Blood Pressure Variability and Age-related Blood Pressure Patterns in Systemic Lupus Erythematosus

George Stojan, Laurence S. Magder, and Michelle Petri

ABSTRACT. ***Objective.*** Despite the high prevalence of cardiovascular (CV) disease among patients with systemic lupus erythematosus (SLE), the relationship between age, blood pressure (BP), and BP variability (BPV) is not well understood. We studied visit-to-visit BPV, its relationship to age, clinical, and demographic characteristics, and its potential role as a CV risk factor in patients with SLE.

Methods. We analyzed systolic (SBP) and diastolic BP (DBP) measures in our cohort using mixed-effects regression models. From these models, we then obtained estimates of the mean BP, the visit-to-visit SD, and the between-person SD. The estimated means were compared to the general population using data from the National Health Statistics Reports from 2001 to 2008. In addition, we examined the relationship between BP (means, variances), patient demographic and clinical characteristics, and subsequent CV events.

Results. The mean SBP in SLE increased with age and was significantly higher in younger patients compared to the general population. BPV in SLE was elevated across all ages. BPV was significantly higher in African Americans, in patients with traditional CV risk factors, those with high disease activity, and in patients taking prednisone. Hydroxychloroquine was associated with significantly lower BPV. Within-person variability in DBP of ≥ 9 mmHg was highly associated with CV events in a multivariate analysis.

Conclusion. Age-related BP patterns in SLE differ from the general population. Increased visit-to-visit BPV is affected by many disease-specific and traditional CV factors. Increased DBP variability is highly associated with CV events in SLE. (First Release December 15 2019; J Rheumatol 2020;47:387–93; doi:10.3899/jrheum.181131)

Key Indexing Terms:
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Based on 2007 to 2010 data, 33% of US adults over 20 years of age had hypertension (HTN). This represented 78 million US adults with HTN[1]. It is estimated that the implementation of the new 2017 American College of Cardiology and American Heart Association definition of HTN (> 130/80 mmHg) will result in nearly half (46%) of the US adult population being classified as hypertensive[2]. The National Health and Nutritional Examination Survey (NHANES)[3] and the Framingham Study[4] demonstrated that aging in the general population is accompanied by steady increases in systolic blood pressure (SBP) and gradual declines in diastolic blood pressure (DBP). Elderly hypertensive patients tend to exhibit isolated systolic HTN and an elevated pulse pressure as a result of reduced arterial compliance, while hypertensive individuals younger than 50 years usually exhibit systolic and diastolic HTN and a narrowed pulse pressure, reflecting increased peripheral vascular resistance[5].

Mean BP is widely considered of primary importance as a risk factor for cardiovascular (CV) disease[6] and in diagnosis and treatment of HTN[7]. Visit-to-visit variability in BP was previously considered an obstacle to the reliable estimation of usual BP[8,9]. Visit-to-visit variability in measured clinic BP is common[10,11,12] and guidelines recommend continued monitoring or 24-h ambulatory BP monitoring in patients with episodic HTN[13,14] with treatment decisions based on mean BP.

Rothwell, *et al,* however, demonstrated that visit-to-visit BP variability (BPV) is increased in cohorts at high risk of stroke[11,15], and that visit-to-visit variability in SBP is a powerful predictor of stroke and coronary events independent of mean SBP[16]. Increased visit-to-visit BPV has been shown to be a predictor of all-cause mortality and CV mortality[17],

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and has been associated with decreased endothelial function[18], albuminuria and microalbuminuria[19], left ventricular diastolic dysfunction[20], and cognitive impairment[21].

