daytime SBP <90 mmHg (or two episodes of daytime SBP <90 mmHg, if mean 24 h SBP is <125 mmHg) is the best cut-off for the identification of reflex syncope patients with hypotensive susceptibility. These results were consistent in both the derivation and validation samples (*Structured Graphical Abstract*).

Hypotension is the most common mechanism underlying reflex syncope. Although European guidelines suggest the use of ABPM to detect abnormally low BP,[1,14] ABPM parameters which should guide the diagnosis in this setting are unclear. Moreover, there is no consensus on the definition of hypotension on ABPM and the cut-off value below which BP should be considered as being abnormally low has yet to be defined.[11,18–20] Previous studies applied arbitrary cut-offs[19] or defined hypotension based on the association between BP and adverse cardiovascular events.[18,21–23] In this study, we have identified SBP cut-offs which are able to distinguish syncope from non-syncopal subjects. In particular, the SBP value of 90 mmHg was much more frequent in syncope patients than in controls, thus appearing as the most appropriate cut-off to define BP drops in these patients.

Table 2 **Derivation and validation sample. Prevalence of systolic blood pressure drops in syncope patients and controls according to different predefined cut-offs**

	Derivation sample						Validation sample					
	SBP drop in syncope ($n = 158$)	**SBP drop in controls ($n = 329$)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**OR (95% CI)**	***P* value***	**SBP drop in syncope ($n = 164$)**	**SBP drop in controls ($n = 164$)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**OR (95% CI)**	***P* value***
Daytime SBP <80, ≥1 episode	17 (11)	5 (2)	11 (7–17)	98 (96–99)	7.8 (2.8–21)	0.0001	17 (10)	1 (1)	10 (7–16)	99 (97–100)	18.8 (2.5–143)	0.0001
Daytime SBP <90, ≥1 episode	**50 (32)**	**30 (9)**	**32 (25–39)**	**91 (87–94)**	**4.6 (2.8–7.6)**	**0.0001**	**47 (29)**	**10 (6)**	**29 (22–36)**	**94 (89–97)**	**6.2 (3.0–12.8)**	**0.0001**
Daytime SBP <100, ≥1 episode	90 (57)	88 (27)	57 (49–64)	73 (68–78)	3.6 (2.4–5.4)	0.0001	90 (55)	47 (29)	55 (47–62)	71 (64–78)	3.0 (1.9–4.8)	0.0001
Daytime SBP <110, ≥1 episode	125 (79)	185 (56)	79 (72–85)	44 (38–49)	2.9 (1.9–4.6)	0.0001	119 (73)	83 (51)	73 (65–79)	49 (42–57)	2.6 (1.6–4.1)	0.0001
Night-time SBP <80, ≥1 episode	14 (9)	21 (6)	9 (5–14)	94 (90–96)	1.4 (0.7–2.9)	0.32	17 (10)	7 (4)	10 (7–16)	96 (91–98)	2.6 (1.0–6.4)	0.03
Night-time SBP <90, ≥1 episode	60 (38)	85 (26)	38 (31–46)	74 (69–79)	1.8 (1.2–2.6)	0.006	54 (33)	34 (21)	33 (26–40)	79 (72–85)	1.9 (1.1–3.1)	0.02
Night-time SBP <100, ≥1 episode	105 (66)	172 (52)	66 (59–73)	48 (42–53)	1.8 (1.2–2.7)	0.003	94 (57)	77 (47)	57 (50–65)	53 (45–61)	1.5 (0.9–1.6)	0.08
Night-time SBP <110, ≥1 episode	126 (80)	255 (78)	80 (73–85)	22 (18–27)	1.1 (0.7–1.8)	0.57	119 (73)	122 (74)	73 (65–79)	26 (20–33)	0.9 (0.6–1.5)	0.80
Daytime SBP <80, ≥2 episodes	5 (3)	2 (1)	3 (1–7)	99 (98–100)	5.3 (1.0–28)	0. 15†	7 (4)	0 (0)	4 (2–9)	100 (98–100)	NA	0.01
Daytime SBP <90, ≥2 episodes	22 (14)	18 (5)	14 (9–20)	95 (92–98)	2.9 (1.5–5.6)	0.001	21 (13)	3 (2)	13 (9–19)	98 (95–99)	7.9 (2.3–27.0)	0.001

