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Immunological and inflammatory processes in systemic autoimmune disease may not only cause pericardium inflammation, but may also cause mitral valve deterioration and left ventricular wall thickening

Atsushi Sugiura [1], Nobusada Funabashi *[,1], Koya Ozawa, Yoshio Kobayashi

Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba City, Chiba 260-8670, Japan

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ABSTRACT

Purpose: Systemic autoimmune disease (SAD) frequently affects the pericardium, and pathology is characterized by both immunological and inflammatory processes. We hypothesized that these processes simultaneously influence mitral-valve (MV) deterioration and left-ventricular (LV) wall thickening in SAD subjects.
Methods: 101 SAD subjects were selected (76 female; 53 ± 17 years; systemic-lupus-erythematosus, 26%; vasculitis, 20%; scleroderma, 14%; polymyositis/dermatomyositis complex, 10%; mixed connective tissue disease, 11% and rheumatoid-arthritis, 2%). MV anterior-mitral-leaflet (AML) length, AML thickness index, AML doming height and LV mass index (LVMI) were measured using transthoracic-echocardiography (TTE) and the presence of MV calcification, MV sub-valvular thickening and pericardial effusion (PE) were estimated. AML thickness index was calculated as the ratio of AML thickness to aortic posterior wall thickness. The correlation between LVMI and ECG V1S + V5R voltage was used to assess the etiology of LV wall thickening.
Results: 19 subjects (19%) had significant PE. PE subjects had a significantly greater AML thickness index (1.55 ± 0.48 vs. 1.14 ± 0.32, $P < 0.001$), AML doming height (1.26 ± 1.54 mm vs. 0.03 ± 0.91 mm, $P < 0.001$), more frequent MV sub-valvular thickening (26% vs. 5%, $P = 0.003$) and greater LVMI (104.7 ± 34.6 g/m2 vs. 80.6 ± 21.0 g/m2, $P = 0.002$). Significant correlation was observed between LVMI and ECG V1S + V5R voltage in 79 subjects without PE ($R = 0.39$, $P < 0.001$). However, in 18 subjects with PE, no such correlation was observed ($R = 0.30$, $P = 0.23$).
Conclusions: MV, MV sub-valvular deterioration and increased LVMI, unrelated to high voltage ECG criteria, were frequently detected in SAD subjects with PE. Immunological and inflammatory processes in SAD may not only cause pericardium inflammation, but may also cause MV deterioration and LV wall thickening.

1. Background

Systemic autoimmune diseases (SAD) occur when the host immune system attacks healthy tissue and may occur in multiple tissue types and organs [1]. Published articles report that SAD subjects with cardiac involvement are at greater risk of death and that primary cardiac involvement is a risk factor for the occurrence of further advanced cardiac involvement [2].

The most common cardiac involvement in SAD subjects is at the pericardium and generally reflects autoimmune and inflammatory activities of an underlying disease [2–8]. Pericardial effusion (PE) in SAD subjects has been well documented by echocardiography and may be used as a representative indicator of pericardial involvement [1]. Left ventricular (LV) wall thickening and mitral valve (MV) deterioration may also occur in SAD subjects [4,6,9–11]. Furthermore, MV deterioration often causes significant valvular regurgitations that may lead to heart failure [12,13].

We hypothesized that in SAD subjects pericardial immunological and inflammatory processes, in which significant PE is shown, may simultaneously affect MV deterioration and LV wall thickening (not LV hypertrophy).

In this study, we have used TTE to evaluate the clinical consequences of significant PE in SAD subjects.

2. Material and methods

2.1. Study design

This is a retrospective analysis of 111 consecutive SAD subjects who presented to our hospital and underwent TTE (Vivid E9, GE Healthcare or iE33, Philips) between April 2013 and May 2015. Eight subjects who produced inadequate images and two subjects with atrial fibrillation were excluded. The remaining 101 SAD subjects (76 female (75%); 53 ± 17 years, systemic lupus erythematosus, 26%; vasculitis,

* Corresponding author.
E-mail address: nobusada@w8.dion.ne.jp (N. Funabashi).
[1] These authors contributed equally to this work.

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20%; systemic sclerosis, 14%; mixed connective tissue disease, 11%; polymyositis/dermatomyositis complex, 10%; and rheumatoid arthritis, 2%) were analyzed.

All subjects underwent comprehensive TTE as part of our standard management plan for SAD patients. Significant PE was defined as 'equal to' or 'more than' trivial PE (seen only in systole), as determined by the American Society of Echocardiography [14].

In addition to our standard TTE measurements, we assessed MV morphology and function (including the MV itself) and MV subvalvular components using a parasternal long axis view during the end-diastole (Fig. 1). The MV anterior mitral leaflet (AML) length, AML thickness index, and AML doming height were also measured. AML thickness index was calculated as the ratio of AML thickness to aortic posterior wall thickness. AML doming height is regarded as an indicator of AML motion since it increases when MV motion decreases due to MV deterioration, such as that observed in MV stenosis.

