In patients with systemic lupus erythematosus and antiphospholipid syndrome renal function is associated with endothelial dysfunction and an NT-proBNP increase: Pilot study

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INTRODUCTION

Cardiovascular complications of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are frequent and show specific clinical features, rare in the general population [1, 2]. Hypertension is common among SLE patients as it occurs in up to 56% of this population, almost twice as frequently as in healthy age-matched subjects [3]. The etiology of hypertension in SLE is multifactorial, yet not completely understood. According to the available data, it is not only driven by renal glomerular damage but also renal vascular endothelial dysfunction. However, it may occur in patients without renal dysfunction [4] and is attributed, by some authors, to generalized endothelial dysfunction [5]. Among factors contributing to the development of hypertension, there are also abnormalities in the immune system, and blood pressure (BP) may be influenced by the current state of the disease [6].

Abnormal 24-hour BP pattern in the form of non-dipping is observed in up to 62% of the SLE population already in childhood [7]. Non-dipping is associated with increased arterial stiffness expressed by pulse wave velocity (PWV) and constitutes an independent cardiovascular risk factor [8]. However, to date, no study has evaluated association between endothelial dysfunction and 24-hour BP pattern in adult SLE patients. We aimed to evaluate the association between endothelial dysfunction assessed by the reactive hyperemia index (RHI) and 24-hour ambulatory blood pressure monitoring (ABPM) in patients with SLE and APS.

METHODS

In this prospective observational study, we screened consecutive patients diagnosed with SLE, APS, or both at the Department of Connective Tissue Diseases, National Institute of Geriatrics, Rheumatology and Rehabilitation between 2017 and 2020. The 2012 SLE classification criteria according to SLICC (Systemic Lupus International Collaborating Clinics) were applied [9]. APS diagnosis was verified based on the 2006 APS classification criteria [10]. The exact inclusion and exclusion criteria are described in Supplementary material. Subsequently, all included patients were evaluated at the outpatient center of the First Department of Cardiology, Medical University of Warsaw. Data on medical history, physical examination, cardiovascular risk factors, laboratory results, and treatment were collected. Every patient underwent measurement of digital flow-mediated dilation during reactive hyperemia (EndoPAT®, Itamar Medical, Caesarea, Israel), 24-hour ABPM (Spacelabs Healthcare, US), and simultaneous labora-