Patients with systemic lupus erythematosus (SLE) have a significantly increased risk of CV events due to atherosclerosis. The latest data from the Hopkins Lupus Cohort estimates the risk of CV events among patients with SLE to be 2.66 times higher compared to the general population[22]. Traditional Framingham CV risk factors do not account for the entire risk in patients with SLE[23]. In the Hopkins Lupus Cohort, 74% of patients are hypertensive[24]. Over the first 3 years of followup the percentage of hypertensive SLE patients in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort increased from 39.2% to 58.3%[25]. Despite the high prevalence of CV events in SLE, it is not known whether BP patterns are similar to the general population and differ with age, whether BPV is increased in patients with SLE, and whether it plays a role in the highly elevated CV risk in patients with SLE. We thus hypothesized that the BP patterns differ in SLE compared to the general population, that visit-to-visit BPV is increased, and that it is an independent CV risk marker.

MATERIALS AND METHODS

Patients and activity indices. As previously described[26], the Hopkins Lupus Cohort is a prospective cohort study of predictors of lupus flare, atherosclerosis, and health status in SLE. The study cohort includes all patients at the Hopkins Lupus Center who have a clinical diagnosis of SLE and give informed consent to participate in the study. Subjects enrolled in the cohort are followed quarterly or more frequently if clinically necessary. The clinical features, laboratory testing, and damage accrual data are recorded at the time of entry into the cohort and are updated at subsequent visits. The Hopkins Lupus Cohort has been approved by the Johns Hopkins University School of Medicine Institutional Review Board (NA_00039294) and complies with the Health Insurance Portability and Accountability Act. All patients gave written informed consent.

Ninety-five percent of patients fulfilled 4 or more of the American College of Rheumatology 1982 revised classification criteria for SLE[27,28] and the SLICC classification criteria for SLE[29]. Disease activity was measured with the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) revision of the SELENA–Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) instrument score[30] and the physician's global assessment[31].

BP was measured at each visit using a Carescape Dinamap V100 monitor, which was calibrated once every 12 months according to manufacturer guidelines. Patients were in a seated position with the arm supported at heart level. Cuff sizes used included adult small (23–33 cm) and adult large (31–40 cm).

The analyses were based on different subsets of patients from the cohort. Each subset was about 92% female. Most (60%) were under 40 years of age at cohort entry while a small proportion (6%) were 60 years or older. Most were either white (55%) or African American (38%).

Statistical methods for estimating means and variances of BP in patients with SLE. The mean SBP and DBP measures in this cohort were estimated using random intercept models, fit by restricted maximum likelihood. Using this approach, we obtained estimates of the mean BP, the within-person SD (i.e., the SD of individual's BP around their personal mean), and the between-person SD (i.e., the SD of the person-specific mean BP).

To compare means with national data from 2001 to 2008, we analyzed data from 22,672 clinic visits of 1509 cohort members that took place between 2001 and 2008. Of the 1509 patients, 661 (44%) contributed < 10 visits, 329 (22%) contributed 10–19 visits, and 520 (34%) contributed 20 or more visits. The estimated means were compared to the mean SBP and DBP in the general population using data from the National Health Statistics Reports (19,921 adults aged 18 yrs and over with BP estimates calculated using the mean of up to 3 measurements)[32]. To obtain more precise estimates of the means and variances of BP by age, we used a larger sample, including data from 52,791 cohort visits of 2128 patients seen from 1987 to 2013.

Statistical methods for the analysis of the relationship between clinical and demographic characteristics and BPV. This analysis was based on 63,890 clinic visits of 2525 cohort members from 1987 to 2018. Within and between-patient BPV was estimated using random intercept models. The statistical significance of differences between clinical subgroups regarding BPV was determined using likelihood ratio tests.

Statistical methods for the analysis of the relationship between BP variables and CV events. This analysis was based on 1340 cohort members who had at least 8 clinical assessments of BP in the cohort between 1987 and 2013. They were 92% female (n = 1235). The average duration of followup per patient was 74 months (6.2 yrs). Four hundred fifty-nine (34%) were followed for less than 3 years, 331 (25%) were followed for 3–6 years, 210 (16%) were followed for 6–9 years, and 340 (25%) were followed for 10 or more years.

