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ORIGINAL RESEARCH

# Twenty-Four-Hour Ambulatory Blood Pressure Profile in Patients With Reflex Syncope and Matched Controls

Bashaaer Sharad, MD; Giulia Rivasi, MD; Viktor Hamrefors, MD, PhD; Madeleine Johansson, MD, PhD; Andrea Ungar, MD, PhD; Richard Sutton, DSc, MB, BS; Michele Brignole, MD; Gianfranco Parati, MD; Artur Fedorowski, MD, PhD

**BACKGROUND:** Ambulatory blood pressure (BP) monitoring has long been used to monitor BP in hypertension and lately emerged as a useful tool to detect hypotensive susceptibility in reflex syncope. However, hemodynamic characteristics in reflex syncope have not been sufficiently explored. The present study investigated the differences between ambulatory BP monitoring profiles associated with reflex syncope and normal population.

**METHODS AND RESULTS:** This is an observational study comparing ambulatory BP monitoring data from 50 patients with reflex syncope and 100 controls without syncope, age- and sex-matched 1:2. Mean 24-hour systolic (SBP) and diastolic BP, pulse pressure (24-hour PP), dipping status, and number of daytime SBP drops <90 to 100 mm Hg were analyzed. Variables associated with reflex syncope were investigated using multivariable logistic regression. Patients with reflex syncope displayed significantly lower 24-hour SBP (112.9±12.6 versus 119.3±11.5 mm Hg, $P$=0.002), higher 24-hour diastolic BP (85.2±9.6 versus 79.1±10.6 mm Hg, $P$<0.001), and markedly lower 24-hour PP (27.7±7.6 versus 40.3±9.0 mm Hg, $P$<0.001) compared with controls. Daytime SBP drops <90 mm Hg were more prevalent in patients with syncope (44% versus 17%, $P$<0.001). Daytime SBP drops <90 mm Hg, 24-hour PP <32 mm Hg, 24-hour SBP ≤110 mm Hg, and 24-hour diastolic BP ≥82 mm Hg were independently associated with reflex syncope, with 24-hour PP <32 mm Hg achieving the highest sensitivity (80%) and specificity (86%).

**CONCLUSIONS:** Patients with reflex syncope have lower 24-hour SBP but higher 24-hour diastolic BP and more frequent daytime SBP drops <90 mm Hg than individuals without syncope. Our results support the presence of lower SBP and PP in reflex syncope and suggest a role for ambulatory BP monitoring in the diagnostic work-up of this condition.

**Key Words:** ambulatory monitoring ■ blood pressure ■ blood pressure ■ hypotension ■ syncope ■ vasovagal syncope

Syncope is a common problem that affects individuals of all ages: one-third of all people experience at least 1 episode during life.[1] The most common form of syncope is reflex syncope, which is responsible for approximately one-half of all syncopal episodes across all age groups.[1] Although benign in origin, reflex syncope can be disabling and may negatively impact quality of life and employment, especially if it is repetitive and unpredictable.[2,3] Moreover, fall-related injuries such as fractures and head traumas may result in hospitalization, reduced mobility, and disability, particularly in older adults.[2,4,5]

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is a noninvasive method for blood pressure (BP) assessment throughout a 24-hour period, providing comprehensive information on hemodynamic variations related to the day and night periods, as well as to emotional and environmental conditions.[6]

Correspondence to: Artur Fedorowski, MD, PhD, Department of Cardiology, Karolinska University Hospital, Eugeniavägen 23, 171 64 Solna, Sweden. Email: artur.fedorowski@ki.se

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## CLINICAL PERSPECTIVE

### What Is New?

- The present study investigated the 24-hour ambulatory blood pressure (BP) monitoring profile associated with reflex syncope, showing lower 24-hour systolic BP, higher 24-hour diastolic BP, lower 24-hour pulse pressure, and more frequent daytime systolic BP drops <90 mm Hg in patients with reflex syncope compared with controls without syncope controls.
- Daytime systolic BP drops <90 mm Hg, 24-hour pulse pressure <32 mm Hg, 24-hour systolic BP ≤110 mm Hg, and 24-hour diastolic BP ≥82 mm Hg were independently associated with reflex syncope.
- Twenty-four-hour pulse pressure <32 mm Hg had the highest predictive ability for reflex syncope (80% sensitivity, 86% specificity).