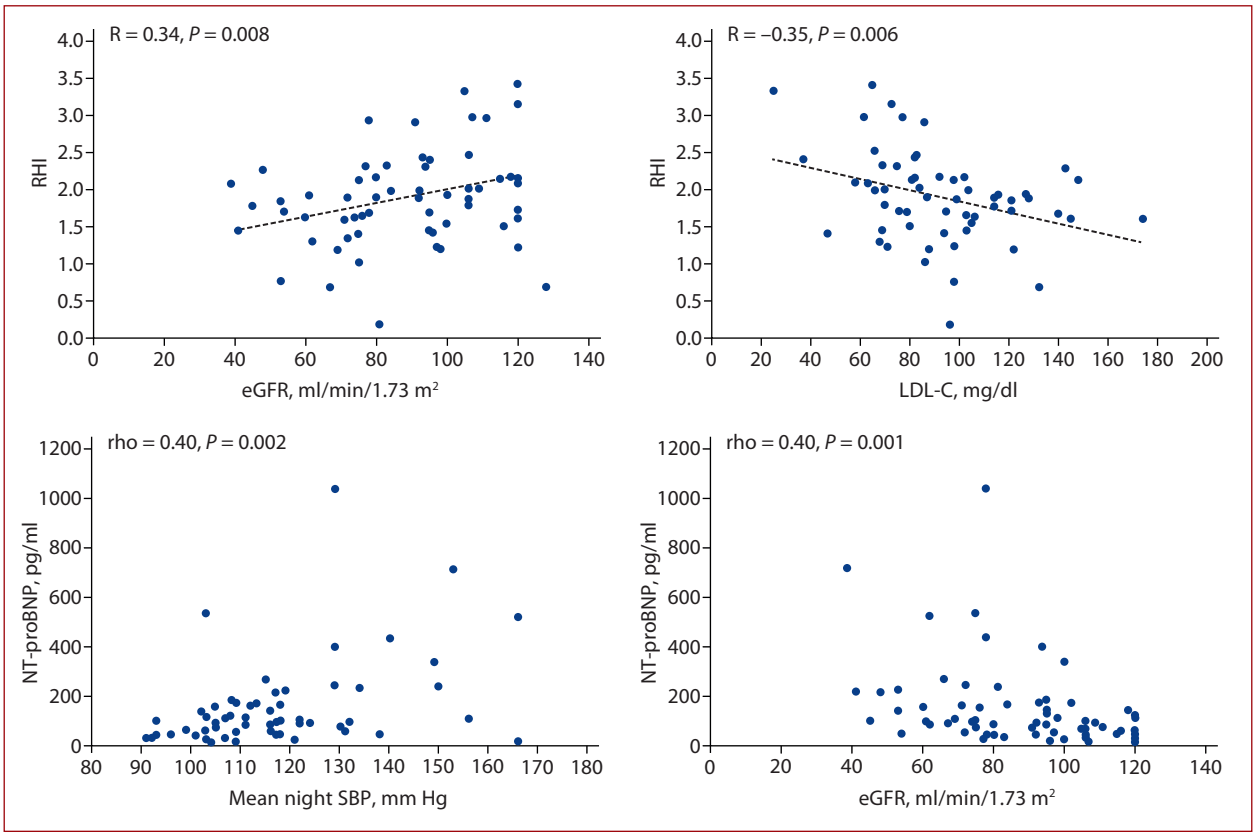

Figure 1. Correlations between investigated variables

Abbreviations: eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; RHI, relative hyperemia index

tory assessment. The study was approved by the ethics committee (no. KB/19/2017) and conducted in accordance with the Declaration of Helsinki. All the included patients signed informed consent.

Statistical analysis

Continuous variables with normal distribution were presented as mean (standard deviation, SD), whereas the median and interquartile range (IQR) were presented in the case of non-normality. Categorical variables were presented as counts and percentages. The Pearson or Spearman correlations were used to investigate the association between numerical variables. Pearson correlation coefficient R and Spearman rho were presented. For categorical variables, Fisher's exact test was used. *P*-values <0.05 were considered significant. All analyses were performed with SPSS (IBM Corp. Released 2022, Version 29.0. Armonk, NY, US).

RESULTS AND DISCUSSION

The study included 66 patients (60 [90%] females, mean age [SD] 42 [13] years). Of them, 50 were diagnosed with SLE (33 without APS, 17 with APS associated with SLE), and 16 with primary APS. Among APS patients (n = 33), 17 (51%) were triple positive and 23 (70%) had positive lupus anticoagulant. Twenty-three of 33 (70%) APS patients had thrombotic APS defined as APS diagnosed on the basis of venous and/or arterial thrombosis and persistent laboratory results for antiphospholipid antibodies (aPL). The mean estimated glomerular filtration rate (eGFR) was 88 (±22) ml/min/1.73 m^2, LDL-C was 93 (±29) mg/dl, and median NT-proBNP was 97 (120) pg/ml.

Overall, the mean RHI in the study population was 1.91 (±0.62). The RHI was abnormal (<1.67) in 21 (32%) patients. Mean daytime systolic blood pressure (mdSBP) was 128 (±15) mm Hg, mean daytime diastolic blood pressure (mdDBP) was 79 (±9) mm Hg, median nocturnal SBP (mnSBP) was 115 (24) mm Hg, and mean nocturnal DBP (mnDBP) was 69 (±11) mm Hg. Non-dipping was observed in 46% of patients. We found no significant correlation between RHI and ABPM values including mdSBP, mdDBP, mnSBP, mnDBP as well as night-day SBP (ND-SBP) ratio and night-day DBP (ND-DBP) ratio.

