

Prediction of subclinical left ventricular dysfunction by speckle-tracking echocardiography in patients with anti-neutrophil cytoplasmic antibody--associated vasculitis

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ABSTRACT

Objectives: This study aims to evaluate left ventricular functions using speckle-tracking echocardiography (STE) in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Patients and methods: Between June 2018 and July 2019, a total of 31 AAV patients (17 males, 14 females; median age: 53 years; range, 47 to 62 years) and 21 healthy controls (11 males, 10 females; median age: 56 years; range, 46 to 60 years) were included in the study. Clinical and biochemical characteristics of all participants were recorded. All participants underwent conventional and two-dimensional STE. The receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of serum N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) that predicted subclinical left ventricular dysfunction. The Spearman correlation analysis was used to determine the correlation between left ventricular global longitudinal strain (LV-GLS) and NT-pro-BNP.

Results: The LV-GLS was lower in AAV patients (19.3% vs. 21.7%, respectively; $p=0.014$). NT-pro-BNP was negatively correlated with LV-GLS ($p=0.005$, $r=0.401$).

Conclusion: Subclinical left ventricular dysfunction can be detected by STE in patients with AAV who have free of clinically overt cardiovascular disease. The LV-GLS is negatively correlated with serum NT-pro-BNP levels.

Keywords: Anti-neutrophil cytoplasmic antibody-associated vasculitis, cardiovascular risk, speckle-tracking echocardiography, strain.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by small vessel inflammation, showing similar findings on renal histology.¹ It includes microscopic polyangiitis (MPA), granulomatosis polyangiitis (GPA), and eosinophilic granulomatosis polyangiitis (EGPA). Although patients with AAV

commonly present with involvement of airways, pulmonary system, gastrointestinal tract and renal system, some AAV patients may present with cardiovascular involvement.² Clinically overt cardiac manifestations in AAV are rare, but if present, they are associated with poor prognosis.³ Despite the increased survival rates

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after introducing immunosuppressive treatment, the leading cause of mortality after the first year is cardiovascular disease (CVD). The risk of coronary heart disease is increased by two or four folds in AAV patients, compared to the healthy population. Approximately 14% of patients undergo major cardiovascular events within five years after the diagnosis of AAV.^{4,5} Therefore, there is a need for a novel tool to predict development and presence of CVD in these patients.

Conventional echocardiography is used to evaluate myocardial deformation and to assess global and regional myocardial strain. However, it cannot detect subclinical myocardial disease. In recent years, speckle-tracking echocardiography (STE) has emerged as a novel technique for diagnosing subclinical myocardial disease, particularly at an earlier stage.^{6,7} In this study, we aimed to investigate subclinical left ventricular dysfunction using STE in AAV patients.

PATIENTS AND METHODS

Study population

This cross-sectional study was conducted at Marmara University, Faculty Medicine, Department of Nephrology, Cardiology and Rheumatology between June 2018 and July 2019. Patients between the ages of 18 and 75 years with a clinical diagnosis of GPA or MPA, and ANCA positivity (with PR3 or MPO specificity) were included in the study. Patients with heart failure, cardiomyopathy, coronary and valvular heart disease, arrhythmia, peripheral arterial disease, end-stage renal disease or malignancy were excluded from the study. Finally, a total of 31 AAV patients (17 males, 14 females; median age: 53 years; range, 47 to 62 years) and 21 healthy controls (11 males, 10 females; median age: 56 years; range, 46 to 60 years) were included in the study. Demographic data and medical history including disease duration, ANCA type, activity and chronicity scores, past and current immunosuppressive treatment were recorded. Fasting glucose, hemoglobin A1c (HbA1c), troponin T, serum N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), lipid profile, routine biochemical tests, and complete blood counts were measured. A written informed

consent was obtained from each participant. The study protocol was approved by the institutional review board of Marmara University, Faculty Medicine (date/no: 2018/09.2018.653). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Echocardiographic evaluation

Two independent cardiologists performed all echocardiographic measurements using the Philips iE33 echocardiography system (Philips Medical Systems, Andover, MA, USA), according to the American Society of Echocardiography (ASE) guidelines.⁸ Images were at a breath-hold from three consecutive beats and transferred into the QLAB Philips off line software (Philips Healthcare Medical Imaging System, Andover, MA, USA). Multidirectional analysis of left ventricle speckle-tracking was also performed using 2D STE.⁹ The change in the position of the speckles within a myocardial segment was used to calculate myocardial strain. Left ventricular global longitudinal strain (LV-GLS) was assessed in the apical two, three, and four-chamber views of the left ventricle, which was divided into six segments in each apical view. The average of the six measurements was recorded to obtain LV-GLS.