### What Are the Clinical Implications?

- This study confirms the presence of a hypotensive hemodynamic profile in reflex syncope, expressed as a lower systolic BP and tendency for daytime BP drops.
- The present study expands current indications for ambulatory BP monitoring suggesting a role in the diagnostic work-up of reflex syncope.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ABPM** | ambulatory blood pressure monitoring |
| **DBP** | diastolic blood pressure |
| **PP** | pulse pressure |
| **SBP** | systolic blood pressure |

ABPM has long been used in patients with hypertension to confirm hypertension and assess BP control.[7] More recently, ABPM has also emerged as a useful diagnostic tool for hypotension and syncope.[1,8] Indeed, while providing an overview of BP values throughout the day, ABPM may allow detection of BP drop episodes, possibly associated with symptoms in the daily diary. Therefore, ABPM may offer a valuable contribution to identification of patients with hypotensive susceptibility (ie, individuals prone to low BP episodes that may trigger reflex syncope).[9,10]

According to the 2018 European guidelines on syncope,[1] ABPM should be considered for detection of hypotension in patients with autonomic failure or suspected orthostatic intolerance. By contrast, there is a paucity of data on the utility of ABPM in patients with recurrent syncope, where reflex mechanism has been confirmed or is likely and hypotensive susceptibility is suspected.

A recent study suggested that patients with reflex syncope present a different hemodynamic profile compared with the general population, with lower systolic blood pressure (SBP) and higher diastolic blood pressure (DBP) and heart rate.[11] However, the 24-hour ambulatory BP profile of patients with reflex syncope has not been fully addressed to date.

The aim of the present study was to investigate if patients diagnosed with reflex syncope demonstrate a specific ABPM profile that supports the hypothesis of hypotensive susceptibility as a potential trigger of reflex syncope.[9,10] Further, we planned to identify ABPM parameters that might support the diagnosis of hypotensive susceptibility in reflex syncope.

## METHODS

### Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Population Characteristics

The study group consisted of 50 consecutive patients aged 18 to 70 years referred to the tertiary Syncope Unit of Skåne University Hospital, Malmö, for syncopal evaluation, and diagnosed with reflex syncope by means of medical history or head-up tilt testing according to current European Society of Cardiology syncope guidelines.[1] Exclusion criteria were orthostatic hypotension, cardioinhibitory reflex syncope, and other competing causes of syncope. All patients underwent a 24-hour ABPM within 1 to 4 weeks after head-up tilt testing.

The control group consisted of 100 subjects matched 1:2 by age and sex randomly selected from the MOS (Malmö Offspring Study) with complete 24-hour ABPM data, with an age tolerance margin set at 3 years. MOS is a Swedish population-based cohort, initiated in March 2013 to map family patterns of major public diseases based on gene–environment interactions.[12] The MOS study protocol consists of several clinical assessments, including cardiovascular investigation such as ABPM. Patient inclusion and study flowchart are displayed in Figure 1.

### Twenty-Four-Hour ABPM

Twenty-four-hour ABPM was performed using validated oscillometric devices (Spacelabs Healthcare, model 90207, United States) with adequate cuffs for arm size. Readings were performed automatically at 15-minute intervals during daytime (between 7 AM and 10 PM) and at 30-minute intervals during nighttime (between 10 PM and 7 AM). The records were checked for deviating values

