N-Terminal Pro-Brain Natriuretic Peptide in Systemic Lupus Erythematosus: Relationship with Inflammation, Augmentation Index, and Coronary Calcification

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ABSTRACT. ***Objective.*** Cardiovascular mortality is increased in systemic lupus erythematosus (SLE). Increased plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) are associated with cardiovascular morbidity and mortality in the general population. We examined the hypothesis that NT-proBNP concentrations are higher in patients with SLE, and are related to inflammation, augmentation index, coronary atherosclerosis, and cardiovascular risk factors.

Methods. Serum concentrations of NT-proBNP were measured in 113 patients with SLE and in 80 control subjects. Coronary calcification and augmentation index were measured by electron beam computed tomography and noninvasive pulse wave analysis, respectively.

Results. Patients with SLE had higher concentrations of NT-proBNP [median 38.6 (interquartile range 2.5–126.9) pg/ml] than controls [11.7 (1.6-47.9) pg/ml] ($p = 0.002$). Augmentation index was higher in patients with SLE [25.0% (20.5%–31.5%)] than controls [20.5% (12.0%–29.0%)] ($p = 0.04$). In patients with SLE, NT-proBNP concentrations were associated with disease damage (rho = 0.31, $p < 0.001$) and duration (rho = 0.21, $p = 0.02$) but not with disease activity, C-reactive protein, erythrocyte sedimentation rate, tumor necrosis factor-α, interleukin 6, coronary calcium score, or augmentation index (all $p \geq 0.18$).

Conclusion. Patients with SLE have increased concentrations of NT-proBNP, but this is not explained by atherosclerotic burden, augmentation index, or inflammatory state. (First Release June 1 2008; J Rheumatol 2008;35:1314–9)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS ATHEROSCLEROSIS
N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE

Several biomarkers are associated with cardiovascular risk in the general population. One such biomarker is N-terminal pro-brain natriuretic peptide (NT-proBNP), a hormone synthesized and secreted primarily in the heart in response to myocyte stretch[1]. Measurement of plasma NT-proBNP concentrations is useful to diagnose and monitor heart failure and to determine its prognosis[2,3]. However, more recent studies suggest that NT-proBNP is also associated with atherosclerosis. Data from the Framingham Heart Study indicate that higher concentrations of BNP are associated with increased risk of cardiovascular events[4]. This association between NT-proBNP and atherosclerosis was independent of heart failure in patients with diabetes[5], and in the general population[6].

Patients with systemic lupus erythematosus (SLE) have accelerated atherosclerosis and increased cardiovascular risk[7-10]. However, this increased risk is not accounted for by traditional risk factors[11,12]. In a recent study we showed that despite a markedly increased prevalence of coronary atherosclerosis in patients with SLE, their Framingham cardiovascular risk scores were similar to those of matched controls[12]. Thus, there is a need for identification of novel factors to better predict the development and presence of atherosclerosis in patients with SLE.

Little is known about NT-proBNP concentration in the setting of inflammatory diseases, particularly in patients with lupus. Thus, we examined the hypothesis that NT-proBNP concentrations are increased in patients with SLE and associated with inflammation and cardiovascular risk factors, including coronary calcification, a noninvasive measure of coronary atherosclerosis, and augmentation index, a noninvasive measure of vascular stiffness.

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MATERIALS AND METHODS

Subjects. One hundred thirteen eligible patients 18 years of age or older who met the classification criteria for SLE[13] with disease duration of more than 1 year and 80 age and sex-matched control subjects were studied. These subjects are part of ongoing studies of cardiovascular disease in SLE and the characteristics of the patients and methods used have been described in detail[9,12,14-17]. Patients were recruited from practices of local rheumatologists, through a Lupus Foundation newsletter, and by advertisements. Control subjects were recruited from patients' acquaintances, by local advertisement, and from a database of volunteers maintained by the General Clinical Research Center. The study was approved by the Institutional Review Board of Vanderbilt University Hospital and all subjects gave written informed consent.