CV events were defined as either stroke, myocardial infarction, incident angina, a coronary procedure (coronary artery bypass graft surgery or percutaneous coronary intervention), or claudication. Considering only the first CV event for each person, there were 105 events. This is a rate of 12.7 per thousand person-years. Of these, 60 were strokes, 23 were myocardial infarctions, 24 were angina or coronary procedures, 14 were claudications, and 3 were mixed.

For each month of followup for a patient in the cohort, the previous 8 BP measurements were included in the analysis. The following variables were calculated based on those most recent 8 measures: mean prior SBP and DBP, SD of prior SBP and DBP, and coefficient of variation of prior SBP and DBP. This information was then linked with whether the patient had a CV event in that month. Person-months were aggregated, and the risks of a CV event by monthly characteristics were calculated. Person-months after a previous CV event were excluded. In addition to adjusting for age, race, and sex, the rate ratios are also adjusted for diabetes, cholesterol ≥ 240 mg/dl, body mass index (BMI) > 25 kg/m^2, most recent prednisone dose, and past or current smoking.

RESULTS

Table 1 compares the mean BP in the Hopkins Lupus Cohort to the NHANES mean BP in broad age groups from 2001 to 2008[32]. The SBP in SLE follows the trend of increase with age seen in the general population. SBP was significantly higher among young patients with SLE, regardless of ethnicity or sex. With age, this difference narrowed, only to be reversed in women older than 60 years of age ($p < 0.001$), but not in men.

Table 2 provides estimates of the mean and SD of SBP and DBP in patients with SLE in each decade of life. There are 2 components of SD: (1) SD within a person around his/her personal mean BP; and (2) SD between people regarding personal mean BP. The total SD is determined by the component SD. BPV in SLE is elevated across all age groups. Within-person SD of SBP increased with age and ranged between 12.5 mmHg among 20-year-olds and 16.0 mmHg among 80-year-olds, while DBP variability remained stable through all age groups and ranged between 8.6 mmHg and 11.8 mmHg. These values are substantially higher than

Table 1. Comparison of the Hopkins Lupus Cohort with the NHANES sample regarding mean systolic (SBP) and mean diastolic blood pressure (DBP) from 2001 to 2008 by age and ethnicity.

Sex	Ethnicity	Age, yrs	Mean (SE) SBP, mmHg			Mean (SE) DBP, mmHg		
			Cohort	NHANES	p	Cohort	NHANES	p
Female	White	18–39	117.9 (0.5)	109 (0.3)	< 0.0001	71.1 (0.4)	68 (0.3)	< 0.0001
		40–59	122.4 (0.6)	120 (0.5)	0.002	71.7 (0.4)	74 (0.4)	< 0.0001
		60+	132.1 (1.2)	138 (0.6)	< 0.0001	70.7 (0.7)	67 (0.4)	< 0.0001
	African American	18–39	121.7 (0.7)	114 (0.5)	< 0.0001	74.4 (0.5)	69 (0.4)	< 0.0001
		40–59	129.5 (0.8)	128 (0.9)	0.21	76.4 (0.4)	75 (0.6)	0.052
		60+	134.6 (1.8)	144 (1.2)	< 0.0001	75.1 (1.1)	70 (0.5)	< 0.0001
Male	White	18–39	125.7 (2.1)	118 (0.3)	0.0003	73.3 (1.7)	70 (0.3)	0.056
		40–59	127.5 (1.5)	124 (0.5)	0.027	76.3 (0.9)	76 (0.3)	0.75
		60+	135.7 (4.1)	132 (0.6)	0.37	75.6 (2.3)	69 (0.4)	0.0047
	African American	18–39	130.8 (2.2)	121 (0.4)	< 0.0001	77.3 (2.6)	71 (0.4)	0.017
		40–59	133.4 (2.6)	129 (0.8)	0.11	79.1 (1.6)	79 (0.6)	0.95
		60+	143.2 (9.5)	137 (0.9)	0.52	81.3 (7.9)	71 (0.9)	0.20

NHANES: National Health and Nutritional Examination Survey; SE: standard error.