Continued

Table 2 *Continued*

	Derivation sample						Validation sample					
	SBP drop in syncope ($n = 158$)	**SBP drop in controls ($n = 329$)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**OR (95% CI)**	***P* value***	**SBP drop in syncope ($n = 164$)**	**SBP drop in controls ($n = 164$)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**OR (95% CI)**	***P* value***
Daytime SBP <100, ≥2 episodes	**63 (40)**	**53 (16)**	**40 (33–48)**	**84 (81–87)**	**3.5 (2.2–5.3)**	**0.0001**	**57 (35)**	**28 (17)**	**35 (28–42)**	**83 (76–88)**	**2.6 (1.5–4.3)**	**0.0001**
Daytime SBP <110, ≥2 episodes	109 (69)	147 (45)	69 (61–76)	56 (50–61)	2.8 (1.8–4.1	0.0001	100 (61)	58 (35)	61 (53–68)	65 (57–72)	2.9 (1.8–4.5)	0.0001
Night-time SBP <80, ≥2 episodes	7 (4)	6 (2)	4 (2–9)	98 (96–99)	2.5 (0.8–7.6)	0. 64†	9 (5)	2 (1)	5 (3–10)	99 (96–100)	4.7 (1.0–22.1)	0. 06
Night-time SBP <90, ≥2 episodes	45 (28)	53 (16)	28 (22–36)	84 (80–88)	2.1 (1.3–3.3)	0.001	39 (24)	21 (13)	24 (18–31)	87 (81–91)	2.1 (1.2–3.8)	0.01
Night-time SBP <100, ≥2 episodes	83 (53)	135 (41)	53 (45–60)	59 (54–64)	1.6 (1.1–2.3)	0.01	77 (47)	50 (30)	47 (39–55)	70 (62–76)	2.0 (1.3–3.2)	**0.02**
Night-time SBP <110, ≥2 episodes	118 (75)	230 (70)	75 (67–81)	30 (26–36)	1.4 (0.9–2.1)	0.25	100 (61)	97 (59)	61 (53–68)	41 (34–49)	1.1 (0.7–1.7)	0.73

For definitions of daytime and night-time, see text. Ambulatory blood pressure monitoring parameters showing the best discriminating values between syncope patients and controls are indicated in bold.
CI, confidence interval; OR, odds ratio; SBP, systolic blood pressure (mmHg).

