Association Between Morning Surge in Systolic Blood Pressure and SYNTAX Score I in Patients With Stable Coronary Artery Disease

Alaa Quisi, MD1; Gokhan Alici, MD2; Hazar Harbalioglu, MD3; Omer Genc, MD4; Ibrahim Halil Kurt, MD4; Murat Cayli, MD1

1Department of Cardiology, Medline Adana Hospital, Adana, Turkey
2Department of Cardiology, Okmeydani Training and Research Hospital, Istanbul, Turkey
3Department of Cardiology, Duzce Ataturk State Hospital, Duzce, Turkey
4Department of Cardiology, Adana City Training and Research Hospital, Adana, Turkey

A high morning surge in systolic blood pressure poses a risk in people who have cardiovascular disease. We investigated the relationship between this phenomenon and the SYNTAX score I in patients who had stable coronary artery disease.

Our single-center study included 125 consecutive patients (109 men and 16 women; mean age, 54.3 ± 9 yr) in whom coronary angiography revealed stable coronary artery disease. We calculated each patient’s sleep-trough morning surge in systolic blood pressure, then calculated the SYNTAX score I.

The morning surge was significantly higher in patients whose score was >22 (mean, 22.7 ± 13.2) than in those whose score was ≤22 (mean, 12.4 ± 7.5) (P <0.001). Forward stepwise logistic regression analysis revealed that morning surge in systolic blood pressure was the only independent predictor of an intermediate-to-high score (odds ratio=1.183; 95% CI, 1.025–1.364; P=0.021).

To our knowledge, this is the first study to show an association between morning surge in systolic blood pressure and the SYNTAX score I in patients who have stable coronary artery disease. (Tex Heart Inst J 2021;48(2):e197092)

The onset of cardiovascular (CV) events peaks shortly after people awaken.1-3 This finding raised interest in the circadian pattern of blood pressure (BP), which generally decreases at night and sharply increases in the morning, and suggested that high morning surge (MS) in systolic BP (SBP) may be involved in CV events. The link has been studied in hypertensive patients4,5 and in the general population.6,7 Although the surge level at which risk increases is still unknown, its usefulness in predicting CV events, including myocardial infarction, stroke, and sudden death, has been shown.8-10 A major BP surge can cause target-organ damage (including left ventricular hypertrophy),9,11 and it affects carotid artery intima-media thickness.12 Until now, MS in BP has not been studied in patients who have extensive coronary atherosclerosis.

The SYNTAX score I (SSI) is used to evaluate the extent and complexity of coronary artery disease (CAD) and to determine its optimal treatment.13 A higher score indicates a higher risk of major adverse CV events and a greater therapeutic challenge.14,15 In this study, we used the SSI to determine the relationship between MS in SBP and the extent, severity, and complexity of disease in patients with stable CAD.

Patients and Methods

This single-center, cross-sectional study included 125 consecutive patients (109 men and 16 women; mean age, 54.3 ± 9 yr) who underwent coronary angiography (CA) from July through December 2018 (Table I). Patients included in the study had signs of ischemic heart disease (such as angina pectoris), positive or equivocal results on...
noninvasive myocardial ischemia screening tests, or both. Ninety-one patients (73%) had positive treadmill exercise test results, 29 (23%) had positive myocardial perfusion scintigraphy results, and 5 (4%) had positive results on computed tomographic CA (at least 64-slice).

We excluded patients who had a history of coronary artery bypass grafting, severe heart failure, severe valvular heart disease, atrial fibrillation, obstructive sleep apnea, infective or inflammatory disease, malignancy, cerebrovascular disease, chronic kidney disease (estimated glomerular filtration rate [eGFR], <60 mL/min/1.73 m²), or chronic liver disease. During the study period, 158 patients had undergone CA; 33 (8 men and 25 women) were excluded because they had normal coronary arteries. In-office BP and noninvasive 24-hour ambulatory BP monitoring (ABPM) measurements were obtained from each patient, and cardiac medications were recorded. The body mass index of each patient was calculated.

