Nighttime Blood Pressure Patterns and Subclinical Atherosclerosis in Women with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To compare 24-h ambulatory blood pressure (BP) monitoring (ABPM) values and patterns in women with systemic lupus erythematosus (SLE) with those of a matched control group and their relationship with the presence of subclinical atherosclerosis.

Methods. ABPM was assessed in 70 women with SLE and in 65 sex- and age-matched controls without a history of clinic cardiovascular disease (CVD). Carotid-femoral pulse wave velocity (PWV), which is a marker of subclinical atherosclerosis and a predictor of future CVD, was measured. Multivariate logistic analysis was used to determine which explanatory variables were independently associated with the non-dipper pattern and the presence of nocturnal hypertension (HTN) in women with SLE.

Results. No differences in PWV were found between patients and controls [median 7.3, interquartile range (IQR) 6.5–8.1 m/s vs median 7.1, IQR 6.5-7.8 m/s, p = 0.474]. The frequency of nondipper pattern (p = 0.025) and nocturnal HTN (p = 0.004) was significantly higher in women with SLE than in controls. White-coat and masked HTN were present in 10% and 11% of patients and in 20% and 8% of controls, respectively (p > 0.05 in all cases). The concordance between office and ambulatory HTN in the SLE and control groups was modest (κ = 0.325 and κ = 0.451, respectively). PWV and chronic kidney disease, and PWV and the Systemic Lupus Erythematosus Disease Activity Index were found to be independently associated with nocturnal HTN and nondipper pattern, respectively.

Conclusion. Women with SLE were more likely to have an altered nighttime BP pattern than controls. In women with SLE, nondipper pattern and nocturnal HTN were independently associated with increased subclinical atherosclerosis measured by PWV. (J Rheumatol First Release November 15 2015; doi:10.3899/ jrheum.150531)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS   HYPERTENSION   ATHEROSCLEROSIS
AMBULATORY BLOOD PRESSURE MONITORING   NONDIPPER PATTERN

Patients with systemic lupus erythematosus (SLE) have a 4- to 10-fold increased risk of developing cardiovascular (CV) diseases (CVD) compared with the general population[1] because they experience early and accelerated atherosclerosis[2]. Hypertension (HTN) is one of the most important modifiable factors implicated in the development of the ather-osclerosis and CVD in SLE[3]. Its physiopathology is complex and a combination of SLE-related and neuroendocrine factors has been suggested[4,5,6,7,8]. Although most authors agree that HTN is more common in SLE than in the general population, the prevalence ranges from 14%[9] to 60%[10] because of the differences in the definition of HTN used, the variability

reading-to-reading of blood pressure (BP), and the method-ologies used in its measurement. BP measurements made in the physician's office (office BP) continues to be the basis of HTN diagnosis; however, 24-h ambulatory BP monitoring (ABPM) has emerged as a valuable tool in determining BP because it provides a more accurate assessment with respect to office BP[11]. ABPM measures a person's BP during regular daily life, including sleeping hours at night, and hence provides accurate risk estimation of exposure to abnormal BP. Moreover, ABPM identifies white-coat and masked HTN. Specifically, nighttime BP is a stronger predictor of CV risk than office or daytime ambulatory BP[12]. In addition, a nondipper pattern, defined as a decrease in the average BP while asleep below 10% with respect to the average awake BP, is also a strong prognostic indicator of CV morbidity and mortality for both hypertensive and normotensive individuals. Female sex, which represents about 90% of patients with SLE, has been identified as an independent predictor of nondipper pattern[13]. In addition, higher target organ damage has been observed among women who experience an atten-uated BP decline at nighttime[14], and the association between nocturnal BP and CV outcome has been reported to be stronger in women compared with men[15]. In spite of all this evidence, ABPM and its association with clinical and subclinical CVD in SLE has been scarcely investigated[16].