Statistical analysis

Statistical analysis was performed using the SPSS version 15.1 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in median and interquartile range (IQR), while categorical variables were expressed in number and frequency. The Kolmogorov-Smirnov or Shapiro-Wilk test was performed to determine whether continuous variables distributed normally. The Chi-square test and Fisher exact were used to compare categorical variables. Continuous variables were compared using the Mann-Whitney U test. The receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of the NT-pro-BNP with specificity and sensitivity that predicted subclinical left ventricular dysfunction. The Spearman correlation analysis was used to determine the correlation between LV-GLS and NT-pro-BNP. A *p* value of <0.05 was considered statistically significant.

Table 1. Demographic, clinical, and laboratory data of study population

	Patients group (n=31)				Control group (n=21)				p
	n	%	Median	IQR	n	%	Median	IQR	
Age (year)			53	15			56	14	0.949
Sex									
Male	17	54.8			11	52.4			0.862
Body mass index (kg/m ²)	27.8	6.7			27.3	4.6			0.478
Hypertension	14	45.2			1	4.8			0.001
Smoking	2	6.5			3	1.3			0.383
Diabetes mellitus	4	12.9			1	4.8			0.514
Glucose (mg/dL)			91	18			90	12	0.699
Creatinine (mg/dL)			1.06	1.28			0.70	0.24	<0.001
Total cholesterol (mg/dL)			223	53			201	46	0.130
Low-density lipoprotein cholesterol (mg/dL)			127	40			128	53	0.407
High-density lipoprotein cholesterol (mg/dL)			51	23			52	18	0.794
Triglyceride (mg/dL)			194	107			104	117	0.019
C-reactive protein (mg/L)			3.23	2.82			3.13	0.10	0.032
Troponin T-hs (ng/L)			7.57	9.2			5.45	2.43	0.137
NT-pro-BNP (pg/mL)			141	182.2			3.48	49.9	<0.001
Duration of disease			36	73	-				-
Positive p-ANCA	12	38.7			-				-
Positive c-ANCA	18	58.1			-				-
Granulomatosis/microscopic	20/11				-				-
Birmingham Vasculitis Activity Score	2	2			-				-
Vasculitis Damage Index	3	3			-				-

IQR: Interquartile range; hs: High sensitive; NT-pro-BNP: N-terminal prohormone of brain natriuretic peptide; p-ANCA: Perinuclear anti-neutrophil cytoplasmic antibody; c-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibody.

Table 2. Conventional echocardiographic and speckle-tracking measurements of study population

	Patients group (n=31)		Control group (n=21)		p
	Median	IQR	Median	IQR	
LVEDD (mm)	48.5	6	47.0	9.5	0.570
LVESD (mm)	31.5	5	31.0	6	0.834
Ejection fraction (%)	58.5	8	60.0	8.7	0.796
Interventricular septum (mm)	11	2	10	1	0.044
Posterior wall (mm)	10	2	9	2	0.032
Left atrial diameter (mm)	33	7	31	5	0.905
Systolic PAP (mmHg)	30	18	27	15	0.564
E (m/s)	0.81	0.58	0.91	0.50	0.804
A (m/s)	0.86	0.40	1.02	0.40	0.206
DT (ms)	169	45	151	52	0.507
E' (cm/s)	11.0	6	10.5	6	0.781
A' (cm/s)	10	6	10	4	0.689
E/E'	8.8	3.4	8.9	3.8	0.992
RV s' (cm/s)	12	2	12	2	0.492
TAPSE (mm)	23.5	4	23.0	3	0.928
LV-GLS (%)	19.3	4.5	21.7	4.7	0.014
RV-GLS (%)	22.2	5	21.7	3.7	0.572

IQR: Interquartile range; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; PAP: Pulmonary artery pressure; DT: Deceleration time; RVs': Right ventricular systolic velocity; TAPSE: Tricuspid annular plane systolic excursion; LV-GLS: Left ventricular global longitudinal strain; NS: Non-significant; RV-GLS: Right ventricular global longitudinal strain; Data are presented in median (IQR).