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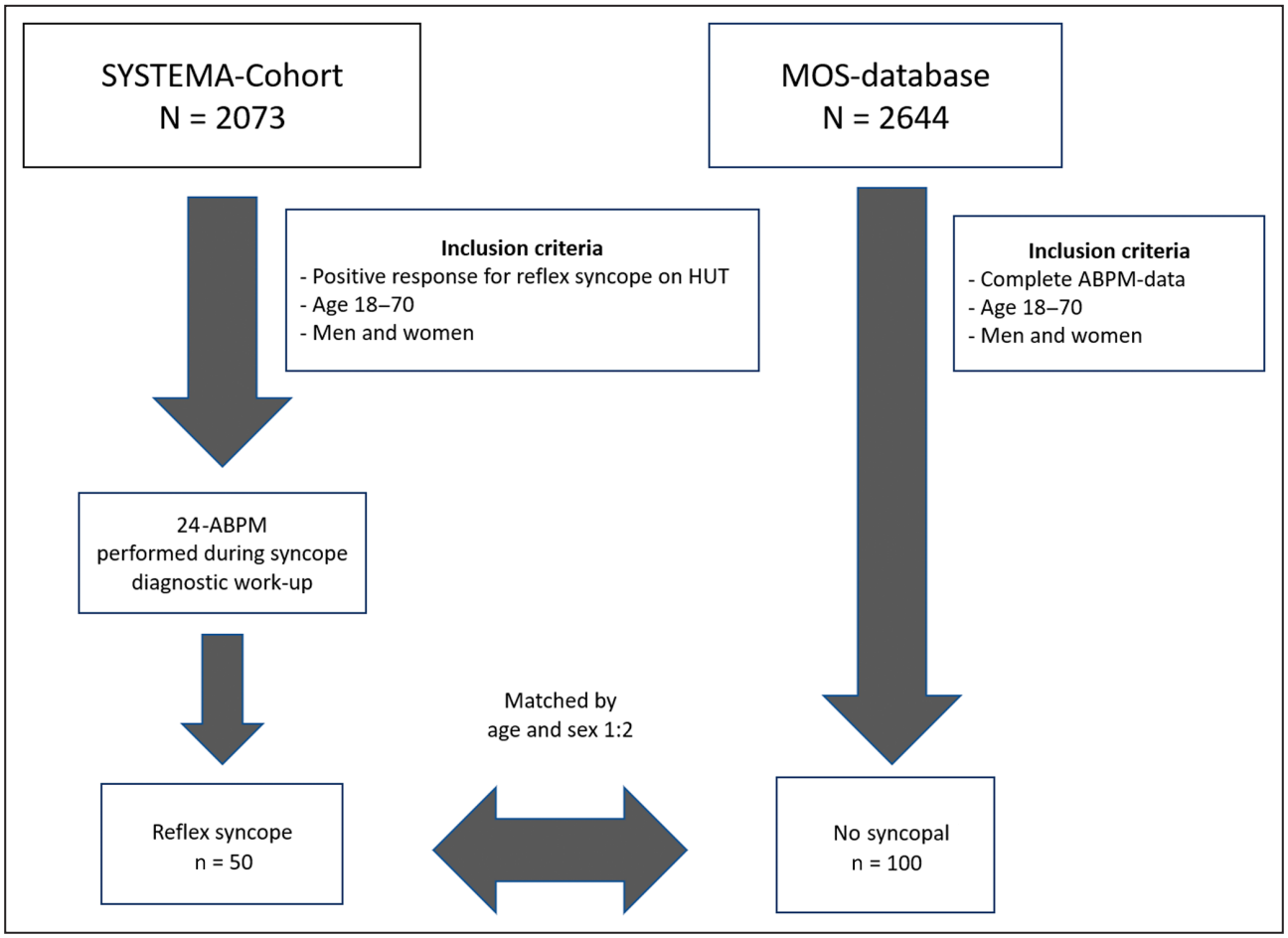



**Figure 1. Flowchart of subject selection.**
The study group was randomly selected from SYSTEMA (Syncope Study of Unselected Population in Malmö). From 2019 to 2020, ambulatory blood pressure monitoring was performed in selected subjects of the SYSTEMA cohort who met the diagnostic criteria of vasovagal syncope (typical history and positive result of head-up tilt testing) and accepted participation in the study. Fifty patients and 100 age- and sex-matched healthy controls from the MOS (Malmö Offspring Study) were included.[12] ABPM indicates ambulatory blood pressure monitoring; and HUT, head-up tilt testing.

before inserting measurements in the database for analysis. All subjects had at least 85% of the expected readings recorded. Patients were informed to follow their normal activities while ABPM was recorded.