Carotid-femoral pulse wave velocity (PWV) is considered to be the gold standard for assessing arterial stiffness and has shown to be an independent marker of CVD both in high-risk and in general populations[17]. Stiffness is affected by endothelial cell function and vascular wall elasticity, and it can be altered in the early stage of atherosclerosis[18].

The purpose of our study was to evaluate the hypothesis that nighttime BP disturbances are more frequent in women with SLE than in controls, and that these disorders can be associated with increased PWV.

MATERIALS AND METHODS

Participants. Consecutive, nonpregnant women with SLE aged 18–60 years who were followed during at least 1 year and a matched control group for sex, age, and educational level recruited among nonconsanguineous acquain-tances of patients and nonmedical staff from our hospital were invited to participate. Subjects with a history of overt CVD (acute myocardial infarction, angina pectoris, stroke, or peripheral arterial disease), sleep disorders, tachyarrhythmia, or with a body mass index (BMI) ≥ 40 that could hinder PWV measurement were excluded. All participants were white. The Institutional Review Board of our hospital approved our study and all subjects gave written informed consent.

Protocol, and BP and PWV measurements. Participants were evaluated using a standardized clinical interview. Fasting blood specimens for biochemical and immunological tests were collected and routinely processed using the techniques performed by the central laboratory of our hospital. Additional information necessary for our study was obtained from medical records. The office BP was taken in duplicate separated by 5 min on the dominant arm with the subject in a seated position after at least 5 min of rest using a validated automatic oscillometric device (HEM-7051T; Omron Health Care). BP was considered the lowest measure. Next, a 24-h ABPM was done according to the international recommendations[19]. An automated nonin-vasive oscillometric device (SpaceLabs 90207) was used and programmed to register BP at 20-min intervals during the daytime and every 30 min during the nighttime, starting between 10:00 AM and 11:00 AM on a workday, until the same time the following day. Registries were considered valid when $\geq 80\%$ of BP measurements were successfully recorded during the daytime and nighttime, and at least 1 BP measurement was taken per hour. Daytime and nighttime periods were defined individually according to each patient's self-reported data of going-to-bed and getting-up times. In treated hypertensive participants, BP-lowering drugs were discontinued 24 h before the ABPM. Arterial stiffness was evaluated by measuring PWV using an automatic device (Complior Analyse from ALAM-MEDICAL), as previously described[5].

BP definitions. Office HTN was deemed to be present if systolic BP (SBP) was > 140 mmHg and/or diastolic BP (DBP) was > 90 mmHg or if the subject was taking medications for HTN. Diagnostic criteria of HTN based on ABPM measurement are shown in Table 1. Nighttime SBP dipping was defined as the percentage of the decline in nighttime SBP with respect to the daytime SBP. When a participant had a nighttime SBP dipping < 10%, she was classified as nondipper. White-coat HTN referred to participants who had elevated office BP but normal ABPM. Its frequency was calculated with respect to the number of individuals with office HTN. Masked HTN was diagnosed when office BP was normal but a diagnosis of ambulatory HTN was made, and its frequency was calculated with respect to the number of normotensive subjects.

Other definitions. Diabetes was considered to be present when the participant was taking antidiabetics or if fasting glucose was > 126 mg/dl. The estimated glomerular filtration rate (eGFR) was automatically calculated using the Modification of Diet in Renal Disease 7 equation (www.semergencantabria.org/calc/cacalc.htm). An eGFR < 60 ml/min/1.73 m^2 for 3 months indicated chronic kidney disease (CKD)[20]. Obesity, low physical activity, smoking, menopausal status, and metabolic syndrome (MetS) have been defined[5]. Disease activity and cumulated organ damage were measured using the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI)[21] and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI)[22].