### TABLE I. Baseline Characteristics of the Study Groups

| Variable                                | SYNTAX Score I ≤22 (n=80) | SYNTAX Score I >22 (n=45) | P Value* |
|-----------------------------------------|---------------------------|---------------------------|----------|
| Age (yr)                                | 54.5 ± 9.3                | 54 ± 8.5                  | 0.781    |
| Men                                     | 69 (86.3)                 | 40 (88.9)                 | 0.672    |
| Body mass index                         | 28.4 (23.9–41.5)          | 26.8 (21.3–31.7)          | 0.998    |
| Diabetes                                | 23 (28.8)                 | 11 (24.4)                 | 0.604    |
| Hypertension                            | 51 (62.8)                 | 23 (51.1)                 | 0.168    |
| Hyperlipidemia                          | 18 (22.5)                 | 9 (20)                    | 0.744    |
| Family history of CAD                   | 38 (47.5)                 | 31 (68.9)                 | 0.021    |
| Smoking                                 | 29 (36.3)                 | 23 (51.1)                 | 0.106    |
| Hemoglobin level (mmol/L)               | 8.8 ± 1                   | 8.7 ± 0.9                 | 0.594    |
| Leukocyte count (×10³/µL)               | 9.7 (5.4–20.5)            | 9.4 (5.4–16)              | 0.271    |
| Platelet count (×10³/µL)                | 235.3 ± 65.2              | 272.4 ± 144.3             | 0.051    |
| eGFR (mL/min/1.73 m²)                   | 95.2 (61.9–143.3)         | 95 (79.7–165.6)           | 0.328    |
| Triglycerides (mmol/L)                  | 1.8 (0.6–7.6)             | 1.5 (0.5–6)               | 0.597    |
| Total cholesterol (mmol/L)              | 5.1 ± 1.1                 | 5.4 ± 1.2                 | 0.324    |
| HDL cholesterol (mmol/L)                | 1 ± 0.3                   | 0.9 ± 0.3                 | 0.549    |
| LDL cholesterol (mmol/L)                | 4.2 (1.4–5.2)             | 4.3 (1.1–6.1)             | 0.321    |
| LVEF (%)                                | 62.9 (43–73)              | 58.8 (30.7–67.1)          | <0.001   |
| CCS grade of angina pectoris            | —                         | —                         | 0.094    |
| I                                       | 20 (25)                   | 7 (15.6)                  | —        |
| II                                      | 38 (47.5)                 | 16 (35.6)                 | —        |
| III                                     | 17 (21.3)                 | 15 (33.3)                 | —        |
| IV                                      | 5 (6.3)                   | 7 (15.6)                  | —        |
| Coronary arteries involved              | —                         | —                         | <0.001   |
| 1                                       | 44 (55)                   | 0                         | —        |
| 2                                       | 31 (38.8)                 | 11 (24.4)                 | —        |
| 3                                       | 3 (3.8)                   | 27 (60)                   | —        |
| 4                                       | 2 (2.5)                   | 7 (15.6)                  | —        |
| ACEI/ARB use                            | 67 (83.8)                 | 37 (62.2)                 | 0.826    |
| Calcium channel blocker use             | 4 (5)                     | 1 (2.2)                   | 0.653    |
| β-blocker use                           | 72 (90)                   | 44 (97.8)                 | 0.155    |
| Statin use                              | 73 (91.3)                 | 40 (88.9)                 | 0.755    |

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; eGFR = estimated glomerular filtration rate; HDL = high-density-lipoprotein, LDL = low-density-lipoprotein; LVEF = left ventricular ejection fraction

*P values were calculated by using the independent-samples t or Mann-Whitney U test for continuous variables, and the χ² or Fisher exact test for categorical variables, as appropriate. The Fisher exact test was performed for calcium channel blocker, β-blocker, and statin use.

Data are presented as mean ± SD, number and percentage, or median and range. P <0.05 was considered statistically significant.
The eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation.