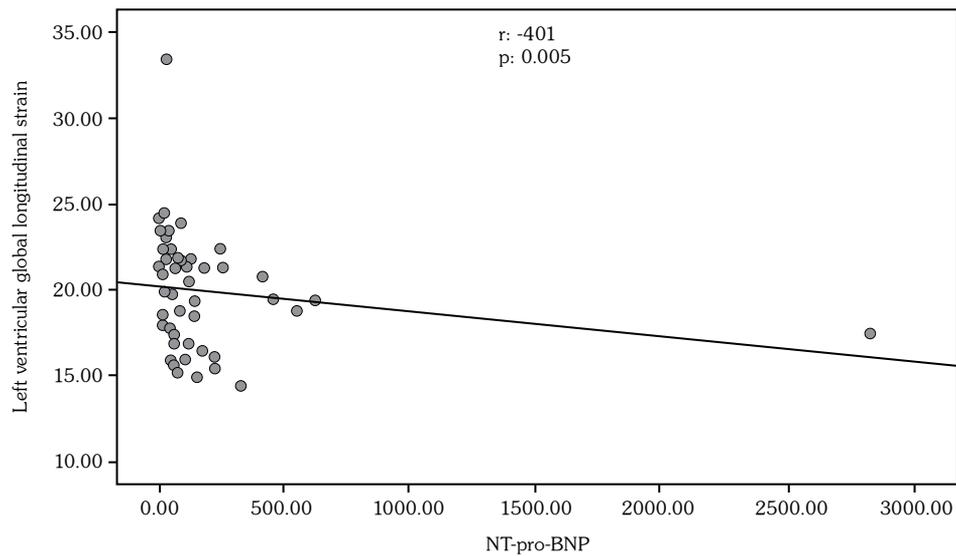


Figure 1. Correlation analysis showing that LV-GLS is inversely correlated with NT-pro-BNP.

LV-GLS: Left ventricular global longitudinal strain; NT-pro-BNP: N-terminal prohormone of brain natriuretic peptide.

RESULTS

Of 31 patients with AAV, 20 (64.5%) had GPA and 11 (35.5%) had MPA. Sex and age were similar between the study groups. Median disease duration was 36 (range, 18 to 91) months. The frequency of hypertension, serum triglyceride, creatinine, C-reactive protein (CRP),

and NT-pro-BNP levels were higher in AAV patients, while low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were comparable between the two groups. Baseline demographic, clinical, and laboratory data of the study population are shown in Table 1.

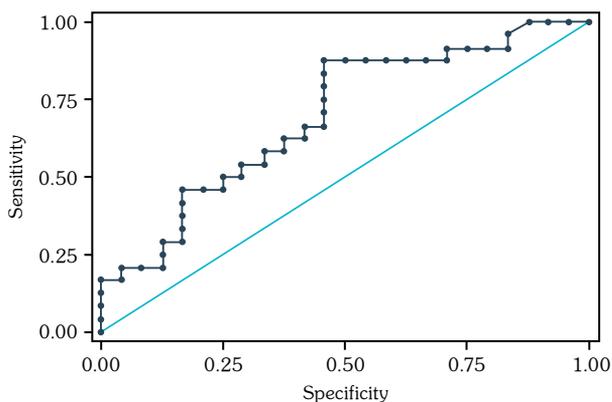


Figure 2. The ROC curve showing that NT-pro-BNP >42.5 pg/mL can predict subclinical myocardial dysfunction with 87.5% sensitivity and 69.5% specificity (Area under ROC curve = 0.695 (95% CI: 0.544-0.846).

ROC: Receiver operating characteristic; NT-pro-BNP: N-terminal prohormone of brain natriuretic peptide.

Conventional echocardiographic and speckle-tracking measurements are presented in Table 2. While the median LV-GLS was lower in AAV patients (19.3% vs. 21.7%, respectively; $p=0.014$), interventricular thickness (11 mm vs. 10 mm, respectively; $p=0.044$) and posterior wall thickness (10 mm vs. 9 mm, respectively; $p=0.032$) were higher in the patients with AAV compared to healthy controls. Correlation analysis showed that LV-GLS was negatively correlated with NT-pro-BNP ($p=0.005$, $r=0.401$) (Figure 1). The cut-off LV-GLS value of left ventricular dysfunction was considered 20% based on the ASE guidelines. The ROC analysis revealed that a NT-pro-BNP of >42.5 pg/mL could predict subclinical left ventricular dysfunction with 87.5% sensitivity and 69.5% specificity (area under curve [AUC]: 0.695, 95% CI: 0.544-0.846) (Figure 2).