Statistical analysis. Data were presented as the median (interquartile range) for continuous variables and as a percentage for categorical variables. The Shapiro-Wilk test was used for the normality distribution of continuous variables. The Student t test, Mann-Whitney U test, and chi-square test were used to compare parametric, nonparametric, and categorical variables, respectively. OR and 95% CI were calculated. Cohen κ statistic was used for measuring the concordance between the diagnosis of office and ambulatory HTN. A multivariate logistic analysis was used to determine which explanatory variables were independently associated with nondipper pattern and nocturnal HTN. Since no significant differences were found between dippers and nondippers patients with SLE in the univariable analysis, the independent variables included in the multivariable analysis were chosen according to their clinical relevance in the general population (age, CKD) and the potential interest in patients with SLE [use of prednisone

Table 1. Diagnostic criteria of HTN based on 24-h ABPM measurement.

Variable	Systolic/diastolic Blood Pressure, mmHg		
	Daytime		Nighttime
Ambulatory normotension	< 135/85	and	< 120/70
Ambulatory HTN	≥ 135/85	and/or	≥ 120/70
Isolated daytime HTN	≥ 135/85	and	< 120/70
Isolated nocturnal HTN	< 135/85	and	≥ 120/70
Day-night sustained HTN	≥ 135/85	and	≥ 120/70
Nocturnal HTN	Any	and	≥ 120/70

HTN: hypertension; ABPM: ambulatory blood pressure monitoring.

(PRED), PWV, SELENA-SLEDAI, and SLICC/ACR-DI]. Likewise, the variables included in the model for nocturnal HTN (dependent variable) were age, SLICC/ACR-DI, PWV, disease duration, CKD, and office HTN, which were significantly higher in patients with nocturnal HTN. All analyses used a 5% two-sided significance level and were done using SPSS statistical software, version 15.0 (SPSS).

RESULTS

Sample characteristics. We recruited 70 women with SLE and 65 controls. The median duration of SLE was 8 (5–16) years and the median age at diagnosis was 25 (20–33) years. Most of the patients had stable disease with a median SELENA-SLEDAI score of 2 (0–4), 26% with a SELENA-SLEDAI score = 0, and 91% with a SELENA-SLEDAI ≤ 4. Also, organ damage was low (SLICC/ACR-DI 0, 0–1). Clinically, the cumulated frequency of lupus nephritis, neurological involvement, hematological involvement, serositis, and antiphospholipid was 40%, 4%, 28%, 26%, and 10%, respectively. Eight patients with a history of lupus nephritis developed CKD. PRED and hydroxychloroquine (HCQ) were being taken by 61% and 94% of patients, respectively. The median daily PRED dose was 5.0 (0–7.5) mg/day, and immunosuppressive drugs were being used by 39% of patients (azathioprine 7%, methotrexate 7%, mycophenolate 27%).

Demographic and cardiometabolic data of participants. Baseline demographic and CV characteristics of women with SLE and controls are presented in Table 2.

Twenty-seven patients (39%) and 4 controls (6.2%) were receiving antihypertensive agents. Of them, 13 patients (48%) and 3 controls (75%) used ≥ 2 agents. The cumulative frequency of BP-lowering drugs was angiotensin-converting enzyme inhibitors (70%), angiotensin II antagonists (37%), calcium channel blockers (22%), β-blockers (22%), and diuretics (22%) in patients, and angiotensin II antagonists (75%), diuretics (50%), and β-blockers (25%) in controls.

BP measurements. The average correct reading rates were 97% (93–98) in SLE group and 97% (88–98) in controls. As shown in Table 3 and in Figure 1, office HTN (OR 4.8, 95% CI 1.7–13.7) and ambulatory HTN (OR 2.7, 95% CI 1.02–6.9) were more frequent in the SLE group. Likewise, nocturnal HTN (OR 4.9, 95% CI 1.5–15.4), nondipper pattern (OR 2.2, 95% CI 1.1–4.5), and isolated nighttime HTN (OR 3.1, 95% CI 1.5–11.8) were more likely to be present in women with SLE. Most women with SLE with nocturnal HTN had isolated nighttime HTN. The average nighttime SBP decline was lower in the SLE group (p = 0.027). Finally, the frequency of white-coat HTN and masked HTN was similar in both groups.