Subjects with a history of myocardial infarction or any coronary procedure, or with evidence of congestive heart failure (CHF) as determined from the medical history, were excluded. Information was obtained using a structured interview, examination, laboratory tests, and review of medical records. In patients, disease activity was ascertained by the SLE Disease Activity Index (SLEDAI)[18], and disease damage was determined by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI)[19]. Hypertension was defined as the use of antihypertensive agents or a systolic blood pressure ≥ 140 mm Hg, or a diastolic blood pressure ≥ 90 mm Hg.

Laboratory tests. Serum NT-proBNP concentrations were measured by multiplex enzyme linked immunosorbent assay (ELISA; Linco Research/Millipore Corp., Billerica, MA, USA) according to the manufacturer's instructions, with inter- and intraassay coefficients of variation of 8.4% and 8.3%, respectively. Serum interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) concentrations were measured by ELISA. Other laboratory tests included a complete blood count, creatinine, fasting total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, lipoprotein(a) [Lp(a)], and homocysteine. The glomerular filtration rate was estimated with the Modification of Diet in Renal Disease (MDRD) study equation[20].

Procedures. Subjects underwent chest computed tomography imaging with an Imatron C-150 scanner (GE/Imatron, South San Francisco, CA, USA) as described. All scans were interpreted by a single expert investigator (PR) who was unaware of the subjects' clinical status[9]. The extent of coronary artery calcification was calculated as described by Agatston, *et al*[21].

Sixty patients and 42 controls also underwent noninvasive pulse wave analysis using the SphygmoCor system (AtCor Medical, Sydney, Australia). After at least 10 min of supine rest, peripheral blood pressure was measured twice by an automated sphygmomanometer and augmentation index determined by applanation tonometry. The tonometer was held at the point of maximal pulsation and pressed lightly against the radial artery. Measurements were recorded after at least 12 consecutive beats and the quality of the waveforms confirmed by the program software. After these measurements were obtained, the software generated a corresponding central aortic pressure waveform[22]. Because it is affected by heart rate, augmentation index was normalized to a heart rate of 75 beats per min.

Statistical methods. Demographic characteristics are presented as median and interquartile range for continuous variables, and as frequencies and percentages for categorical variables. Univariate analyses were performed to compare differences among patients and controls using Wilcoxon rank-sum tests for continuous variables, and Pearson's chi-squared tests for categorical variables. Spearman correlation coefficients were used to determine the associations among NT-proBNP, clinical characteristics, and laboratory tests. A linear regression model was used to examine if the association between SLE and NT-proBNP was independent of potential confounders. Logarithmically transformed NT-proBNP was the dependent variable, disease status (SLE or control) the independent variable, and age, sex, race, body mass index (BMI), hypertension, and augmentation index the covariates. The assumptions of the linear regression model were assessed using the skewness-kurtosis test to check the distribution of the residuals. Based on a post hoc calculation, assuming a mean NT-proBNP concentration of 43.7 pg/ml and a standard deviation of 83.9 in control subjects, this study that included 113 patients and 80 controls had power to detect a difference of 35.6 pg/ml. All the analyses used a 2-sided significance level of 5% and were performed with the use of Stata software (version 9.1).

RESULTS

Demographic data for 113 patients with SLE and 80 controls are shown in Table 1. There was a predominance of Caucasian women in both patient and control groups, and the 2 groups were of similar age. The mean duration of disease among patients with SLE was 8 years, their median disease activity measured by the SLEDAI was 4 (0–6), and median damage, as quantified by the SLICC score, was 0 (0–1). Patients with SLE had higher NT-proBNP concentrations [38.6 (2.5–126.9) pg/ml] than controls [11.7 (1.6–47.9) pg/ml] ($p = 0.002$) (Figure 1). The differences remained significant after adjustment for age, sex, race, hypertension, BMI, and augmentation index ($p = 0.026$).