## Definition of Included Variables

ABPM records from patients and controls were collected in a shared database and included the following variables: age, sex, mean 24-hour SBP, mean 24-hour DBP, mean 24-hour pulse pressure (PP), nighttime SBP, daytime SBP, prevalence of daytime SBP drops (≥1 episodes), and dipping status. PP was defined as the difference between 24-hour SBP and 24-hour DBP. Mean nighttime SBP, mean daytime SBP, and mean 24-hour DBP were manually calculated for controls. Nighttime BP dipping was defined as the difference between mean daytime and nighttime SBP, expressed as percentage of daytime SBP. Based on the nocturnal dipping, participants were classified as "dippers" (dipping >10%), "nondippers" (dipping between 0%–9%), and "reverse dippers" (nocturnal rise in BP). Daytime SBP drops were defined as single daytime SBP measures <90 mm Hg and <100 mm Hg, in agreement with Rivasi et al.[10]

## Statistical Analysis

Descriptive analysis was performed for an overview of data points. Continuous data were expressed as mean and SD. Statistical comparison of categorical variables was performed using chi-square test. Comparisons between 2 means were expressed using Student independent samples *t*-test, based on the sample distribution. Logistic regression analysis was used to identify the independent ABPM parameters associated with reflex syncope diagnosis. ABPM parameters showing an association with the outcome in univariate analysis ($P<0.05$) were tested as independent variables in multivariable logistic regression models having reflex

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syncope as dependent variable adjusted for age, sex, office BP, and antihypertensive treatment. For continuous ABPM variables associated with reflex syncope in univariate analysis, the receiver operating characteristic (ROC) curves method was used to define the cut-off values corresponding to the optimal combination of sensitivity and specificity. These cut-off values were then tested as independent variables in multivariable logistic regression analysis. A *P* value of <0.05 was considered as statistically significant for all tests. Data were analyzed using Statistical Analysis System Software version 27 (SPSS, Chicago, IL).

## Ethics

Informed consent was obtained from all subjects, and the study was performed in accordance with the Helsinki Declaration. All data were handled with caution, to prevent dissemination of sensitive data. The SYSTEMA study (Syncope Study of Unselected Population in Malmö) was approved by Ethical Review Board at Lund University (82/2008). The MOS was approved by the Regional Ethics committee in Lund (Dnr. 2012/594). Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

# RESULTS

## Patient Characteristics

The study sample included 50 patients with reflex syncope (mean age, 45.5±14.6 years) and 100 age- and sex-matched controls (mean age, 45.5±14.5 years), 70% being women. Four patients with syncope (8%) and 13 controls (13%) were receiving antihypertensive medications. Resting SBP did not differ between groups (*P*=0.105). Baseline characteristics of the study groups are reported in Table 1.

## Twenty-Four-Hour ABPM Parameters

As shown in Table 1, mean 24-hour SBP was significantly lower in patients with syncope compared with controls (112.9±12.6 mm Hg versus 119.3±11.5, *P*=0.002), whereas mean 24-hour DBP was significantly higher in patients with reflex syncope compared with controls (85.2±9.6 mm Hg versus 79.1±10.6, *P*<0.001). Mean 24-hour PP was markedly lower in the reflex syncope group (27.7±7.6 mm Hg versus 40.3±9.0 mm Hg, *P*<0.001). Additionally, patients with reflex syncope showed a higher prevalence of nocturnal BP dipping (76% versus 46%, *P*<0.001) (Table 1). Prevalence of daytime SBP drops <90 mm Hg was higher in patients with reflex syncope than in controls (44% versus 17%, *P*<0.001), while prevalence of drops <100 mm Hg was similar in the 2 groups (Table 1, Figure 2).