Concordance between the diagnosis of office and ambulatory HTN in the SLE and control groups. The concordance between the diagnosis of office and ambulatory HTN in controls (κ 0.451, p < 0.001) and in women with SLE (κ 0.325, p = 0.007) was modest. Thus, in controls, out of 5 subjects with office HTN, 3 (60%) were also classified as

Table 2. Demographic and cardiometabolic characteristics of participants. Values are n (%) or median (interquartile range) unless otherwise specified.

Characteristics	Women with SLE, n = 70	Controls, n = 65	p†
Age, yrs	38 (30–46)	42 (28–49)	0.353
Secondary education	38 (49)	18 (30)	0.287
BMI, kg/m²	24 (22–27)	23 (20–26)	0.156
Obesity	7 (10)	5 (7.8)	0.767
Diabetes	3 (4.3)	1 (1.5)	0.620
Fasting glucose, mg/dl	79 (74–84)	81 (76–87)	0.430
Metabolic syndrome	9 (13)	1 (1.6)	0.018
Total cholesterol	171 (156–192)	190 (168–219)	0.001
LDL, mg/dl	93 (76–107)	101 (79–118)	0.056
HDL, mg/dl	59 (45–72)	73 (64–84)	< 0.001
Triglycerides, mg/dl	87 (63–119)	67 (54–93)	0.010
eGFR, ml/min/1.73 m²	85 (71–105)	85 (77–95)	0.706
CKD, n (%)	8 (11)	1 (1.5)	0.034
Homocysteine, μmol/l	11 (9–15)	10 (9–12)	0.003
CRP, mg/dl	0.2 (0.1–0.4)	0.1 (0.1–0.2)	0.039
ESR, mm/h	20 (12–37)	9 (7–15)	< 0.001
PWV, m/s	7.3 (6.5–8.1)	7.1 (6.5–7.8)	0.474
Smokers	18 (26)	19 (29)	0.702
Low physical activity	33 (47)	26 (40)	0.488
Menopause status	14 (20)	13 (20)	1.000
Statins	14 (20)	4 (6.2)	0.022
Antihypertensives*	27 (39)	4 (6.2)	< 0.001

† Student t test for continuous variables and chi-square for categorical variables. * Included drugs for treatment of HTN and antiproteinuric drugs. SLE: systemic lupus erythematosus; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PWV: pulse wave velocity.

Table 3. Blood pressure characteristics in patients and in controls. Values are n (%) or median (interquartile range) unless otherwise specified.

Characteristic	Women with SLE, n = 70	Control, n = 65	p[†]
Office HTN	20 (29)	5 (7.7)	0.002
Office SBP, mmHg	116 (107–126)	114 (107–119)	0.492
Office DBP, mmHg	75 (68–82)	72 (65–77)	0.074
Ambulatory HTN	19 (27)	7 (11)	0.017
Isolated daytime HTN	2 (2.9)	3 (4.6)	0.672
Isolated nighttime HTN	12 (17)	4 (6.2)	0.042
Day-night sustained HTN	5 (7.1)	0	0.053
Nocturnal HTN	17 (24)	4 (6.2)	0.004
24-h SBP, mmHg	112 (105–119)	109 (105–116)	0.203
24-h DBP, mmHg	71 (65–76)	69 (66–73)	0.318
24-h MBP, mmHg	84 (79–91)	83 (80–88)	0.344
Daytime SBP, mmHg	116 (109–124)	114 (109–120)	0.311
Daytime DBP, mmHg	74 (68–80)	73 (70–76)	0.475
Daytime MBP, mmHg	88 (83–94)	87 (84–91)	0.415
Nighttime SBP, mmHg	103 (97–112)	98 (94–107)	0.010
Nighttime DBP, mmHg	62 (56–69)	59 (55–64)	0.014
Nighttime MBP, mmHg	77 (70–83)	73 (69–79)	0.036
Nighttime SBP dipping, %	9 (6–14)	12 (12–17)	0.027
Nondipping	43 (61)	27 (42)	0.025
White-coat HTN	2 (10)	1 (20)	0.504
Masked HTN	8 (16)	5 (8.3)	0.565