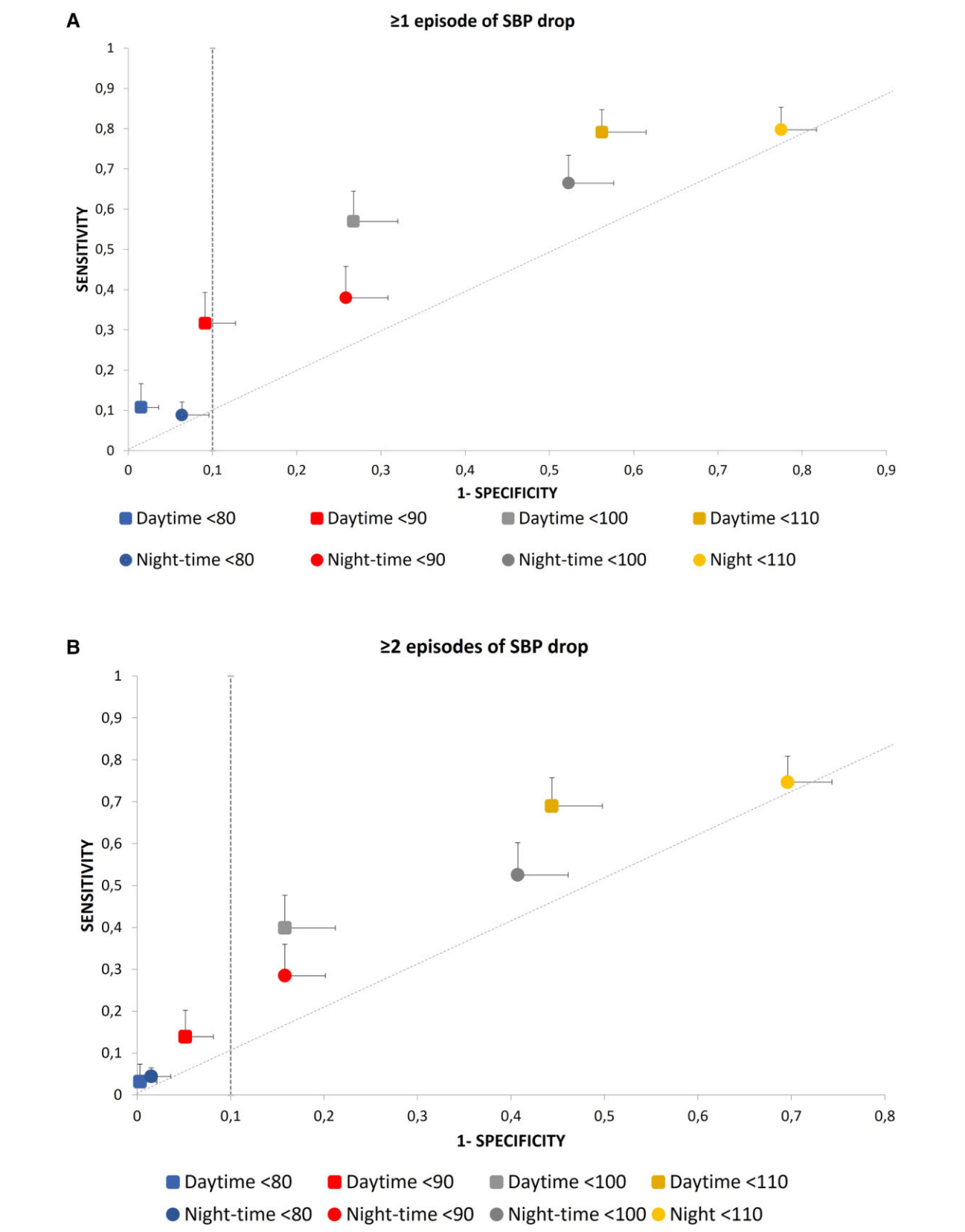


Figure 2 Diagnostic yield of ≥1 or ≥2 systolic blood pressure drops according to different cut-off values. For each cut-off value shown in the figure, the standard error of sensitivity (vertical line) and specificity (horizontal line) are given. Vertical dotted lines indicate the threshold of 90% specificity that was considered to provide an acceptably low rate of false positive diagnoses. (*A*) ≥1 systolic blood pressure drop during daytime or night-time. (*B*) ≥2 systolic blood pressure drops during daytime or night-time.