**Table 1. Baseline Characteristics of Patients With Syncope and Controls Without Syncope**

| | Patients with syncope (n=50) | Controls (n=100) | *P* value |
|---|---|---|---|
| Age, y (±SD) | 45.5±14.6 | 45.5±14.5 | … |
| Women, n (%) | 35 (70) | 70 (70) | … |
| Antihypertensive therapy, n (%) | 4 (8) | 13 (13) | 0.352 |
| Mean office SBP, mm Hg (±SD) | 115.5±11.3 | 119.7±16.3 | 0.105 |
| Tilt-testing positive response, n | 45/48 | … | |
| ABPM parameters | | | |
| Mean 24-h SBP, mm Hg (±SD) | 112.9±12.6 | 119.3±11.5 | 0.002* |
| Mean daytime SBP, mm Hg (±SD) | 116.7±12.9 | 122.2±11.3 | 0.082 |
| Mean nighttime SBP, mm Hg (±SD) | 101.3±11.6 | 103.1±11.4 | 0.370 |
| Mean 24-h DBP, mm Hg (±SD) | 85.2±9.6 | 79.1±10.6 | <0.001* |
| Mean 24-h PP, mm Hg (±SD) | 27.7±7.6 | 40.3±9.0 | <0.001* |
| Dipping, % (±SD) | 13.1±5.7 | 15.3±9.0 | 0.107 |
| Dippers, n (%) | 38 (76) | 46 (46) | <0.001* |
| Nondipper, n (%) | 12 (24) | 43 (43) | |
| Reverse dippers, n (%) | 0 (0) | 11 (11) | |
| Daytime SBP drops <90 mm Hg (≥1 episodes), n (%) | 22 (44) | 17 (17) | <0.001* |
| Daytime SBP drops <100 mm Hg (≥1 episodes), n (%) | 29 (58) | 45 (45) | 0.133 |

ABPM indicates ambulatory blood pressure monitoring; DBP, diastolic blood pressure; PP, pulse pressure; and SBP, systolic blood pressure.
*Significant inter-group difference (*P*<0.05).

## ABPM Blood Pressure Cut-Offs Predicting Reflex Syncope

Based on the ROC curve analysis, BP cut-offs best predicting reflex syncope were 110 mm Hg for mean 24-hour SBP, 82 mm Hg for mean 24-hour DBP, and 32 mm Hg for 24-hour PP (Table 2). In particular, 24-hour PP <32 mm Hg achieved the best prediction of reflex syncope, providing the best combination of sensitivity (80%) and specificity (86%) (Table 2).

In a multivariable logistic regression adjusted for age, sex, office BP, and antihypertensive treatment, we found that 24-hour PP <32 mm Hg, mean 24-hour SBP ≤110 mm Hg, and mean 24-hour DBP ≥82 mm Hg were independently associated with the diagnosis of reflex syncope (all *P*<0.001, Table 3). Reflex syncope was also correlated with ≥1 episodes of daytime SBP drops <90 mm Hg (*P*=0.002). Having both 24-hour PP <32 mm Hg and mean 24-hour SBP ≤110 mm Hg substantially increased the probability of having a reflex syncope diagnosis (Table 3).

# DISCUSSION

In this study we have shown that patients diagnosed with reflex syncope have a specific ABPM profile,