DISCUSSION

The current study demonstrated that LV-GLS was significantly reduced and NT-pro-BNP measurements increased in the patients with AAV compared to healthy controls. Since CVD is the most common cause of mortality in AAV patients, several studies have investigated cardiac involvement and left ventricular function in AAV patients. They have shown that overt clinical cardiac involvement is rare, and left ventricular ejection fraction is commonly preserved.^{10,11} Miszalski-Jamka et al.¹¹ conducted a study in GPA patients to evaluate myocardial function by STE and compared left ventricular global longitudinal, circumferential, and radial strain of patients with age- and sex-matched controls. The authors reported that global radial strain (GRS), global circumferential strain (GCS), and LV-GLS were lower in GPA patients than healthy controls. Similarly, we showed that LV-GLS decreased in the AAV patients. The exact underlying mechanism of systolic dysfunction in these patients still remains unclear. Decreased LV-GLS may lead to subclinical myocardial dysfunction in patients with AAV, despite normal baseline physical examination, electrocardiogram, and conventional transthoracic echocardiography. Of note, AAV is characterized by significant vascular inflammation in small vessels, and systemic inflammation has recently been associated with endothelial dysfunction.¹² Endothelial dysfunction may lead to chronic ischemia and microvascular dysfunction and be responsible for the subclinical myocardial dysfunction in these patients.¹³ In our study, there was a significant impairment only in the LV-GLS, but not in the GCS measurements. Since subendocardial longitudinal fibers are commonly responsible for longitudinal deformation and mid-myocardial circumferential fibers are accountable for radial and circumferential shortening, these findings suggest that subendocardial fibers are affected earlier than mid-myocardial fibers. However, the preserved GCS in the present study cannot rule out the involvement of the mid-myocardial layer. Indeed, there are a few studies and case reports using cardiac magnetic resonance imaging (MRI) showing that all myocardial layers might be affected in AAV patients.^{14,15}

The NT-pro-BNP is used to diagnose and manage heart failure and many CVD.^{16,17} It

has been already proven that NT-pro-BNP is associated with morbidity and mortality in various cardiac conditions.¹⁸ In the current study, NT-pro-BNP significantly increased in the AAV patients. There are several potential explanations for this finding. First, the increased NT-pro-BNP levels may precede atherosclerosis development and, thus, identify patients with silent vascular disease who may be at risk for accelerated atherosclerosis. Second, elevated NT-pro-BNP concentrations may be due to subclinical myocardial dysfunction. Indeed, the NT-pro-BNP concentration was inversely correlated with LV-GLS in our study. Another potential explanation for the elevated NT-pro-BNP concentrations and subclinical myocardial dysfunction in AAV patients is kidney disease. Since the majority of AAV patients have kidney involvement to a varying extent, this may have played a role, despite excluding patients with overt uremia. The ROC analysis demonstrated that a cut-off value of 42.5 pg/mL for NT-pro-BNP could predict subclinical myocardial dysfunction with a sensitivity of 87.5% and specificity of 69.5%. We believe that the low specificity may be associated with the confounding effect of kidney involvement.

Several studies have previously shown that traditional cardiovascular risk factors, including dyslipidemia, hypertension, and metabolic syndrome, are more common in AAV patients.^{19,20} In our patient cohort, the prevalence of hypertension was more common, as expected. There was no significant difference in LDL-C and HDL-C levels between the patient and control groups; however, triglyceride levels were higher in the patient group. Petermann Smits et al.²⁰ previously demonstrated that metabolic syndrome increased in AAV patients. They also reported that LDL-C and triglyceride levels were similar, whereas HDL-C levels increased in these patients. In addition to traditional risk factors, endothelial dysfunction due to vascular inflammation may also contribute to increased atherosclerosis in vasculitis. The CRP is a marker of systemic inflammation and is defined as an independent prognostic factor for atherosclerotic disease. Although most of the patients were in remission in our study, CRP levels were still significantly higher than controls. Thus, CRP might be another link between vasculitis, characterized by systemic inflammation, and accelerated CVD.²¹ However,

the question of whether this reflects a higher prevalence of CVD in the vessel wall or vasculitis activity needs further investigation.

The main limitations of the current study are the cross-sectional design and relatively small sample size. We also did not use an additional functional imaging tool, such as cardiac MRI or nuclear imaging. However, both nuclear imaging and cardiac MRI are not yet feasible and reproducible for daily clinical practice. Furthermore, the patients were not followed and there was no follow-up for incident cardiovascular events. Despite the exclusion of patients with evident coronary artery disease and kidney involvement, there were probably patients with subclinical cardiac and kidney disease, which could have affected STE and NT-pro-BNP measurements. The use of immunosuppressive medications, including steroids, was another confounding factor. Finally, since most AAV patients were in remission, we could not evaluate the effect of active disease on STE parameters.

In conclusion, our study results show that LV-GLS measurements are lower in AAV patients than healthy individuals. While STE can be used for detecting subclinical myocardial dysfunction, NT-pro-BNP measurement is a simple method in identifying patients at high risk. These preliminary data suggests that conventional echocardiography may underestimate the risk of CVD in AAV patients.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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