Features of cardiac remodeling in Patients with Acute Coronary Syndrome Complicated with Rheumatoid Arthritis

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Cardiovascular diseases are important factors to increased morbidity and mortality in patients with rheumatoid arthritis (RA). The aim of this study is to investigate the effects of RA on cardiac remodeling in patients with acute coronary syndrome (ACS). Sixty-one patients with ACS complicated with RA (RA group) and 55 age- and sex-matched patients with ACS without RA (control group) were enrolled. We compared the parameters of laboratory and echocardiogram across the 2 groups. Levels of serum brain natriuretic peptide in patients with RA were significantly higher than control group. Prevalence of left ventricular hypertrophy (LVH), and LV diastolic dysfunction (E/A < 1) were significantly higher in the RA patients, while the LV ejection fraction (EF%) was significantly lower in RA patients. Incidence of tricuspid regurgitation and pulmonary regurgitation were significantly higher in ACS patients with RA than in the ACS patients without RA. In RA group, levels of serum high density lipoprotein cholesterol were negatively correlated with C reactive protein (CRP). EF% was also negatively correlated with CRP. The prevalence of LVH and mitral regurgitation showed positive correlations with ESR. Early intervention for controlling the inflammation associated with RA can play a significant role in preventing cardiac remodeling in ACS patients.

Materials and Methods

Subjects. A retrospective cross-sectional study was performed. Sixty-one patients with ACS complicated with RA (RA group) were recruited from January 2012 to December 2015 in Beijing Anzhen Hospital, Capital Medical University. 1 |

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University, Beijing, China. All patients fulfilled the classification criteria of RA revised by American College of Rheumatology in 1987. 55 age- and sex-matched ACS patients without RA were recruited as controls. All patients had acute myocardial infarction (AMI) and unstable angina pectoris (UAP), which were diagnosed based on symptoms, physical examination, electrocardiograms, myocardial enzyme determination, echocardiography, and coronary angiography according to the current European Society Cardiology guidelines.

The following medical examinations were performed for all subjects after hospitalization: height, weight, Body Mass Index (BMI) calculated as weight to square of height ratio, and blood pressure. Cardiovascular risk factors include smoking (ever and current), family history of CVD, hypertension, dyslipidemia and diabetes mellitus. Traditional cardiovascular risk factors were defined as: cigarette smoking (in the previous 10 years), hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg), diabetes mellitus (fasting serum glucose >126 mg/dl or use of antidiabetic medications), hyperlipidemia (total cholesterol >200 mg/dL, low-density lipoprotein (LDL-C) >130 mg/dl, triglycerides >130 mg/dl, or high-density lipoprotein (HDL-C) <40 mg/dL).

Patients with the following conditions were excluded from the study: other autoimmune disease, liver and kidney diseases. The informed consent was obtained from all participants and/or their legal guardians. The study was conducted in accordance with the Declaration of Helsinki and this study was approved by the Ethics Committee of Beijing Anzhen Hospital (approval number: 2016012X, Capital Medical University).

Methods
For each subject, 4 ml venous blood was drawn in the morning after a 12-hour fast. The blood was then placed in a tube without anticoagulant, and the serum was collected from the coagulated blood and centrifuged 3000 rpm/min for 5 min. Serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), high sensitive C reactve protein (hs-CRP), homocysteine (HCY), and serum brain natriuretic peptide (BNP) were tested for all patients using an automatic biochemical analyzer (Hitachi 7600-120, Tokyo, Japan).

Echocardiograms were obtained on all the patients preoperatively with use of the Vivid 7 cardiac ultrasound system (GE Ving Med Ultrasound AS; Horten, Norway). Left ventricular end diameter (LVEDd), interventricular septal thickness (IVSd), and left ventricular posterior wall thickness (PWTd) were measured by taking the mean values of three continuous heartbeat cycles in the expiratory state. Then, left ventricular mass (LVM) (g) was calculated with formula: 1.04 \times 0.8 \times [(IVSd + PWTd + LVEDd) – LVEDd^3] + 0.6.