The study was conducted in accordance with the Declaration of Helsinki. An institutional ethics committee approved the study protocol, and each participant provided written informed consent.

**Ambulatory Blood Pressure Measurements and Morning Surge in Blood Pressure**

Each patient underwent noninvasive 24-hour ABPM with use of a Tracker NIBP2 portable digital recorder (Del Mar Reynolds Medical Ltd.) during a day of typical activity. Participants whose sleep-trough SBP decreased by >20% or more in comparison with awake SBP were classified as extreme dippers; those with a decrease of 0 to <20%, as dippers; and those whose decrease was <0%, as nondippers.

In this study, the sleep-trough MS in SBP was calculated as the difference between the average of 4 SBP readings during the 2 hours after awakening and the mean SBP during the hour that included the lowest reading during sleep.4

**SYNTAX Score I Measurements**

The SSI for each patient was calculated by using the online SYNTAX score I calculator (syntaxscore.org). A low SSI was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33.46 The number of patients with SSI >22 was small, so we divided the study population into 2 groups by score: the ≤22 group (the low-score tertile; n=80) and the >22 group (the intermediate- and high-score tertiles; n=45).

**Statistical Analysis**

Data were analyzed with use of SPSS version 22.0 software (SPSS Inc., an IBM company). Continuous variables were expressed as mean ± SD or as median and range, and categorical variables as number and percentage. Normal distribution of continuous variables was evaluated by using the Kolmogorov-Smirnov test. The χ² or Fisher exact test was used to compare categorical variables, and the independent-samples t or Mann-Whitney U test to compare continuous variables. Correlation between variables was analyzed with use of the Pearson correlation coefficient. All significant values in the univariate analysis (P <0.05) were selected for the multivariable model, and forward stepwise logistic regression revealed MS in SBP, nighttime diastolic BP, MS in SBP, and systolic dipper status, were included in the multivariate analysis. All significant factors related to the intermediate-to-high SSI (odds ratio=1.183; 95% CI, 1.025–1.364; P=0.021).

**Results**

The SSI ≤22 group comprised 80 patients (mean age, 54.5 ± 9.3 yr; 69 men), and the SSI >22 group comprised 45 patients (mean age, 54 ± 8.5 yr; 45 men) (Table I). Family history of CAD was significantly more prevalent in patients whose SSI was >22 (68.9%) than in patients whose score was ≤22 (47.5%) (P=0.021). Left ventricular ejection fraction was significantly lower in patients whose score was >22 (58.8%; range, 30.7%–67.1%) than in patients whose score was ≤22 (62.9%; range, 43%–73%) (P<0.001). Most patients with a score ≤22 had 1 or 2 involved coronary arteries, whereas most patients with a score >22 had 2 or 3 involved arteries (P<0.001).

Patients whose SSI was >22 had significantly higher in-office and mean 24-hour BP measurements than did patients whose score was ≤22 (Table II). The sleep-trough MS in SBP was significantly higher in patients whose score was >22, and systolic dipper status differed significantly between the 2 groups.

In-office BP, mean 24-hour BP, daytime BP, SSI (Fig. 1), and the number of involved coronary arteries were significantly associated with MS in SBP (Table III).

All significant factors in the univariate analysis (P<0.01), including family history of CAD, platelet count, left ventricular ejection fraction, Canadian Cardiovascular Society angina grade, number of involved coronary arteries, in-office BP, mean 24-hour BP, daytime SBP, nighttime diastolic BP, MS in SBP, and systolic dipper status, were included in the multivariate analysis. Forward stepwise logistic regression revealed MS in SBP as the only independent predictor of intermediate-to-high SSI (odds ratio=1.183; 95% CI, 1.025–1.364; P=0.021).

**Discussion**

Major surges in BP are closely associated with CV events.4,6,17 Our major finding is that an MS in SBP independently predicts an intermediate-to-high SSI in patients who have stable CAD. To our knowledge, this is the first report to associate MS in SBP with the extent and complexity of CAD.