Table 2. Mean and variance of systolic (SBP) and diastolic blood pressure (DBP) by decade of life in SLE.

Decade of Life	SBP, mmHg				DBP, mmHg			
	Mean (95% CI)	Within-person SD	Between-person SD	Total SD	Mean (95% CI)	Within-person SD	Between-person SD	Total SD
20s	119.8 (119.0–120.7)	12.5	10.2	16.1	73.4 (72.8–74.1)	9.0	7.8	11.9
30s	120.4 (119.7–121.2)	13.2	10.7	17.0	74.0 (73.4–74.5)	8.9	8.0	12.0
40s	124.3 (123.6–125.2)	14.4	11.6	18.5	75.2 (74.6–75.7)	8.8	7.3	11.5
50s	127.7 (126.6–128.7)	14.8	12.3	19.2	74.2 (73.4–74.9)	8.6	8.0	11.7
60s	131.9 (130.3–133.5)	16.0	11.6	19.8	72.9 (71.9–74.0)	8.9	8.2	12.1
70s	136.6 (133.7–139.4)	17.4	11.2	20.7	72.4 (70.5–74.3)	9.0	7.8	11.9
80s	133.2 (125.0–141.4)	14.4	15.1	20.9	72.7 (66.6–78.7)	11.8	7.7	14.1

SLE: systemic lupus erythematosus.

the within-person BPV reported by NHANES (i.e., 7.7 mmHg for SBP and 5.8 mmHg for DBP)[33] but are comparable to previously published data in stroke cohorts[34,35,36].

Table 3 shows the relationship between BPV and clinical and demographic characteristics. BPV was statistically significantly higher ($p < 0.0001$) in African American patients. High disease activity (SLEDAI > 4), positive anti-dsDNA, hypocomplementemia, and antiphospholipid antibodies were all significantly ($p < 0.0001$) associated with higher BPV. Hypercholesterolemia, diabetes, and smoking were also associated with higher BPV ($p < 0.0001$). Patients taking hydroxychloroquine (HCQ) had significantly ($p < 0.0001$) lower BPV, while BPV increased with prednisone dose and was significantly higher ($p < 0.0001$) in patients taking prednisone > 12.5 mg/day.

Table 4 shows the relationship between SBP and DBP summary measures (based on the prior 8 BP assessments) and rates of CV events in the Hopkins Lupus Cohort. Visit-to-visit SBP variability of ≥ 14 mmHg [relative risk (RR) 1.9, 95% CI 1.0–3.3, $p < 0.05$] and DBP variability of ≥ 9 mmHg (RR 2.5, 95% CI 1.3–4.9, $p < 0.01$) were predictive of future CV events in a univariate analysis. After adjustment for age, ethnicity, sex, diabetes, hypercholesterolemia, BMI > 25 kg/m^2, most recent prednisone use, and smoking, DBP variability of > 9 mmHg (RR 2.1, 95% CI 1.0–4.1, $p < 0.05$) remained significantly associated with cardiovascular events.

The mean SBP in the previous 8 visits was a stronger predictor of CV events than any other BP measurement. Table 5 shows the association between the other measures of recent BP and CV events after adjustment for age, race, sex, and mean SBP in the past 8 visits. None of the measurements were significantly associated with events after these adjustments. In contrast, for every model shown in the table, mean SBP was a significant predictor of CV events, with OR ranging from 1.5 to 1.7 per SD increase.

DISCUSSION

Accelerated atherosclerosis remains a major cause of morbidity and mortality in patients with SLE and other autoimmune diseases[37]. Traditional Framingham CV risk factors do not account for the entire risk in SLE and the search for disease-specific factors that elevate this risk has been ongoing for decades.

Compared to general population data from the National

Table 3. Variability of blood pressure in subgroups of clinic visits defined by patient or clinical characteristics.