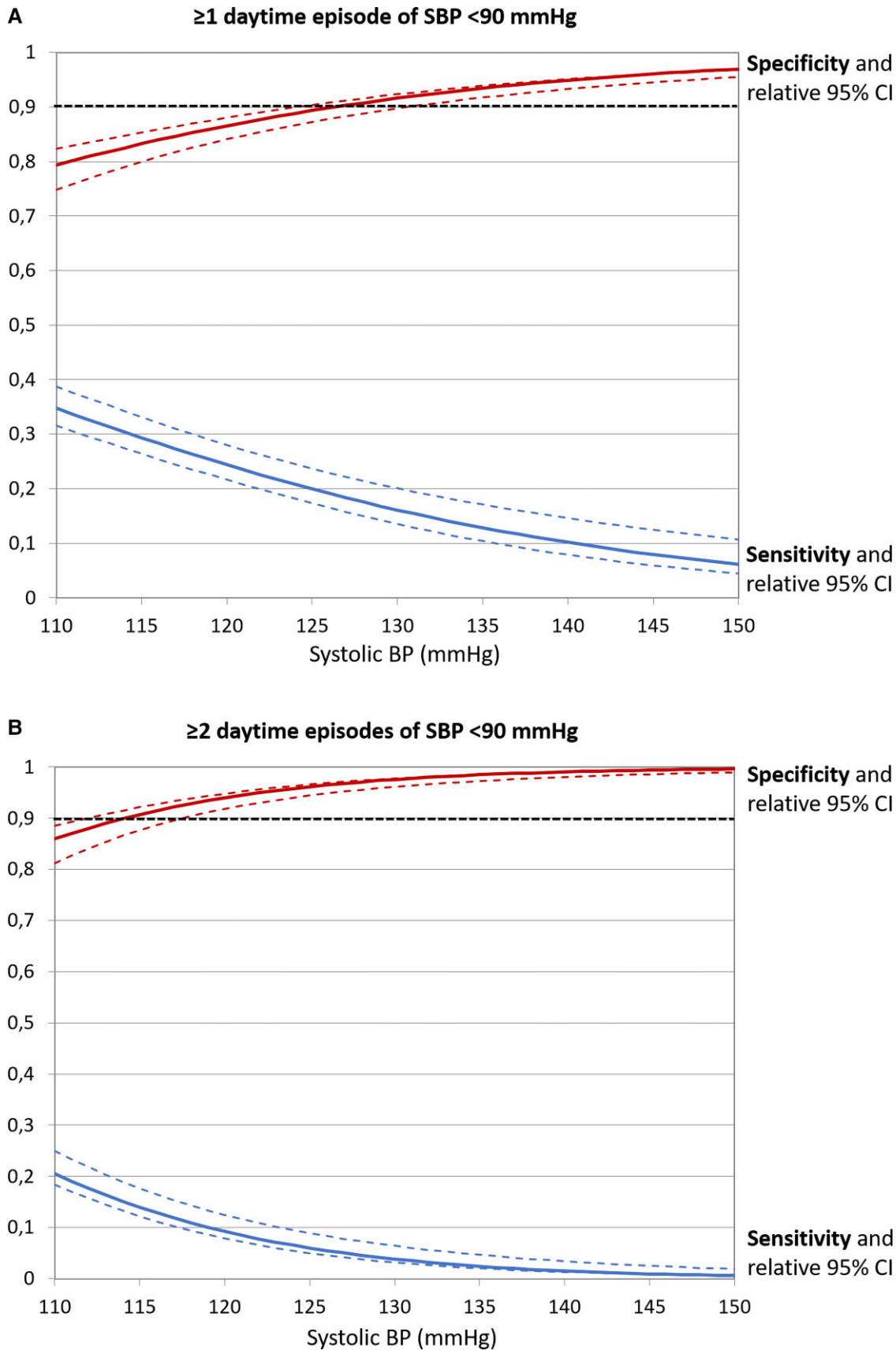


Figure 3 Sensitivity and specificity of daytime systolic blood pressure drops <90 mmHg according to mean 24 h systolic blood pressure values: one or more episodes (*A*), two or more episodes (*B*). The dashed horizontal line indicates the 90% specificity.

Table 3 Cut-off values of systolic blood pressure achieving the best sensitivity for likely diagnosis (specificity >90%) and possible diagnosis (specificity 80–90%) of hypotensive susceptibility

	Derivation sample		Validation sample	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
All patients				
Daytime SBP <90, ≥1 episode	32 (26–36)	91 (88–93)	29 (22–36)	94 (89–97)
Daytime SBP <100, ≥2 episodes	40 (34–46)	84 (81–87)	35 (28–42)	83 (76–88)
Mean 24 hr SBP <125 mmHg				
Daytime SBP <90, ≥2 episodes	22 (15–28)	90 (87–94)	22 (16–29)	100 (98–100)
Daytime SBP <90, ≥1 episode	43 (35–51)	85 (81–89)	40 (33–47)	92 (86–95)
Mean 24 hr SBP ≥125 mmHg				
Daytime SBP <90, ≥1 episode	19 (13–22)	97 (95–99)	21 (15–28)	96 (91–98)
Daytime SBP <100, ≥2 episodes	13 (8–18)	95 (92–97)	16 (11–22)	90 (85–94)
Daytime SBP <100, ≥1 episode	33 (25–41)	89 (85–92)	38 (30–45)	88 (82–92)

CI, confidence interval; SBP, systolic blood pressure (mmHg).

A recent study revealed that reflex syncope is associated with a specific haemodynamic profile, characterized by lower SBP, higher diastolic BP, and higher heart rate than the general population.[24] These particular haemodynamic features likely underpin a tendency to hypotension which is counterbalanced by the chronic activation of compensatory mechanisms aimed to preserve cardiovascular homeostasis and organ perfusion, especially at brain level. We suppose that reflex syncope occurs in presence of triggering situations which overcome the compensatory capacity of these mechanisms, leading to a drop in BP and subsequent cerebral hypoperfusion. Regarding our results, SBP drops on ABPM could represent asymptomatic manifestations of hypotensive susceptibility, manifesting when compensatory mechanisms temporarily fail, and may contribute to identify patients with the so-called hypotensive phenotype of reflex syncope.[1,24] We infer that, in such patients, (greater) SBP drops may potentially evoke a reflex syncope in some circumstances (e.g. in presence of a trigger).

In this context, our paper provides guidance on how ABPM could be applied in diagnosing reflex syncope, with a purpose of identifying patients with hypotensive susceptibility. ABPM may be especially useful in patients with suspected reflex syncope presenting with office BP values within the normal range. If one or more SBP drops <90 mmHg are detected or, two or more in patients with 24 h mean SBP <125 mmHg, the presence of hypotensive susceptibility can be deemed likely, and the patient can be offered treatment to counteract hypotension. If one or more SBP drops <100 mmHg are detected on ABPM, hypotensive susceptibility can only be considered possible. In these patients, tilt testing could be helpful to confirm presence of hypotensive susceptibility.[8,9] As the negative predictive value of the above variables was relatively high (74–78%), the probability of hypotensive susceptibility can instead be considered low in those patients without SBP drops on ABPM. In such cases, patients should be referred for additional diagnostic testing to investigate alternative mechanisms of syncope. Ultimately, in reflex syncope, hypotension is a herald of cardioinhibition, especially in younger subjects.[25,26] The presence of a hypotensive pattern on ABPM does not rule out the possibility that a cardioinhibitory reflex, triggered by hypotension, plays a relevant role in reflex syncope pathophysiology.