[†] Student t test for continuous variables and chi-square for categorical variables. SLE: systemic lupus erythematosus; HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure, MBP: mean blood pressure.
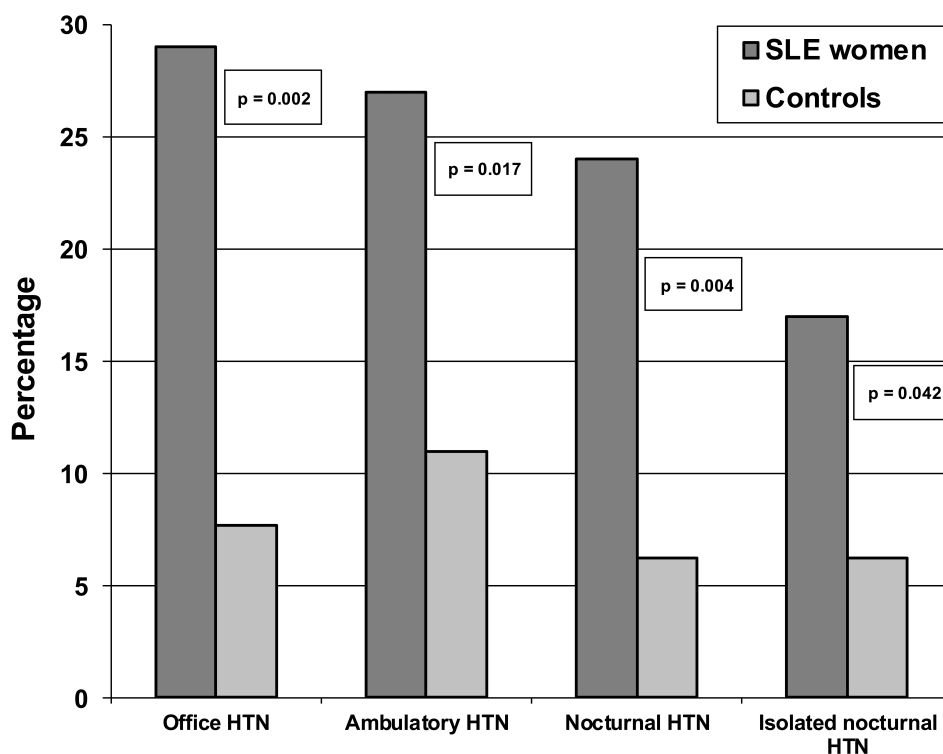

Figure 1. Frequencies of office, ambulatory, nocturnal, and isolated nighttime HTN in women with systemic SLE. HTN: hypertension; SLE: systemic lupus erythematosus.

having ambulatory HTN. Conversely, out of 60 controls considered as having normal office BP, 56 (93%) were also normotensives for ABPM measurements. In contrast, in women with SLE, out of 20 patients with office HTN, only 10 (50%) were diagnosed with ambulatory HTN. In addition, out of 50 patients with normal office BP, ABPM measurement was normal in 41 (82%).

Comparison between patients with and without nocturnal HTN, and between dippers and nondippers. Patients with nocturnal HTN were older (p = 0.002), had a longer disease duration (p = 0.008), and were more often menopausal (OR 4.6, 95% CI 1.3–16.1). Also, they were more likely to have CKD (OR 6.9, 95% CI 1.5–33) and office HTN (OR 4.3, 95% CI 1.3–13.7). Finally, they had higher PWV (p = 0.003; Table 4).