Augmentation index. Patients with SLE had a higher augmentation index [25.0% (20.5%–31.5%)] than controls [20.5% (12.0%–29.0%)] ($p = 0.04$). Augmentation index was associated with diastolic blood pressure (rho = 0.32, $p = 0.01$), systolic blood pressure (rho = 0.28, $p = 0.03$), and Framingham score (rho = 0.26, $p = 0.05$), but not with disease activity ($p = 0.55$) or disease duration ($p = 0.62$). After adjusting for age, sex, race, and height the association between SLE and augmentation index remained significant (ß = 4.2, $p = 0.03$).

NT-proBNP and cardiovascular risk factors. In patients with lupus, NT-proBNP concentrations were significantly higher in women, 44.8 (6.8–134.6) pg/ml, than men, 2.3 (1.6–6.0) pg/ml ($p = 0.02$); in controls this trend was less marked, 12.1 (2.0–47.9) pg/ml in women compared to 1.6 (1.6–58.6) pg/ml in men ($p = 0.46$). In patients with SLE, neither coronary atherosclerosis, as determined by the Agatston coronary calcium score, nor traditional cardiovascular risk factors were associated with NT-proBNP concentrations (Table 2).

NT-proBNP and SLE disease markers. In patients with SLE, NT-proBNP concentrations were associated with the SLICC damage score (rho = 0.31, $p < 0.001$) (Figure 2) and disease duration (rho = 0.21, $p = 0.02$), but not with disease activity (SLEDAI) ($p = 0.41$) or with markers of acute inflammation such as C-reactive protein (CRP) ($p = 0.81$), erythrocyte sedimentation rate (ESR) ($p = 0.60$), and TNF-α ($p = 0.18$) and IL-6 ($p = 0.17$) concentrations (Table 2).

DISCUSSION

The main findings of our study are that patients with SLE have increased concentrations of NT-proBNP, and elevated concentrations are not associated with markers of vascular stiffness, coronary atherosclerosis, or acute inflammation.

Table 1. Characteristics of patients with SLE and control subjects.

Characteristic	Patients with SLE, n = 113	Control, n = 80	p
Age, yrs (IQR)	40 (31–47)	41 (30–49)	0.98
Female, %	92	86	0.23
Caucasian, %	67	73	0.53
Current smoking, %	25	24	1.0
Pack/yrs of smoking	0 (0–5)	0 (0–0.7)	0.26
Diabetes, %	4	3	1.0
Hypertension, %	45	16	< 0.001
Body mass index, kg/m^2	27.3 (23.8–33.2)	25.2 (22.1–30.0)	0.04
Family history of early CAD, %	19	11	0.16
Total cholesterol, mg/dl	165 (141–204)	180 (154–206)	0.13
Low-density lipoprotein, mg/dl	96 (78–129)	108 (89–137)	0.04
High-density lipoprotein, mg/dl	48 (36–55)	47 (38–61)	0.58
Homocysteine, µmol/l	9.2 (7.3–11.1)	7.6 (6.5–8.9)	< 0.001
Augmentation index†, %	25 (21–32)	21 (12–29)	0.04
White blood cells, per/µl	5,600 (4,300–7,700)	6,000 (4,900–6,900)	0.45
Platelets, thousand per/µl	244 (211–299)	267 (232–312)	0.07
Creatinine, mg/dl	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.84
Estimated glomerular filtration rate, ml/min/1.73 m^2	95 (79–109)	91 (82–104)	0.80
Triglycerides, mg/dl	103 (71–150)	81 (62–108)	0.03
Lipoprotein (a), mg/dl	12 (5–37)	11 (5–32)	0.71
TNF-α, pg/ml	4.8 (3.1–7.9)	2.4 (1.8–3.0)	< 0.001
IL-6, pg/ml	5.7 (2.3–22.4)	1.8 (0.9–4.7)	< 0.001
Coronary calcium, Agatston units, mean ± SD	43.4 ± 189.8	3.8 ± 27.9	0.002

† Data available in 60 patients with SLE and 42 controls. CAD: coronary artery disease. TNF-α: tumor necrosis factor-α.

