Impact of serum uric acid on left ventricular diastolic function in patients with autoimmune diseases

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To the Editor: Left ventricular diastolic dysfunction (LVDD) is an unrecognized subclinical presentation of autoimmune diseases (AD) and carries a worse prognosis. Elevated serum uric acid (SUA), as a proinflammatory factor, is associated with changes in cardiac function in the general population as well as in those with cardiac diseases; however, it has never been investigated in patients with AD. Therefore, we conducted this retrospective study in a large population of patients with a wide spectrum of AD to explore the burden of LVDD and its relationship with quartiles of SUA level.

Patients admitted to the Rheumatology Department (West China Hospital) from January 2011 to December 2017 were screened. They were enrolled if they fulfilled the inclusion criteria, which were determined as the following: (1) having a definite AD diagnosis at discharge; (2) age ≥18 years; (3) having a standard transthoracic echocardiography (TTE) examination; and (4) having at least one SUA measurement during the index hospitalization. The exclusion criteria were the following: (1) confirmed gout; (2) atrial fibrillation or flutter; and (3) structural heart diseases. The study was approved by the Ethics Committee of West China Hospital, Sichuan University (No. 2017–479).

Data were extracted from the hospital information system according to the unique patient identifier (PID) (if one PID had multiple records of hospitalization, the first record was taken). Clinical data included demographics, blood pressure (BP) at admission, last laboratory tests before discharge, AD diagnosis, comorbidities, and medication recorded in the discharge summary. Hyperuricemia was defined as SUA >420 μmol/L.[1] Echocardiographic data were extracted from the TTE report, including (1) left ventricular dimension (LVD), thickness (i.e., interventricular septal [IVS] and left ventricular posterior wall [LVPW]), mass (LVM), and ejection fraction (LVEF); (2) LA dimension (LAD); (3) Doppler-derived transmitral E wave divided by mitral annular e' (E/e'); and (4) any positive comment in the report, including LA enlargement (LAE), LV hypertrophy (LVH), pericardial effusion, pulmonary hypertension, and valvular lesions. With LV thickness, LA size or E/e' being related to LV diastolic function, LVDD was defined as (1) E/e' ≥ 13; or (2) coexisting LVH and LAE if E/e' < 13 in those patients with an LVEF ≥ 50%.[2]

Data analysis was performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the means ± standard deviations or medians (interquartile ranges) when appropriate. Categorical variables are shown as frequencies (percentages). Differences among SUA quartiles were assessed using the χ^2 test for categorical variables, by one-way analysis of variance with Fisher least significant difference *post hoc* analysis for normally distributed variables, or by the Kruskal–Wallis *H* test with Dunn–Bonferroni *post hoc* tests for nonnormally distributed variables. Comparisons between patients with and without LVDD were performed using Student *t* test and the chi-square test, and those variables associated with LVDD with a *P* value of ≤0.20 were selected into the multivariate logistic regression model using the enter method to identify the factors related to LVDD. A *P* value of <0.05 was considered statistically significant.

A total of 5873 patients (aged 45 ± 16 years, 78.9% female) were included. Systemic lupus erythematosus (SLE) (1726, 29.4%) and rheumatic arthritis (RA) (1171, 20.2%) were the leading types of AD, and the remaining types are displayed in [Supplementary Figure 1A, http://links.lww.com/CM9/A861]. As shown in [Supplementary Figure 1B, http://links.lww.com/CM9/A861], an LVEF < 50% (42 ± 6%) was observed in 92 (1.6%) patients. LVDD+ was identified in 1570 (26.7%) patients. The remaining 4211 (71.7%) patients who had isolated LVH, isolated LAE, or none of the features of LVDD were categorized as LVDD–. Meanwhile, valvular

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lesions were observed in 1278 (21.8%) patients, predominately a mild regurgitation. Pericardial effusion was found in 891 (15.2%) patients, 88.2% of which was mild. Pulmonary hypertension was detected in 244 (4.2%) patients and was mild in 85 (34.8%), moderate in 95 (38.9%), and severe in 64 (26.2%) patients.

The mean SUA of the study population was 300 ± 115 μmol/L (ranging from 49 μmol/L to 996 μmol/L). The patients were divided into four groups according to the quartiles of SUA, i.e., the first quartile of SUA of total patients (Q1) (49–222 μmol/L, $n = 1461$), the second quartile of SUA of total patients (Q2) (223–283 μmol/L, $n = 1468$), the third quartile of SUA of total patients (Q3) (284–362 μmol/L, $n = 1469$), and the fourth quartile of SUA of total patients (Q4) (363–996 μmol/L, $n = 1472$). A total of 802 (54.5%) patients in Q4 were labeled as having hyperuricemia. The percentages of males, hypertension, angiotensin-converting-enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), SUA-lowering drugs, and BP showed increasing trends from Q1 to Q4. The proportion of renal insufficiency was the highest, whereas the use of disease-modifying anti-rheumatic drugs (DMARDs), cytotoxic drugs, or nonsteroid anti-inflammatory drugs (NSAIDs) was the lowest in Q4. More patients with diabetes were found in Q1 and Q4 than in Q2 or Q3. Higher C-reactive protein (CRP) levels were observed in Q1 and Q4, while the erythrocyte sedimentation rate (ESR) was the highest in Q1 and decreased from Q1 to Q4. Age and the use of glucocorticoids were comparable among groups. With regard to TTE parameters, LAD, LVD, and LVM progressively increased from Q1 to Q4. IVS and LVPW were thicker in Q3 and Q4 than in Q1 and Q2, while a lower LVEF and a higher E/e' were only observed in Q4 [Supplementary Table 1, http://links.lww.com/CM9/A861]. From Q1 to Q4, the prevalence rates of LVDD were 318 (21.7%), 372 (25.4%), 396 (26.9%), and 533 (36.2%) in Q1 to Q4 ($P < 0.05$), respectively.