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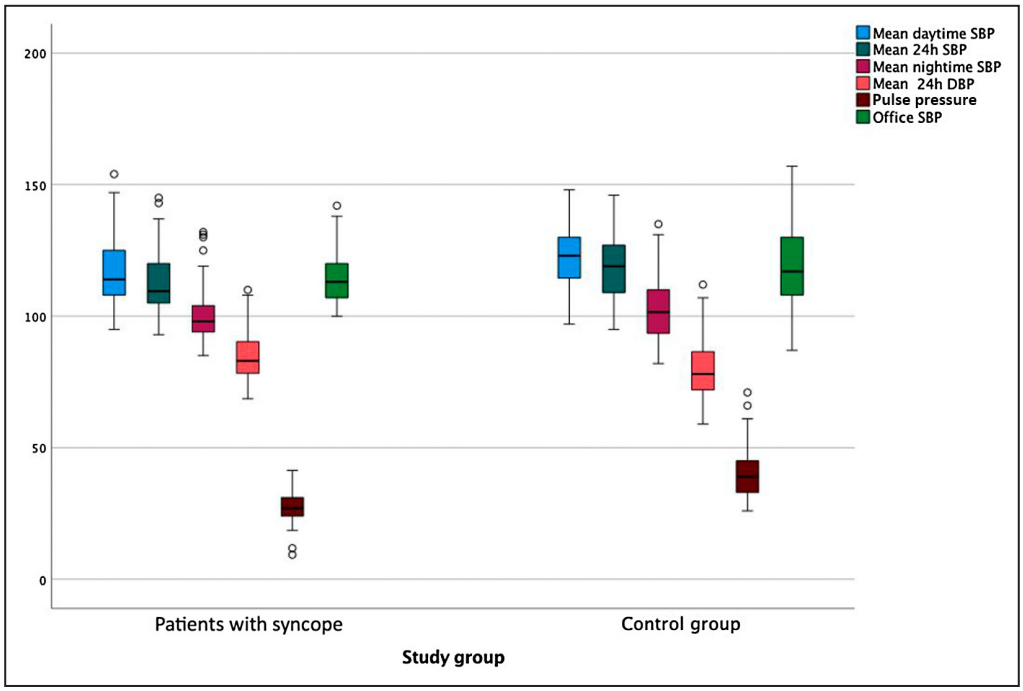



**Figure 2. Distribution of 24-hour ambulatory blood pressure monitoring parameters in patients with reflex syncope vs individuals without syncope.**
The central line within the boxes depicts the median value. The colored boxes include the 50% of the values falling between the 25th and 75th percentiles. Outliers are plotted as individual data points. The y-axis demonstrates blood pressure intervals reported in mm Hg. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

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characterized by lower 24-hour mean SBP and higher 24-hour mean DBP, which result in markedly lower 24-hour mean PP.

Moreover, our results indicate that 24-hour PP <32 mm Hg has the highest predictive ability for reflex syncope, followed by mean 24-hour DBP ≥82 mm Hg and mean 24-hour SBP ≤110 mm Hg. The presence of episodic hypotension manifesting as daytime SBP drops <90 mm Hg might further support the diagnosis of reflex syncope.

These results corroborate recent research suggesting that patients prone to reflex syncope have a different hemodynamic profile expressed as a lower SBP and tendency for daytime BP drops. In a multicohort population-based study, patients with definite or likely reflex syncope were compared with individuals without syncope. The results showed significantly lower SBP and higher DBP and heart rate in reflex syncope compared with the general population.[11] In another study,[13] younger age (<30 years), lower SBP and DBP, and lower heart rate were associated with positive results of head-up tilt testing for reflex syncope. In particular, SBP values ≤128 mm Hg were independently associated with tilt-test positivity, suggesting a different hemodynamic profile in patients with different tilt-testing responses.[13]

This study shows a similar hemodynamic profile on ABPM with lower 24-hour SBP and higher 24-hour DBP, thus confirming the hypothesis that individuals with reflex syncope may have distinct hemodynamic features, even in resting conditions. The explanation for these hemodynamic differences is currently unknown. Some researchers believe that abnormalities of hemodynamics are attributable to dysfunction in the autonomic nervous system, resulting in parasympathetic hyperactivity or decreased sympathetic

**Table 2. ABPM Blood Pressure Cut-off Values Best Predicting Reflex Syncope Diagnosis**

| ABPM parameter | Cut-off value | AUC | 95% CI | Sensitivity | Specificity |
|---|---|---|---|---|---|
| Mean 24-h SBP | ≤110 mm Hg | 0.658 | 0.561–0.754 | 60% | 70% |
| Mean 24-h DBP | ≥82 mm Hg | 0.673 | 0.587–0.759 | 54% | 66% |
| 24-h PP | <32 mm Hg | 0.896 | 0.839–0.953 | 80% | 86% |

ABPM indicates ambulatory blood pressure monitoring; AUC, area under the curve; DBP, diastolic blood pressure; PP, pulse pressure; and SBP, systolic blood pressure.