We evaluated other potential correlates of the RHI with laboratory and clinical variables, and we found a significant correlation between the RHI and eGFR (r = 0.34, *P* = 0.008) and LDL cholesterol (r = –0.35; *P* = 0.006), but no correlation between the RHI and albumin-to-creatinine ratios was observed (Figure 1A, B). Both eGFR and LDL-C correlated with each other significantly; however, the RHI correlated with eGFR also after adjustment for LDL-C (partial correlation R for eGFR = 0.30; *P* = 0.03), and LDL-C correlated with the RHI, also after adjustment for eGFR (partial correlation R for LDL-C = –0.28, *P* = 0.03). The RHI did not correlate with any indices of disease activity such as white blood cells,

C-reactive protein, or erythrocyte sedimentation rate, neither with vitamin D concentrations nor antihypertensive or statin treatment.

We also investigated other potential correlates of BP values. MnSBP (rho = 0.40; $P = 0.002$) and mnDBP (rho = 0.39; $P = 0.002$) as well as the ND-SBP ratio (rho = 0.33; $P = 0.009$), the ND-DBP ratio (rho = 0.37, $P = 0.004$) correlated with NT-proBNP, whereas no other significant correlations between nocturnal BP parameters and remaining variables were found. Other correlates of NT-proBNP included eGFR (rho = –0.40; $P = 0.001$) and age (rho = 0.45; $P = 0.001$).

There were no significant differences between LA-positive and LA-negative APS patient subgroups (Supplementary material, *Table S2*). Moreover, there was no difference between patients with antibodies against beta2-glycoprotein I in class IgG vs. IgM or anticardiolipin antibodies in class IgG vs. IgM with respect to sex, age, RHI, nighttime and daytime BP values, LDL-C, GFR, NT-proBNP, and the prevalence of thrombotic APS.

To the best of our knowledge, this is the first study to assess the relationship between the BP dipping pattern and the RHI in adult SLE patients. We observed that almost half of the study population presented a non-dipping BP pattern. We did not observe a significant association between the ND-SBP/ND-DBP ratio or the RHI in our study population. However, the relationship between the RHI and the BP dipping pattern has been so far evaluated in a small pediatric SLE cohort (n = 18), and the authors found a moderate correlation with the percentage of DBP dipping, as well as a moderate association between the percentage of SBP dipping and mean carotid intima-media thickness, which is a marker of subclinical atherosclerosis [11]. We observed that the nocturnal BP and night-day BP ratios were significantly associated with NT-proBNP, and may therefore indicate an unfavorable prognosis [12].

Importantly, we observed that one-third of our study population presented with an abnormal RHI, which is an independent predictor of coronary microcirculation impairment [13]. Similar to our results, the association between the RHI and the lipid profile was described previously in a population of patients with suspicion of coronary artery disease [14], which raises the question of when to start the treatment with statins in the SLE population as no specific recommendations in this population exist.

We found that renal function is significantly associated with the RHI. The relationship between eGFR and the RHI in a population of pre-dialysis chronic kidney disease patients (stages G1–5) was observed earlier [15]. For the first time, we have described this association in a cohort of SLE patients with relatively good renal function, mostly at stage G1 or G2. These data indicate the importance of considering renal impairment as a CVD risk factor in this population.

One limitation of our study is heterogeneity in terms of patients' sex, with the great majority of patients being female. We aim to increase the size of the male subgroup in the ongoing study.

In conclusion, among SLE and APS patients, nocturnal hypertension was frequently observed, and the RHI was found to correlate with renal function and lipid profile. While no association between nocturnal hypertension and endothelial dysfunction was observed in this investigation, nocturnal BP values and the night-day BP ratio, as well as a decline in renal function, were associated with higher NT-proBNP values.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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