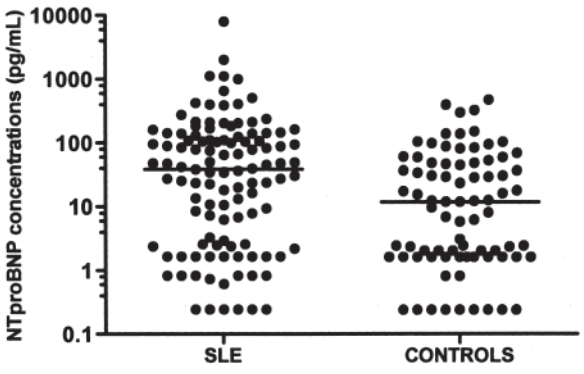

Figure 1. Concentrations of amino-terminal brain natriuretic prepropeptide (NT-proBNP) in patients with SLE and control subjects. Horizontal line represents the median. p = 0.002, comparing SLE vs controls.

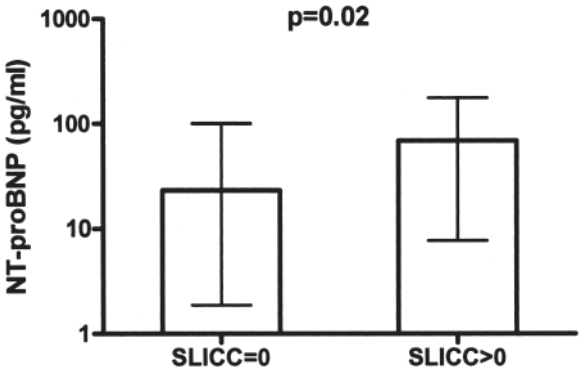

Figure 2. NT-proBNP concentrations in patients with SLE, (right) with and (left) without disease damage. Error bars represent median and interquartile range. p value calculated using Wilcoxon rank-sum test.

As described by Karadag, *et al*, we found that patients with SLE had higher concentrations of NT-proBNP than controls[23]. However, our study defined the association of NT-proBNP with coronary calcification, arterial stiffness, and selected markers of inflammation in a larger group of patients.

NT-proBNP is a cardiac biomarker with clinical utility in the diagnosis and management of congestive heart failure. In patients with heart failure, BNP is produced primarily by cardiac myocytes as a mechanism to offset left ventricular dysfunction[24-28]. Another source of NT-proBNP may be the intima of human coronary arteries in response to ischemia[27,28]. Studies in the general population suggest that higher concentrations of NT-proBNP, although not as high as those observed in heart failure, are a marker of coronary atherosclerosis[6]. Interestingly, as we also observed in patients with SLE, NT-proBNP concentrations in the general population were higher in women than men[29], suggesting that the biomarker may be particularly useful in predicting atherosclerotic disease in women — a group in whom tradi-

Table 2. Association between clinical variables and NT-proBNP concentrations in patients with SLE and controls.

	Patients with SLE	Controls
Categorical Variables, median (interquartile range)		
Sex		
Male, pg/ml	2.3 (1.6–6.0)	1.6 (1.6–58.6)
Female, pg/ml	44.8 (6.8–134.6)*	12.1 (2.0–47.9)
Race		
Caucasian, pg/ml	42.3 (3.0–130.7)	16.3 (1.6–59.7)
Others, pg/ml	35.1 (2.5–106.6)	2.4 (1.6–16.0)
Continuous Variables	**Spearman Rho**	**Spearman Rho**
Age, yrs	0.08	0.04
Body mass index	–0.20*	–0.14
LDL cholesterol, mg/dl	–0.15	0.04
Homocysteine, µmol/l	0.15	–0.08
Creatinine	0.11	0.24
Estimated glomerular filtration rate, ml/min/1.73 m^2	–0.19*	0.04
Pack/yrs of smoking	–0.09	0.14
Agatson score	0.06	–0.05
Augmentation index†	0.14	0.08
Systolic blood pressure, mmHg	–0.02	0.08
Diastolic blood pressure, mmHg	–0.01	–0.27*
Disease duration, yrs	0.21*	NA
SLEDAI	0.08	NA
SLICC	0.31**	NA
Corticosteroid, cumulative dose, units	–0.03	NA
TNF-α, pg/ml	0.13	0.27*
IL-6, pg/ml	0.13	–0.05
C-reactive protein, mg/ml	–0.02	NA
Erythrocyte sedimentation rate, mm/h	0.05	NA

* $p < 0.05$; ** $p < 0.001$. For categorical variables, p values represent comparisons between male and female, or Caucasian and non-Caucasians. † Data available in 60 patients with SLE and 42 control subjects. NA: not applicable. SLEDAI: SLE Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics score.

tional risk factors such as Framingham score perform poorly[30,31].