**Table 3. ABPM Parameters Independently Associated With Reflex Syncope Diagnosis**

| ABPM variable | OR | 95% CI | *P* value |
|---|---|---|---|
| Daytime SBP <90 mm Hg (≥1 episodes) | 3.64 | 1.59–8.33 | 0.002 |
| 24-h PP <32 mm Hg | 27.9 | 10.21–76.42 | <0.001 |
| Mean 24-h DBP ≥82 mm Hg | 5.21 | 2.1–12.93 | <0.001 |
| Mean 24-h SBP ≤110 mm Hg | 4.91 | 1.91–12.65 | <0.001 |
| 24-h PP <32 mm Hg and mean 24-h SBP ≤110 mm Hg | 14.8 | 5.51–39.74 | <0.001 |

Multivariable logistic regression was applied to identify variables associated with the diagnosis of reflex syncope. All variables were tested in separated models because of significant collinearity. Each model was adjusted for age, sex, office blood pressure, and antihypertensive treatment. ABPM indicates ambulatory blood pressure monitoring; DBP, diastolic blood pressure; OR, odds ratio; PP, pulse pressure; and SBP, systolic blood pressure.

tone, expressed as generally lower BP values.[14,15] An alternative explanation is that hypotensive phenotype might indicate a habitually low blood volume, resulting in decreased cardiac output.[16–18] If this were the case, activation of compensatory baroreceptors and neuroendocrine responses would provide an explanation for increased heart rate and DBP. The latter may indeed reflect an increase in peripheral vascular resistance aimed to increase the afterload and thus preserve perfusion of crucial organs such as the brain and kidneys. When these compensatory mechanisms fail, then hypotension and syncope may occur because of cerebral hypoperfusion.

The increased vagal-tone hypothesis is supported by Wieling et al, who explored the hemodynamic variations in patients with persistent hypotension after head-up tilt testing (ie, SBP <85 mm Hg at 2 minutes after tilt down). Their results indicated that a decrease in cardiac output, mediated by bradycardia and low stroke volume, was the main mechanism underlying prolonged hypotension. These patients, however, were relatively uncommon according to the authors. There was no significant difference in total peripheral resistance predisposing to persistent arterial vasodilation, as the authors expected. Consequently, these data support the theory that at least some patients with reflex syncope are more likely to have vagal hyperactivity and blunted sympathetic tone, resulting in cardiac depression.[15]

In the present study, we also noted that nocturnal BP dipping is more frequently preserved in patients with reflex syncope than in population-derived controls. Therefore, physiological circadian BP variability seems to be maintained in individuals prone to reflex syncope. This might imply that the hemodynamics characterizing reflex syncope do not result from central autonomic dysfunction but are related to peripheral phenomena, such as reduced neural outflow and lower blood volume.[19]

Finally, we observed an independent association between reflex syncope and daytime SBP drops <90 mm Hg on ABPM. Consistently, our recent study indicated that daytime SBP drops <90 mm Hg might allow identification of hypotensive susceptibility in reflex syncope with high specificity but lower sensitivity.[10] In this study, sensitivity for both 24-hour SBP and PP exceeded sensitivity of daytime SBP drops reported earlier, which suggests using multiple parameters for precision phenotyping of reflex syncope. This further reinforces the hypothesis of a specific hemodynamic profile in reflex syncope, with predisposition to hypotension that may result in either symptomatic or asymptomatic SBP drops when compensatory mechanisms fail, accompanied by generally lower SBP and PP.

Hypotensive susceptibility may also be asymptomatic or it may be present in patients with other syncope diagnoses, leading to an overlap between reflex syncope and syncope of different origin (eg, cardiac syncope).[9] Therefore, it cannot be excluded that lower ambulatory BP values and SBP drops on ABPM might suggest hypotensive susceptibility also in patients with different diagnoses or with no history of syncope. While the present study focused on reflex syncope, detection of hypotension susceptibility using ABPM in other patient subgroups should be investigated in future studies.