No differences between groups (dippers/nondippers and with or without nocturnal HTN) were observed in any of the following cardiometabolic and SLE-related variables evaluated: BMI, lipid profile, frequency of diabetes, MetS, sedentary lifestyle, smoking, homocysteine, age at diagnosis, levels of complement factor 3 (C3) and C4, use of PRED or HCQ, and frequency of lupus nephritis, antiphospholipid syndrome, or proteinuria higher than 0.5 g/24 h.

Multivariable analysis. Results of these analyses are summarized in Table 5. PWV (95% CI 0.028–0.188) and CKD (95% CI 0.052–0.644) were independently associated with nocturnal HTN whereas SLE duration only tended to be associated (p = 0.085). The 3 variables together accounted for 22% of its variance (adjusted R^2 = 0.220; Table 5) and 20% (adjusted R^2 = 0.196) when SLE duration was excluded from the model. On the one hand, the robustness of the planned model was supported by a secondary analysis that found no other potential explanatory variables (SELENA-SLEDAI, BMI, PRED use, MetS, lipid profile) that met the criteria to be included into the model.

On the other hand, PWV (95% CI 0.002–1.198) and SELENA-SLEDAI (95% CI 0.013–0.113) emerged as independent factors associated with nondipper pattern. These factors together with CKD (p = 0.064) accounted for ~13% of its variance (adjusted R^2 = 0.127) and 8.5% when CKD was excluded (adjusted R^2 = 0.085). The inclusion of other variables did not improve the adjusted R^2 of the model and did not change variables independently associated with nondipper pattern.

DISCUSSION

For the first time to our knowledge, we have documented that women with SLE have an altered nighttime pattern and BP values compared with controls. In our study, they were more likely to be nondipper, to have more nocturnal HTN (mainly isolated nighttime HTN), to have higher nighttime BP levels, and to experience a lower nighttime BP decline. In contrast, daytime patterns and diurnal BP values were similar to those observed in controls. In addition, PWV was found to be a factor independently associated with both nondipper pattern and nocturnal HTN in women with SLE.

These findings may be of relevance since the nocturnal HTN and nondipper profile have been separately associated in the general population with an increased risk of CVD and CV mortality[12,13,14,15]. Additionally, in a recent study, the concomitant presence of both factors was associated with a worse CV risk profile than each one separately[23]. In an international register, 577 patients with isolated nighttime HTN had a higher risk of all-cause mortality (HR 1.29) and all CV events (HR 1.36) after adjustment for the classical CV risk factors[24]. Consequently, the fact that patients with SLE are more likely to have a harmful nighttime pattern could constitute an additional CV risk, which has not been taken into consideration to date, since the ABPM is not a technique routinely used in patients with SLE.

Table 4. Comparison between dippers and nondippers, and between with and without nocturnal hypertension in the SLE group. Values are n (%) or median (interquartile range) unless otherwise specified.

Characteristic	Dippers, n = 26	Nondippers, n = 44	p*	With Noct HTN, n = 17	Without Noct HTN, n = 53	p*
Age	34 (28–47)	39 (31–46)	0.454	46 (39–49)	33 (28–44)	0.002
Office HTN	5 (19)	15 (34)	0.274	9 (53)	11 (21)	0.015
CKD	1 (3.8)	7 (16)	0.243	5 (29)	3 (6)	0.017
Menopause	3 (12)	11 (25)	0.225	7 (41)	7 (13)	0.031
PWV, m/s	7.2 (6.1–7.8)	7.4 (6.5–8.3)	0.173	8.1 (7.3–8.9)	7.1 (6.3–7.6)	0.003
Disease duration, yrs	10 (3–16)	8 (7–16)	0.770	16 (7–20)	8 (3–14)	0.008
Age at diagnosis, yrs	22 (15–35)	26 (22–33)	0.319	30 (24–33)	25 (19–35)	0.181
PRED use	13 (50)	30 (68)	0.203	11 (65)	32 (60)	1.0
HCQ use	23 (89)	43 (98)	0.141	16 (94)	50 (94)	1.0
SLEDAI	2.0 (0.0–4.0)	2.0 (2.0–4.0)	0.213	2 (0–4)	2.0 (2.0–4.0)	0.379
SLICC/ACR-DI	0 (0–0)	0 (0–1.0)	0.326	1.0 (0–1.0)	0 (0–0)	0.004