In addition to its association with coronary calcification in the general population, NT-proBNP is related to arterial stiffness. In patients with diabetes, high-normal concentrations of NT-proBNP were associated with augmentation index[32]. That association was significant after statistical adjustment for modifiable cardiovascular risk factors, but not when additional adjustments for age and sex were performed. Our results show that patients with lupus have increased arterial stiffness — as reported by others[33]. However, the association between NT-proBNP and augmentation index was not significant.

We have previously reported that the prevalence and severity of coronary artery calcification is increased in this population of patients with SLE compared to age and sex-matched controls[9]. However, neither coronary atherosclerosis (as measured by the presence and severity of calcification) nor augmentation index (as a marker of arterial stiffness) were associated with higher concentrations of NT-proBNP. There are several potential explanations for these findings. First, elevated NT-proBNP concentrations could precede the development of coronary atherosclerosis or increases in augmentation index, and thus identify patients with clinically silent vascular disease who may be at increased risk of developing atherosclerosis subsequently. Second, there may be no association between atherosclerosis and elevated NT-proBNP concentrations in patients with SLE; these elevated concentrations could be due to other mechanisms, for example, asymptomatic myocardial dysfunction. Further studies will be required to examine these possibilities.

Findings in other populations have suggested that there may be a relationship between NT-proBNP and inflammation. For example, in patients with severe sepsis, NT-proBNP concentrations were comparable to those found in heart failure[34], and high concentrations were associated with increased mortality[35]. Also, increased NT-proBNP concentrations were associated with higher concentrations of CRP in patients with chronic renal failure[36], and recently, we found that NT-proBNP concentrations were increased and associated with markers of acute inflammation in patients

with rheumatoid arthritis (unpublished data). However, in contrast to our findings in patients with rheumatoid arthritis, there was no association between NT-proBNP and CRP, ESR, TNF-α, or IL-6 in patients with lupus.

There was a statistically significant positive correlation between NT-proBNP and TNF-α in control subjects but not in patients with SLE, despite the fact that concentrations of TNF-α were significantly higher in patients with SLE. This suggests that the mechanisms increasing TNF-α in SLE are not correlated with those increasing NT-proBNP and may in fact act to obscure a relationship between baseline TNF-α and NT-proBNP.

We observed significantly higher concentrations of NT-proBNP in women than men. Although this is in agreement with previous reports[37], men accounted for only 8% of patients with SLE and therefore the magnitude of this difference should be interpreted with caution.

Our findings should be interpreted in light of the study design. First, echocardiographic studies were not performed; thus, we cannot exclude the possibility that subclinical myocardial dysfunction or hypertrophy was associated with increased concentrations of NT-proBNP. Second, renal clearance was not measured, and although there was no association of NT-proBNP with serum creatinine, the correlation between the estimated glomerular filtration rate and NT-proBNP concentrations was significant; thus, we cannot rule out subtle impairment of renal function as another potential confounder. Third, the majority of our patients had low to moderate lupus disease activity; nevertheless, it is in this population, free of confounding effects such as renal failure, that coronary calcification was increased[9]. However, our findings may not necessarily apply to patients with more severe disease activity. Fourth, although the analysis was adjusted for potential differences related to hypertension and BMI, residual confounding due to additional unmeasured variables cannot be excluded. Also, the cross-sectional design does not provide a temporal sequence; therefore, longitudinal data to evaluate if concentrations of BNP provide prognostic information independent of other cardiovascular risk markers will be of interest.

Patients with SLE have increased concentrations of NT-proBNP and this is not explained by atherosclerotic burden, augmentation index, or current inflammatory state.

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