The potential pathophysiologic mechanisms of this finding may be related to increased inflammation, oxidative stress, and platelet aggregation in individuals who have a high MS in SBP. An association between peak SBP and CV events in older patients has been shown.8 In addition, high MS in BP has been associated with factors related to atherosclerosis, including increased oxidative stress,19 increased inflammation,20 increased platelet aggregation,21 and coronary microvascular dysfunction.22 Hypertensive patients whose SBP surged had higher levels of carotid intima-media thickness and inflammatory markers than did other patients.23 In addition, histologic studies of carotid endarterectomy specimens revealed that carotid plaques in patients who had a high MS in SBP were associated with characteristics of vulnerable plaques, increased levels of oxidative stress markers, and activation of the ubiquitin-proteasome system.20,24 All
these factors may increase the risk of CV events in patients who have a high MS in SBP.

Investigators have reported an independent clinical impact of SBP surge in predicting CV events such as sudden death, myocardial infarction, and stroke. These studies were often performed in divergent populations with use of different methodologies, perhaps explaining inconsistent findings. Li and colleagues reported that a high MS in SBP posed a significantly higher risk of all-cause death and total CV events in the general population. Verdecchia and colleagues reported that a blunted...
MS was associated with higher CV risk. Conversely, Bombelli and associates reported that MS was not an independent predictor of CV or all-cause death.

In nondippers, an altered circadian BP profile may contribute to the development of CAD as well as subclinical coronary atherosclerosis,26 CAD,9 alterations in hemostasis or endothelial function,22 and increased platelet activation and inflammatory response.23 Considering all of these factors, nondipper status may contribute to the severity of CAD. Indeed, in our study, most patients who had a score $>22$ were nondippers.

The systemic hemodynamic atherothrombotic syndrome, proposed by Kario,7 is a vicious cycle of hemodynamic stress and vascular disease that advances organ damage and triggers CV disease. Coronary artery disease is one of its clinical phenotypes. The MS in BP is an important hypertension biomarker, a significant predictor of adverse CV events, and an independent predictor of SSI in stable CAD. Effectively detecting and managing this important manifestation of hypertension is crucial. A single in-office BP reading may underestimate both the prevalence and severity of hypertension and its associated risks. International guidelines advocate out-of-office BP measurements to diagnose and monitor hypertension.26,29 These approaches maximize the chances of detecting surges, and they facilitate more effective individualized CV protection. Despite inconsistencies in the current definition of MS in BP, ongoing and future research should lead to better scientific understanding that will improve the detection and treatment of arterial hypertension and minimize adverse outcomes.

The molecular mechanisms associating peak MS in BP with vulnerable atherosclerotic plaque are not clear, although inflammation, central to the atherosclerotic cascade, has been related to MS.23 After finding that an exaggerated MS was significantly associated with vulnerable plaques, Marfella and colleagues25 stressed the importance of oxidative stress and activation of the ubiquitin-proteasome system as the mechanism of plaque instability related to MS. Major surge seems to take part in the initial stage and progression of atherosclerosis.29 The current study did not evaluate the role of MS in atherogenesis; it merely describes the association between MS in SBP and the extent and complexity of stable CAD. All patients in this study had substantial CAD, and patients without CAD were excluded, so the impact of MS on the presence of CAD could not be investigated. Further studies of the overall sensitivity and specificity of MS in BP in predicting coronary atherosclerosis are warranted.

**Study Limitations**

Our study has several limitations. First, it included relatively few patients at a single center. A larger multicenter study may produce more significant results and data. Second, the patients were consecutive, and most were men, a condition that was not controlled. Of note, 25 of the 33 patients excluded for having normal coronary arteries after CA screening were women. Third, MS measurements were obtained only from a single recording of 24-hour ABPM (although, in fairness, the lack of reproducibility of MS in SBP has been criticized). Fourth, the lack of data on dosage and timing of antihypertensive drugs may have affected the calculations of MS in BP.

**Conclusion**

We found that a high MS in SBP is associated with the extent and complexity of CAD, evaluated in terms of the SSI, in patients who have stable CAD.

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