Patient Characteristics	No. Visits	Systolic Blood Pressure		Diastolic Blood Pressure	
		Within-person SD	p	Within-person SD	p
Sex					
Female	58,853	14.3	0.027	9.1	0.54
Male	5037	14.7		9.2	
Ethnicity					
White	31,638	13.2	< 0.0001	8.5	< 0.0001
African American	29,368	15.7		9.9	
Other	3884	12.6		8.5	
Current SLEDAI					
0	23,720	13.6	< 0.0001	8.7	< 0.0001
1–3	17,855	14.1		8.9	
4+	21,950	15.2		9.8	
Current prednisone dose, mg/day					
0	30,598	13.1	< 0.0001	8.3	< 0.001
1–7.5	14,814	14.5		9.0	
7.5–12.5	9592	15.6		9.8	
> 12.5	8619	16.3		10.9	
Body mass index					
< 20	8513	14.9	< 0.0001	9.6	< 0.0001
20–24.9	18,406	14.0		8.8	
25–29.9	17,052	14.3		9.1	
30+	19,919	14.4		9.4	
Smoking history					
No	38,451	13.6	< 0.0001	8.9	< 0.0001
Yes	25,439	15.4		9.6	
Current anti-dsDNA					
No	45,067	14.2	0.0002	8.9	< 0.0001
Yes	16,522	14.6		9.6	
Recent low complement					
No	44,105	14.11	< 0.0001	8.9	< 0.0001
Yes	17,956	14.86		9.7	
Current hydroxychloroquine use					
No	20,232	15.3	< 0.0001	9.8	< 0.0001
Yes	43,438	13.9		8.8	
History of lupus anticoagulant					
No	41,992	14.2	< 0.0001	9.0	< 0.0001
Yes	21,221	14.7		9.5	
History of anticardiolipin antibody					
No	24,601	14.1	< 0.0002	9.0	< 0.0001
Yes	38,552	14.5		9.2	
Current cholesterol > 200 mg/dl					
No	39,652	13.7	< 0.0001	8.7	< 0.0001
Yes	18,523	15.3		9.7	
History of diabetes					
No	55,456	14.0	< 0.0001	9.0	< 0.0001
Yes	8416	16.6		10.1	

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Health Statistics Reports, SBP in SLE follows a similar trend of increase with age with substantially higher mean SBP among the young (aged 18–39 yrs) regardless of ethnicity. With age, we observe sex-specific patterns among SLE patients, with elderly females (age 60+ yrs), regardless of ethnicity, having statistically significantly lower mean SBP compared to their non-SLE counterparts. This trend of reversal is not seen among men, where patients with SLE have higher mean SBP among all age groups, although the difference loses its statistical significance among the elderly.

In contrast to mean SBP, the mean DBP is higher in patients with SLE among all age groups regardless of ethnicity or sex, except for middle-aged white women (aged 40–59 yrs), who had a statistically significantly lower mean DBP. In contrast to women, where all age groups had statistically significant differences in DBP compared to the general population, only elderly white men had significantly higher mean DBP compared to their counterparts in NHANES.

SBP variability in SLE expressed as within-person SD and between-person SD rises with age in contrast to the DBP

Table 4. Relationship between systolic (SBP) and diastolic blood pressure (DBP) summary measures and rates of CV events in the Hopkins Lupus Cohort.