* Mann-Whitney U test or chi-square test for continuous or categorical variables, respectively. SLE: systemic lupus erythematosus; Noct: nocturnal; HTN: hypertension; CKD: chronic kidney disease; PWV: pulse wave velocity; PRED: prednisone; HCQ: hydroxychloroquine; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table 5. Multivariable analysis for nocturnal HTN and nondipper pattern. Variables included in the multivariable analysis for nocturnal HTN were age, SDI, PWV, disease duration, CKD, and nocturnal HTN; and for nondipper pattern were age, SLICC/ACR-DI, SLEDAI, PWV, CKD, and use of prednisone.

Variable	Coefficient	95% CI	p
Nocturnal HTN*			
PWV	0.11	0.028–0.188	0.009
CKD	0.35	0.052–0.644	0.022
SLE duration	0.01	–0.002 to 0.024	0.085
Nondipper pattern†			
PWV	0.10	0.002–0.198	0.046
SLEDAI	0.06	0.013–0.113	0.043
CKD	0.34	–0.02 to 0.69	0.064

* Adjusted R^2 = 0.220. † Adjusted R^2 = 0.127. HTN: hypertension; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; PWV: pulse wave velocity; CKD: chronic kidney disease; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus.

The frequency of nondipper pattern among our controls was 42%, similar (50%) to that reported in postmenopausal women without coronary artery disease[25]. Also, the frequency of isolated nocturnal HTN and isolated daytime HTN in our controls were 6.2% and 4.6%, which is also similar to that observed in Western European countries (6.0% and 9.1%)[26]. This agreement in the results found in the control group reinforce those obtained in patients with SLE.

The concordance between the diagnosis of office and ambulatory HTN in both the SLE and control groups was modest. Thus, out of 12 patients with isolated nighttime HTN, only 3 (25%) had also been diagnosed as having office HTN (with BP controlled but on BP-lowering treatment). In other words, if we had measured only office BP, 75% of patients with isolated nighttime HTN would have been classified as normotensives. Similarly, out of 50 women with SLE classified as normotensives according to the office BP definition, 9 (18%) had true HTN according to the ABPM criteria. These results suggest that ABPM could be useful in the assessment of CV risk in patients with SLE to identify those with distorted nighttime BP profiles but with normal office BP.

In our study, PWV emerged as a factor independently associated with both nondipper pattern and nocturnal HTN in women with SLE, suggesting that both conditions separately or in combination could contribute to the increased atherosclerosis burden observed in these patients. These associations have also been reported in hypertensive individuals[27] in other diseases such as diabetes[28] and in diverse ethnicities[29,30]. Nevertheless, circadian BP variations and their association with subclinical atherosclerosis have been poorly investigated in patients with SLE. To the best of our knowledge, the association between ABPM values, subclinical atherosclerosis, and left ventricular hypertrophy

has only been evaluated in 1 small study with 24 patients with juvenile-onset SLE below the age of 21 years[16]. In this study, nighttime SBP positively correlated with PWV and inversely with carotid artery distensibility; also, carotid intima-media thickness significantly correlated with nighttime DBP. In line with our study, these results seem to support the harmful effect of elevated nighttime BP values on subclinical atherosclerosis in SLE, even in younger patients.