When comparing the LVDD+ and LVDD− groups, the LVDD+ group had older patients with higher BP, CRP, and SUA, more female patients, more patients with hypertension, diabetes, renal dysfunction, and hyperuricemia, and more patients treated with glucocorticoids, DMARDs, ACEI/ARBs, and CCBs (all $P < 0.001$). However, there were no differences in the ESR and the use of cytotoxic drugs, NSAIDs, or SUA-lowering drugs [Supplementary Table 2, http://links.lww.com/CM9/A861]. When the variables with $P \leq 0.20$ in the aforementioned intergroup comparisons were included in a multivariate regression analysis (Model I), the adjusted odds ratio (OR) of LVDD increased with a higher level of SUA [Table 1]. Notably, hypertension was a major comorbidity leading to LV diastolic dysfunction, and another regression model (Model II) was established by excluding patients with known hypertension and hypertension as covariates accordingly. The same trend was observed in Model II [Table 1]. Furthermore, if hyperuri-cemia was adopted instead of the quartiles of SUA in the regression models, the ORs were 1.408 in Model I and 1.447 in Model II (both $P < 0.001$).

This study revealed that LVDD was the most common abnormality observed by TTE, affecting one-third of the patients with AD. Emerging evidence supports that AD *per se* could increase LV stiffness via the development of atherosclerosis, endothelial dysfunction, and myocardial fibrosis. Common risk factors for LVDD seen in the general population, i.e., age, sex, hypertension, diabetes, and renal insufficiency, were also found to be significant in the present study. Notably, AD patients with hypertension carried the highest risk of LVDD, more than twice that in

Table 1: Multiple logistic regression analysis of independent impact factors of LVDD.

Items	LVDD (Model I)		LVDD (Model II)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.045 (1.040–1.050)	<0.001*	1.047 (1.042–1.052)	<0.001*
Sex (female)	1.907 (1.599–2.275)	<0.001*	1.938 (1.627–2.308)	<0.001*
Hypertension	2.235 (1.856–2.936)	<0.001*	-	-
Diabetes mellitus	1.263 (0.991–1.610)	0.059	1.323 (1.041–1.681)	0.022
Renal insufficiency	1.329 (1.001–1.765)	0.049*	1.438 (1.086–1.905)	0.011
CRP	1.002 (1.000–1.003)	0.062	1.002 (1.000–1.004)	0.015
Glucocorticoids	1.231 (1.021–1.484)	0.033*	1.190 (0.988–1.433)	0.067
DMARDs	0.982 (0.852–1.131)	0.846	0.975 (0.847–1.123)	0.728
ACEI/ARB	1.333 (1.080–1.645)	0.003*	1.834 (1.518–2.216)	<0.001*
CCB	1.367 (1.071–1.743)	0.012*	2.378 (1.965–2.878)	<0.001*
SUA				
Q1 (49–222 μmol/L)	Ref		Ref	
Q2 (223–283 μmol/L)	1.281 (1.051–1.561)	0.014*	1.273 (1.046–1.550)	0.016
Q3 (284–362 μmol/L)	1.353 (1.110–1.651)	0.003*	1.391 (1.142–1.694)	0.001
Q4 (363–996 μmol/L)	1.777 (1.455–2.170)	<0.001*	1.840 (1.509–2.243)	<0.001

* $P < 0.05$. ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; CCBs: Calcium channel blockers; CRP: C-reactive protein; DBP: Diastolic blood pressure; DMARDS: Disease-modifying anti-rheumatic drugs; LVDD: Left ventricular diastolic dysfunction; OR: Odds ratio; Q1: The first quartile of SUA of total patients; Q2: The second quartile of SUA of total patients; Q3: The third quartile of SUA of total patients; Q4: The fourth quartile of SUA of total patients; SUA: Serum uric acid.

those without hypertension, and the OR was similar to that in the general population.[3] Therefore, BP control is always the cornerstone of prevention and management for heart failure in AD patients. As previously reported, SUA was related to the development of osteoarthritis and renal dysfunction in SLE and RA.[4] This study proposed the link between SUA and the presence of LVDD in patients with a wide spectrum of AD. As a mediator of inflammation and atherosclerosis, further confirmation is needed to ascertain whether elevated SUA might strengthen the association between AD and target organ damage. SUA-lowering drugs have been shown to decrease cardiovascular events[5]; however, it remains unknown whether these drugs could prevent or improve LVDD.

There are some limitations of our retrospective study, such as data selection bias or unavailable duration of medication. Due to the lack of follow-up, the observed relationship between SUA and LVDD could not be regarded as a causal effect, and its prognostic value could not be reflected in cardiovascular events.

In conclusion, LVDD was a predominant echocardiographic abnormality in AD patients. In addition to traditional cardiovascular risk factors, elevated SUA was independently associated with the presence of LVDD. Further investigation is warranted to determine whether the control of SUA would prevent or reverse LVDD.

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Conflicts of interest

None.

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