Subgroups	Observed No. CV Events	Person-yrs Followup	Rate of Events per 1000 Person-yrs	Adjusted[1] Rate Ratios (95% CI)	p
Total	105	8291	12.7		
Mean prior SBP, mmHg					
1st quartile (< 114)	9	1969	4.6	1.0 (Ref. group)	
2nd quartile (114–122)	13	2021	6.4	1.2 (0.5–2.9)	0.68
3rd quartile (122–131)	27	2144	12.6	1.6 (0.7–3.8)	0.23
4th quartile (131+)	56	2156	26.0	2.5 (1.1–5.5)	0.024
SD prior SBP, mmHg					
1st quartile (< 8.5)	16	2129	7.5	1.0 (Ref. group)	
2nd quartile (8.5–10.9)	24	2018	11.9	1.4 (0.7–2.7)	0.37
3rd quartile (10.9–14.0)	23	2069	11.1	1.0 (0.5–2.0)	0.99
4th quartile (14.0+)	42	2075	20.2	1.6 (0.9–3.1)	0.13
CV prior SBP, mmHg					
1st quartile (< 0.07)	17	2021	8.4	1.0 (Ref. group)	
2nd quartile (0.07–0.089)	28	2118	13.2	1.5 (0.8–2.8)	0.26
3rd quartile (0.089–0.112)	23	2079	11.0	1.1 (0.6–2.3)	0.71
4th quartile (0.112+)	37	2074	17.8	1.6 (0.9–3.1)	0.13
Mean prior DBP, mmHg					
1st quartile (< 68)	11	2007	5.5	1.0 (Ref. group)	
2nd quartile (68–74)	29	2233	13.0	2.2 (1.0–4.5)	0.038
3rd quartile (74–80)	24	2109	11.4	1.6 (0.8–3.5)	0.21
4th quartile (80+)	41	1943	21.1	2.6 (1.2–5.3)	0.0118
SD prior DBP, mmHg					
1st quartile (< 5.4)	13	2139	6.1	1.0 (Ref. group)	
2nd quartile (5.4–7.0)	29	1982	14.6	1.9 (0.9–3.7)	0.082
3rd quartile (7.0–9.1)	30	2184	13.7	1.9 (1.0–3.7)	0.069
4th quartile (> 9.1)	33	1986	16.6	2.1 (1.0–4.1)	0.036
CV prior DBP, mmHg					
1st quartile (< 0.117)	17	2095	8.1	1.0 (Ref. group)	
2nd quartile (0.117–0.149)	26	2083	12.5	1.3 (0.7–2.5)	0.46
3rd quartile (0.149–0.189)	25	2049	12.2	1.1 (0.6–2.2)	0.74
4th quartile (0.189+)	37	2064	17.9	1.4 (0.7–2.6)	0.29

[1] Adjusted for age, race, sex, diabetes, cholesterol, body mass index, smoking, and recent prednisone dose. CV: cardiovascular.

Table 5. Association between various recent blood pressure measurements and risk of a CVE after adjusting for age, race, sex, and the mean value of the 8 most recent systolic blood pressures.[1]

Blood Pressure Measurement	OR[2] (95% CI)	p
Single most recent measure of SBP	0.9 (0.7–1.2)	0.62
SD of 8 most recent SBP measures	1.1 (0.9–1.3)	0.48
Maximum of the 8 most recent SBP measures	1.2 (0.8–1.6)	0.40
Mean of the 8 most recent SBP	1.1 (0.9–1.5)	0.42
Single most recent measure of SBP	1.0 (0.8–1.2)	0.88
SD of 8 most recent SBP measures	1.1 (0.9–1.3)	0.39
Maximum of the 8 most recent SBP measures	1.1 (0.9–1.5)	0.36

[1] Each row in the model is based on a different regression model that included the measurement for that row as well as age, race, sex, and the mean value of the 8 most recent systolic blood pressures. [2] OR are scaled so they are interpreted as the factor by which the odds change for every SD increase in the measure. CVE: cardiovascular event; SBP: systolic blood pressure; DBP: diastolic BP.

variability, which remains unchanged. The average intra-individual SD for SBP were 14.1 mmHg in our cohort, comparable to data from stroke cohorts: 13.6 in UK-TIA trial[34], 15.0 in the Dutch TIA trial[38], and 13.9 mmHg in the European Carotid Surgery Trial[39]. These values are substantially higher than the reported SD for SBP in the general population from the NHANES survey, which was 7.7 mmHg[33]. For DBP, the average intraindividual SD was 8.8, compared to 7.6, 7.8, and 7.4 mmHg, respectively, in stroke cohorts. These values are also higher than the within-person DBP variability reported by NHANES of 5.8 mmHg. It should be noted, however, that in NHANES, BPV was based on measures relatively close in time (median of 17 days apart) and based on averages of 2 measures at each visit.