Statistical Methods
Statistical analysis was carried out using SPSS statistical software version 16.0 (SPSS Inc, Chicago, Illinois, USA). Values are expressed as means ± standard error (means ± SEM). Differences between measured parameters in patients and controls were assessed by unpaired t test. The assessment of qualitative parameters was performed by χ^2 test. A level of P < 0.05 was considered to be statistically significant.

Results
Comparison of biochemical parameters and cardiovascular risk factors between ACS patients with or without RA.

In the RA group, 17 were male and 44 were female (age range: from 48 to 80 years; average: 66.44 ± 8.72 years). The mean duration of RA was 18.11 ± 10.74 years. 17 patients had ST-segment elevated myocardial infarction (STEMI) and 23 had non ST-segment elevated myocardial infarction (NSTEMI), 21 had UAP. No difference was observed in type of ACS and treatment of ACS between the 2 groups (Table 1).

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ACS Patients with RA have more prevalence of cardiac morphology and function changes compared with ACS patients without RA.

Table 3 shows the echocardiography characteristics of patients with ACS with and without RA complications. The prevalence of left ventricular hypertrophy (LVH) in the RA group (50.8%) was significantly higher than in the controls (29.1%), (P < 0.05). LVEF% in the patients in the RA group (54.86 ± 12.12%) was significantly lower than that in patients without RA (63.83 ± 5.61%), (P < 0.05). The proportion of patients in the RA group who had left ventricular diastolic dysfunction (E/A < 1) was significantly higher (96.7%) than that of the control group (61.6%), (P < 0.01). About 45.9% of patients with RA were found to have tricuspid regurgitation, which was significantly higher than the proportion in patients with ACS only.
(12.7%), \(P < 0.01\). About 9.8% of patients with RA were found to have pulmonary regurgitation, which was not found in the control group \(P < 0.05\). Comparison of aortic and mitral regurgitation between the two groups showed no statistically significant differences (Table 3).

### Table 1. Comparison of general parameters between patients with ACS complicated with and without RA. STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, UAP: unstable angina pectoris.

| Parameter                  | RA (n = 61) | Control (n = 55) | \(P\) value |
|----------------------------|-------------|-----------------|--------------|
| General demographics       |             |                 |              |
| Age, years                 | 66.44 ± 8.72| 67.03 ± 6.80    | 0.554        |
| Female, n (%)              | 44 (72.1)   | 39 (70.9)       | 0.884        |
| RA duration, years         | 17.11 ± 10.74| —               | —            |
| Type of ACS                |             |                 |              |
| STEMI, n (%)               | 17 (27.9)   | 10 (18.2)       | 0.366        |
| NSTEMI, n (%)              | 23 (37.7)   | 18 (32.7)       | 0.575        |
| UAP, n (%)                 | 21 (34.4)   | 27 (49.1)       | 0.109        |
| ACS Treatment              |             |                 |              |
| Aspirin, n (%)             | 59 (96.7)   | 52 (94.5)       | 0.564        |
| Statins, n (%)             | 55 (90.2)   | 47 (85.4)       | 0.437        |
| β-Blocker, n (%)           | 43 (70.5)   | 42 (76.4)       | 0.475        |
| ACEI/ARB, n (%)            | 27 (45.9)   | 24 (43.6)       | 0.356        |

### Table 2. Comparison of cardiovascular risk factors and Laboratory parameters between patients with ACS complicated with and without RA. BMI: Body Mass Index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglyceride, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, HCY: homocysteine, BNP: brain natriuretic peptide, hs-CRP: high sensitivity C reactive protein. ESR: erythrocyte sedimentation rate.