Our findings could also have therapeutic implications. Scheduling antihypertensive drugs (especially renin-angiotensin system antagonists)[31] at bedtime as opposed to morning has shown to increase the proportion of patients with properly controlled BP, improving the nighttime BP pattern and reducing urinary albumin excretion[32]. Thus, in a prospective study with 448 hypertensive patients with diabetes, bedtime treatment with at least 1 BP-lowering agent improved ABPM control and reduced CV morbidity and mortality[33]. Whether this therapeutic strategy, besides improving CV outcomes, also reduces albuminuria in patients with lupus nephritis is worth investigating.

CKD was independently associated with nocturnal HTN and tended to be associated with nondipper pattern in women with SLE. In general, patients with renal dysfunction frequently have an altered circadian rhythm with an increased rate of nondipping and nocturnal HTN. In fact, the prevalence of nondippers increases progressively as the stage of CKD progresses[34]. A population-based study in patients with CKD showed that ambulatory SBP was significantly elevated, mainly during the hours of nighttime sleep, regardless of the presence or absence of BP-lowering treatment[35]. Moreover, among the uncontrolled hypertensive patients with CKD, 90% had nocturnal HTN[35]. In our study, a history of lupus nephritis was not found to be more frequent in nondipper patients or in those with nocturnal HTN, perhaps because most patients with lupus nephritis did not develop CKD. Finally, the nighttime SBP correlated with 24-h urinary protein excretion in patients with diabetic nephropathy[36]. In our study, proteinuria in women with SLE was independent of nondipping or nocturnal HTN status.

Moreover, we found that SLE activity measured by SELENA-SLEDAI was independently associated with nondipper pattern. Because of the lack of data in the literature and the design of our study, we cannot establish how SELENA-SLEDAI may promote this phenomenon. However, we can speculate that disease activity is closely related to the use of glucocorticoids, which affect electrolyte balance, fluid retention, and increased BP and cardiac output, all of them related to the circadian BP regulation[37]. Hypercorticism has been consistently associated with nondipper pattern in patients with Cushing syndrome[38]. However, no differences in the use or dose of PRED was found between dipper and nondipper women with SLE.

The frequency of white-coat and masked HTN were similar in both groups, and comparable with those reported

in the Spanish population[39]. In contrast with white-coat HTN, several studies have shown that the CVD risk in patients with masked HTN was similar to that found in patients with sustained HTN[40]. In our study, the frequency of masked HTN in women with SLE was 16%. Although this proportion is modest, because of the elevated CVD risk reported in SLE, ABPM may be justified to identify these patients.

Some limitations should be considered. The effects of daytime physical activity and nighttime sleep quality on BP dipping were not taken into account. BP-lowering medications were removed only 24 h before ABPM and a possible residual antihypertensive effect could persist, especially during the daytime period. ABPM was performed only once and there are possible doubts about the reproducibility of the results. In this sense, the reproducibility of nocturnal HTN and the nocturnal nondipping was only moderate ($\kappa \geq 0.46$ and ≥ 0.38, respectively) in a placebo-controlled clinical trial in which ABPM was determined twice separated by 4 to 8 weeks[41]. Despite that PWV was higher in patients with SLE, no significant differences were observed, probably because the controls were slightly older. As a consequence of the relatively small size of the cohort, some statistical significance could not be reached because of a lack of statistical power. In addition, given the characteristics of the study sample (mainly young, female, SLE outpatients with low disease activity and damage who received low PRED doses and very few immunosuppressive drugs) the results obtained cannot be generalized for all patients with SLE. Finally, given that ours was a cross-sectional study, conclusions can only be used for hypothesis generation and not as proof of causality.

Nighttime BP abnormalities were common in women with SLE. In particular, nocturnal HTN and nondipper pattern were associated with a higher PWV, a predictor of CVD. Since these alterations cannot be detected by means of conventional office BP measurement, ABPM could be a useful tool for the assessment and stratification of CV risk in patients with SLE. Further studies are needed to evaluate the reproducibility of these results.

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