BPV in SLE is affected by both traditional CV risk factors and disease-specific factors. Among traditional CV risk factors, diabetes, hypercholesterolemia, and smoking were associated with higher BPV. Surprisingly, patients with a BMI < 20 kg/m^2 had higher BPV than those with normal weight or obese patients, possibly related to higher disease activity in this subgroup. A SLEDAI > 4, anti-dsDNA positivity, and hypocomplementemia were also associated with higher BPV. BPV increased with higher prednisone doses and was highest in patients taking > 12.5 mg/day.

BPV was significantly higher among African Americans. HCQ use was protective and was associated with significantly lower BPV.

Visit-to-visit variability in SBP ≥ 14 mmHg and DBP ≥ 9 mmHg were highly associated with CV events ($p < 0.05$) in a univariate analysis. After adjustments, only visit-to-visit DBP variability remained significantly ($p < 0.05$) associated with CV events.

In contrast to the stroke populations, BPV in patients with SLE was not an independent CV risk factor; after adjusting for mean SBP, none of the studied measures were significantly associated with CV events.

There is no evidence that longterm BPV directly causes CV outcomes, but the current approach in patients with a history of stroke or coronary artery disease is to consider correctable causes when unexpected BP changes occur[40]. Similarly, when faced with a patient with SLE who has high BPV, one should consider correctable underlying causes, for example, high-dose prednisone or noncompliance with HCQ. There is evidence of an antihypertensive drug class effect on BPV in stroke patients, i.e., that calcium channel blockers and thiazide diuretics decrease longterm variability, while beta blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors increase the BPV[41]. It is intriguing to consider the future possibility of pharmacologically modifying BPV in patients with SLE and the effect it could have on CV outcomes.

Age-related BP patterns differ in patients with SLE with significantly higher mean SBP and DBP in younger patients, a difference that diminishes with age and reverses in women over 60 years of age. Visit-to-visit SBP and DBP variability in SLE rises with age and is comparable to the one described in stroke cohorts. BPV in SLE is higher in patients with traditional CV risk factors, such as diabetes, hypercholesterolemia, and smoking, but also in patients with high disease activity, those taking prednisone, and in patients of African American ethnicity. HCQ use is associated with significantly lower BPV. Increased visit-to-visit DBP variability is highly associated with CV events in SLE, but mean BP remains the dominant CV risk factor in this population.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127:e6-245.
2. Whelton PK, Carey RM, Aronow WS, Casey DE JR, Collins KJ, Himmelfarb CD, et al. 2017 ACC/ AHA/ AAPA/ ABC/ ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/P CNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-248.
3. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995;25:305-13.
4. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular diseases: a historical perspective. Lancet 2014;383:999-1008.
5. Rohrscheib MR, Myers OB, Servilla KS, Adams CD, Miskulin D, Bedrick EJ, et al. Age-related blood pressure patterns and blood pressure variability among hemodialysis patients. Clin J Am Soc Nephrol 2008;3:1407-14.
6. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360:1903-13.
7. Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. Lancet 2008;371:2219-21.
8. Klungel OH, de Boer A, Paes AH, Nagelkerke NJ, Seidell JC, Bakker A. Estimating the prevalence of hypertension corrected for the effect of within-person variability in blood pressure. J Clin Epidemiol 2000;53:1158-63.
9. Turner MJ, van Schalkwyk JM. Blood pressure variability causes spurious identification of hypertension in clinical studies: a computer simulation study. Am J Hypertens 2008;21:85-91.
10. Variability of blood pressure and the results of screening in the hypertension detection and follow-up program. J Chronic Dis 1978;31:651-67.
11. Cuffe RL, Howard SC, Algra A, Warlow CP, Rothwell PM. Medium-term variability of blood pressure and potential underdiagnosis of hypertension in patients with previous transient ischemic attack or minor stroke. Stroke 2006;37:2776-83.
12. Marshall T. When measurements are misleading: modelling the effects of blood pressure misclassification in the English population. BMJ 2004;328:933.
13. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72.
14. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87.
15. Howard SC, Rothwell PM; Cerebrovascular Cohort Studies Collaboration. Regression dilution of systolic and diastolic blood pressure in patients with established cerebrovascular disease. J Clin Epidemiol 2003;56:1084-91.
16. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 13;375:895-905.
17. Hsieh YT, Tu ST, Cho TJ, Chang SJ, Chen JF, Hsieh MC. Visit-to-visit variability in blood pressure strongly predicts all-cause mortality in patients with type 2 diabetes: a 5.5-year prospective analysis. Eur J Clin Invest 2012;42:245-53.
18. Diaz KM, Veerabhadrappa P, Kashem MA, Feairheller DL, Sturgeon KM, Williamson ST, et al. Relationship of visit-to-visit and ambulatory blood pressure variability to vascular function in African Americans. Hypertens Res 2012;35:55-61.