Finally, our data suggest that ABPM may also allow to identify constitutional hypotension. Indeed, patients who were excluded from our analysis as outliers had office BP values within the normal range, while ABPM revealed constitutional hypotension. This further reinforces the diagnostic potential of ABPM and confirms that ABPM may contribute to identify a predisposition to hypotension which is not detected by office BP values.

The use of ABPM in syncope patients is still rare in routine practice and mainly limited to patients with suspected autonomic failure, orthostatic, or post-prandial hypotension.[27–30] Indeed, ABPM has proved able to detect post-prandial hypotension in one of four older patients with a history of falls and syncope[31] and in older adults with isolated systolic hypotension.[32] Moreover, a strong association between orthostatic hypotension and hypotensive episodes on ABPM has been described in patients with Parkinson's disease: two or more episodes of SBP drops ≥15 mmHg (compared with 24 h mean SBP) identified orthostatic hypotension with 62% sensitivity and 87% specificity, while a daytime SBP drop ≥15 mmHg achieved 93% specificity.[20]

Data on ABPM use in reflex syncope have been reported only in paediatric patients, to date.[33] In our study, ABPM showed that at least one of three patients with suspected reflex syncope had abnormal SBP drops suggesting hypotensive susceptibility. It is likely that these patients had a greater hypotensive reflex than the other syncope patients who did not have SBP drops. In this context, ABPM might be able to distinguish two different populations of reflex syncope patients with obvious differences in management. ABPM is low cost and has relatively good patient acceptance and tolerability, also at advanced age and in presence of cognitive impairment.[34,35] Moreover, ABPM is very easy to perform in clinical practice and is

widely available in both hospital and primary care settings. By contrast, second-line diagnostic testing for syncope, such as tilt testing, is more time-consuming and has limited availability, requiring patients' referral to a syncope unit. Based on our results, a wider use of ABPM in syncope patients is desirable. Indeed, ABPM can be easily applied to syncope patients following the initial evaluation, if syncope remains unexplained. In case ABPM does not identify hypotensive susceptibility, it may however be helpful to select those patients who deserve referral for additional diagnostic testing.

Limitations

The findings of this study are subject to some limitations. In the derivation sample, there was a difference in the proportion of antihypertensive treatment, but this potential bias was overcome with an exact matching of antihypertensive treatment in the validation sample. By matching for average 24 h SBP, we could not analyse the effect of this variable. Yet, the role of ABPM in the detection of low 24 h SBP and the association of ambulatory 24 h SBP with BP drops have already been discussed in the literature.[11,12,36] In particular, a recent study demonstrated that nursing home residents with hypotensive episodes on ABPM had lower average SBP values over the 24 h course.[36]

Analysed variables and BP cut-off values were predefined and can be considered arbitrary. Consequently, we cannot exclude that intermediate BP values might provide slightly better diagnostic yield. Yet, taking into account the absence of a standard definition of ambulatory hypotension, the analysed cut-off values correspond with those applied in previous studies.[18,19] Referral of syncope patients to ABPM was based on clinical judgment only. Therefore, a selection bias cannot be excluded, with patients with lower BP showing higher probability of having ABPM performed. Moreover, given that as controls we included individuals from the general population, we cannot exclude that some of them might have had a past history of syncope. However, if this were the case, the diagnostic yield of SBP drops would be even higher than estimated by our results. Finally, data on daily activities and symptoms occurring during ABPM were not available, which prevented investigation of their correlation with BP values and SBP drops. Albeit, it is general experience that syncope during the 24 h period of ABPM is a rare event.

Conclusions

Reflex syncope patients demonstrate distinctly higher prevalence of daytime SBP drops compared with non-syncopal subjects. The present study defines cut-off values that may be applied in clinical practice for the identification of patients with hypotensive susceptibility that is low SBP episodes which are potentially capable of triggering reflex syncope. Our study expands the current indications for ABPM to patients with reflex syncope. Tailoring therapy aimed to abolish SBP drops, for the purpose of preventing future syncopal events, is the logical next step of this study, but this assumption requires validation in a future prospective controlled trial.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Data available on request.

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