## Study Importance and Potential Clinical Implications

Our study confirms the existence of a specific hemodynamic profile in reflex syncope and suggests a possible diagnostic value of 24-hour ABPM in the primary assessment of patients with suspected reflex syncope. Although the European Society of Cardiology guidelines on syncope included 24-hour ABPM among diagnostic tools for syncope,[7] in real world clinical practice, routine 24-hour ABPM remains unintegrated with the diagnostic work-up performed in syncope units; 24-hour ABPM is a safe noninvasive diagnostic tool with low costs, has high tolerability by patients, and is widely available, even in primary care settings. Thus, we recommend that 24-hour ABPM should be introduced to clinical practice as a diagnostic instrument for detection of hypotension in the context of syncope assessment. Future studies should aim at further evaluating the possible treatment implications for subjects with reflex syncope and specific ABPM hemodynamic profiles.

## Limitations

Some limitations of the present study must be mentioned. First, we were unable to investigate the correlation between BP and patients' symptoms as information from daily diaries was not available. Additionally, we were not able to provide data on heart rate, which could

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have added relevant information on the hemodynamic profile associated with reflex syncope.

Second, the proportion of patients receiving antihypertensive medications was low in our sample, which prevented us from assessing the influence of antihypertensive therapy on the association between BP and reflex syncope. Yet, the low prevalence of hypertension in our sample might also be considered as a strength, as it provided the opportunity to investigate the ambulatory BP profile of reflex syncope with no interference of hypotensive medications. Third, the interpretation of our results might be limited by the small sample size. Moreover, we were unable to analyze ambulatory BP in subgroups with different tilt-testing response (eg, negative or cardioinhibitory tilt testing). Finally, controls were randomly selected from a database representing the general population. Consequently, the risk that some of the controls might have suffered from syncope cannot be excluded; however, none of the controls had been investigated for unexplained syncope at our unit. Yet, this might reinforce our results, as the predictive value of analyzed variables would be higher than estimated in our study, if any control individuals had suffered unreported reflex syncope.

## CONCLUSIONS

The present study confirms the existence of a specific hemodynamic profile in reflex syncope, demonstrated on 24-hour ABPM. We identified ABPM parameters and related BP cut-offs with a predictive ability for reflex syncope diagnosis. We propose that the use of ABPM should be included in the routine diagnostic work-up of syncope.

## ARTICLE INFORMATION

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### Affiliations

Department of Clinical Sciences, Lund University, and Skåne University Hospital, Malmö, Sweden (B.S., V.H., M.J., R.S., A.F.); Division of Geriatric and Intensive Care Medicine, University of Florence and Azienda Ospedaliero Universitaria Careggi, Florence, Italy (G.R., A.U.); Department of Cardiology, Skåne University Hospital, Malmö, Sweden (V.H., M.J.); Department of Cardiology, National Heart & Lung Institute, Imperial College, Hammersmith Hospital Campus, London, United Kingdom (R.S.); IRCCS, Istituto Auxologico Italiano, Cardiology Unit (M.B., G.P.) and Department of Cardiovascular, Neural and Metabolic Sciences (M.B., G.P.), S.Luca Hospital, Milan, Italy; Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden (A.F.); and Department of Medicine, Karolinska Institute, Stockholm, Sweden (A.F.).

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### Disclosures

R. Sutton declares the following potential conflicts of interest: consulting fees from Medtronic Inc (unrelated to present work); payment for expert testimony in medico-legal cases in UK (related to syncope but unrelated to this work); member of clinical events committee for the BioSync study (published in 2021 in European Heart Journal); Secretary to the Executive Board of World Society of Arrhythmias; private shareholder receiving only dividends from Boston Scientific Corp and Edwards Lifesciences Corp. Dr Fedorowski has received speaker fees from Medtronic Inc., Biotronik, and Bristol-Myers Squibb, and is consultant to Medtronic Inc, and Argenx BV. The remaining authors have no disclosures to report.

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