19. Kawai T, Ohishi M, Kamide K, Onishi M, Takeya Y, Tatara Y, et al. The impact of visit-to-visit variability in blood pressure on renal function. Hypertens Res 2012;35:239-43.
20. Masugata H, Senda S, Murao K, Inukai M, Hosomi N, Iwado Y, et al. Visit-to-visit variability in blood pressure over a 1-year period is a marker of left ventricular diastolic dysfunction in treated hypertensive patients. Hypertens Res 2011;34:846-50.
21. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. J Hypertens 2012;30:1556-63.
22. Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. Am J Epidemiol 2012;176:708-19.
23. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-7.
24. Fang H, Ahmad R, Magder L, Petri MA. Lack of control of hypertension in systemic lupus erythematosus [abstract]. Arthritis Rheum 2012;64 Suppl 10:S1087.
25. Urowitz MB, Gladman D, Ibañez D, Fortin P, Sanchez-Guerrero J, Bae S, et al; Systemic Lupus International Collaborating Clinics. Accumulation of coronary artery disease risk factors over three years: data from an international inception cohort. Arthritis Rheum 2008;59:176-80.
26. Petri M. Hopkins Lupus Cohort. 1999 update. Rheum Dis Clin North Am 2000;26:199-213.
27. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
28. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
29. Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677-86.
30. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al; OC-SELENA Trial. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8.
31. Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus. A prospective cohort study. Arthritis Rheum 1991;34:937-44.
32. Wright JD, Hughes JP, Ostchega Y, Yoon SS, Nwankwo T. Mean systolic and diastolic blood pressure in adults aged 18 and over in the United States, 2001-2008. Natl Health Stat Report 2011;1-22, 24.
33. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population findings from NHANES III, 1988 to 1994. Hypertension 2011;57:160-6.
34. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044-54.
35. Predictors of major vascular events in patients with a transient ischemic attack or nondisabling stroke. The Dutch TIA Trial Study Group. Stroke 1993;24:527-31.
36. Sivenius J, Riekkinen PJ, Laakso M, Smets P, Lowenthal A. European Stroke Prevention Study (ESPS): antithrombotic therapy is also effective in the elderly. Acta Neurol Scand 1993;87:111-4.
37. Stojan G, Petri M. Atherosclerosis in systemic lupus erythematosus. J Cardiovasc Pharmacol 2013;62:255-62.
38. Dutch TIA Trial Study Group, van Gijn J, Algra A, Kappelle J, Koudstaal PJ, van Latum A. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991;325:1261-6.
39. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-87.
40. Weber MA. Blood pressure variability and cardiovascular prognosis: implications for clinical practice. Eur Heart J 2017;38:2823-6.
41. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 2010;375:906-15.