Posterior mitral leaflet (PML) length was also measured. However, due to technical difficulties, PML thickness and PML doming height are not reported. To minimize the effects of gain setting, AML thickness was normalized to the posterior of the aortic root. Furthermore, we qualitatively evaluated the presence of MV calcification and MV subvalvular thickening.

We also measured LV mass index (LVMI), a more accurate indicator of LV wall thickening than intraventricular septal thickness in end-diastole, and LV posterior wall thickness in end-diastole. The correlation between LVMI and ECG V1S + V5R voltage was evaluated to assess the etiology of LV wall thickening, i.e. to determine whether LV wall thickening is due to LV hypertrophy or inflammation.

2.2. Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared with the Student t-test or the Wilcoxon signed-rank test as appropriate. Categorical variables were compared by $\chi 2$ analysis or Fisher's Exact test as appropriate. The Pearson correlation was used to quantify the association between continuous variable parameters.

In multiple regression analysis for predicting AML thickness index (model 1) or AML doming height (model 2) as a dependent variable, five selected variables, those were age, sex female, chronic kidney disease (CKD), c-reactive protein (CRP), and the presence of significant PE, were included since they may relate to the degree of inflammation with a possible but no strong correlation with each other.

3. Results

All 101 subjects revealed sinus rhythm during TTE acquisitions. Nineteen subjects (19%) had significant PE on TTE. We then divided the 101 subjects into 2 groups according to the presence or absence of significant PE (patients with significant PE (N = 19) and those without significant PE (N = 82).

3.1. Clinical and laboratory characteristics

Table 1 describes baseline clinical characteristics and diagnosis while Table 2 defines baseline laboratory data in this study population. The frequency of hypertension that affects occurrence of LV wall thickening tended to be greater in the subjects with significant PE than in those without significant PE, although the difference was not statistically significant (P = 0.075). Serum brain natriuretic peptide concentration was significantly higher in significant PE subjects than in those without significant PE (208.0 ± 454.2 versus 69.1 ± 202.7 pg/mL, P < 0.041). There were no significant differences between other serum parameters in these subjects.

Fig. 2 describes the distribution of corticosteroid dosage categories in subjects with and without significant PE. There were no significant differences between categories in this grouping (P = 0.840).

3.2. TTE data

Conventional TTE parameters in SAD subjects, with or without significant PE, are reproduced in Table 3.

End diastolic interventricular septal thickness and LV posterior wall thickness plus LVMI, left atrial (LA) dimensions, LA volume index, mitral E, mitral E/E′, and estimated systolic pulmonary arterial pressure were significantly increased in subjects with significant PE relative to those without significant PE. Mitral E′ was significantly reduced in subjects

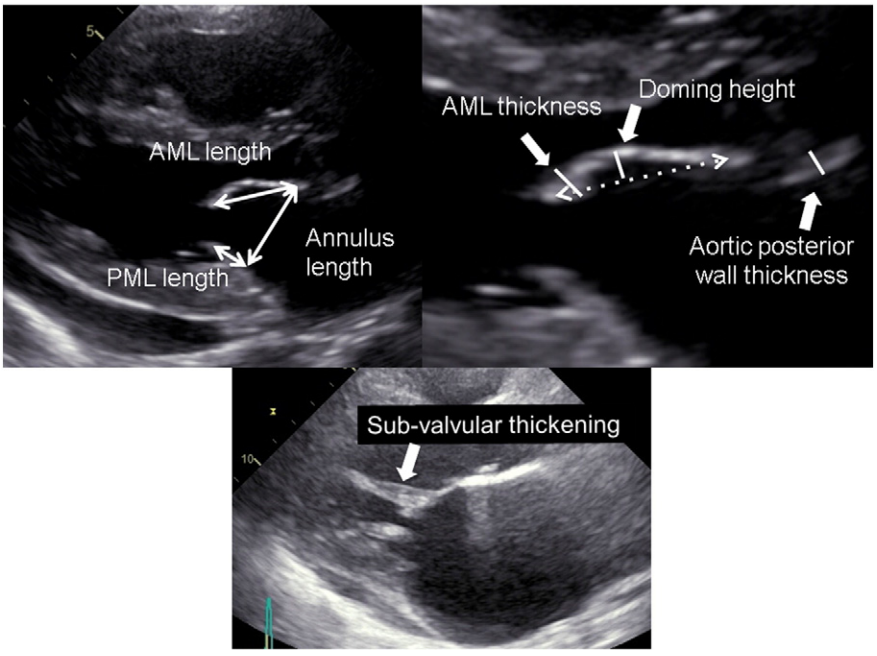

Fig. 1. Actual transthoracic echocardiogram measurement of the mitral valve (MV) leaflet at end-diastole in the parasternal long axis view. Upper Left Figure: Anterior (AML) and posterior mitral leaflet (PML) and annuls length of MV were measured. Upper Right Figure: AML thickness, AML doming height, and aortic posterior wall thickness were measured. AML thickness index was calculated as the ratio of AML thickness to that of the aortic posterior wall thickness. Lower Figure: Typical image of MV sub-valvular thickening.