| Parameter              | RA (n = 61) | Control (n = 55) | \(P\) value |
|------------------------|-------------|-----------------|--------------|
| Cardiovascular risk factors |             |                 |              |
| Ever, n (%)            | 37 (60.1)   | 35 (63.6)       | 0.398        |
| Current, n (%)         | 6 (8.2)     | 5 (9.0)         | 0.774        |
| Family History of CVD, n (%) | 25 (41.0)   | 19 (34.5)       | 0.475        |
| BMI, kg/m\(^2\)        | 27.50 ± 3.53| 24.84 ± 2.36    | 0.044        |
| Hypertension, n (%)    | 35 (57.4)   | 31 (56.4)       | 0.912        |
| Dyslipidaemia, n (%)   | 31 (50.8)   | 30 (54.5)       | 0.688        |
| Diabetes mellitus, n (%)| 25 (41.0)   | 20 (36.3)       | 0.61         |
| SBP, mmHg              | 132.20 ± 19.68| 131.37 ± 13.76 | 0.797        |
| DBP, mmHg              | 79.73 ± 10.81| 77.79 ± 8.59    | 0.565        |
| Laboratory parameters  |             |                 |              |
| TG, mmol/L             | 1.43 ± 0.88 | 1.62 ± 0.68     | 0.297        |
| TC, mmol/L             | 4.37 ± 1.03 | 4.36 ± 0.84     | 0.964        |
| HDL-C, mmol/L          | 0.91 ± 0.20 | 1.10 ± 0.23     | 0.045        |
| LDL-C, mmol/L          | 2.57 ± 0.86 | 2.63 ± 0.67     | 0.689        |
| HCY, mmol/L            | 17.27 ± 4.71| 13.16 ± 4.23    | 0.022        |
| BNP, pg/ml             | 386.31 ± 225.88| 258.43 ± 136.97 | 0.043        |
| hs-CRP, mg/L           | 9.84 ± 5.50 | 4.21 ± 3.25     | 0.002        |
| ESR, mm/1h             | 28.35 ± 15.87| 9.33 ± 3.88     | 0.01         |

Correlations between laboratory and echocardiogram parameters with CRP or ESR in RA patients. Next, we evaluated whether the laboratory and echocardiogram parameters could be correlated to CRP or ESR in the RA group. As shown in Fig. 1, the levels of serum HDL-C were negatively correlated with CRP \(r = -0.401, P = 0.002\), EF\% were negatively correlated with CRP \(r = -0.296, P = 0.025\). The prevalence of LVH \(r = 0.557, P = 0.039\) and mitral regurgitation \(r = 0.761, P = 0.002\) both showed positive correlations with ESR (Fig. 1).
Discussion

This study compared patients with acute coronary syndrome with and without RA. Traditional cardiovascular disease risk factors, laboratory index, and echocardiographic changes of cardiac structure and function of the 2 groups of patients were monitored. Patients with both RA and ACS were more likely to have left ventricular hypertrophy, tricuspid valve and pulmonary valve regurgitation, and cardiac systolic and diastolic dysfunction. In other words, ACS patients with RA were more likely to have changes in cardiac morphology and function.

In this study, among the traditional cardiovascular risk factors, markedly higher levels of BMI were found in ACS patients with RA than those without RA. Previous research has suggested that RA subjects had significantly greater BMI and fat area, and lower muscle area, muscle density, and muscle strength. Another study demonstrated that an increase in RA disease activity causes an increase in BMI via an accumulation of fat tissue. Previous studies have suggested that a decrease in cholesterol is the main characteristic of dyslipidemia in patients with RA. This research showed no difference between the two groups with respect to the levels of serum TG, TC, or LDL-C; but HDL-C levels were significantly lower in the RA group than in controls. In RA patients, serum HDL-C levels were negatively related to RA disease activity. These findings are consistent with the results of our study. Our result suggested that low HDL-C levels negatively correlated with hs-CRP in RA patients. A research showed that the high level of HCY is a predictor of atherosclerotic events in patients with RA, and closely related to cardiovascular events. Our result suggests that high serum HCY level may be an important factor leading to CVD events in ACS patients with RA.

Table 3. Comparison of echocardiography parameters between ACS patients complicated with and without RA. LVH: left ventricular hypertrophy, LVEF: left ventricular ejection fraction.

| Parameter                        | RA (n = 61) | Control (n = 55) | P value |
|----------------------------------|-------------|------------------|---------|
| LVH, n (%)                       | 31 (50.8)   | 16 (29.1)        | 0.017   |
| LVEF %                           | 54.86 ± 12.12| 65.83 ± 5.61     | 0.038   |
| LV diastolic dysfunction, n (%)  | 59 (96.7)   | 35 (61.6)        | 0       |
| Aortic Regurgitation, n (%)      | 13 (21.3)   | 14 (25.5)        | 0.598   |
| Mitral Regurgitation, n (%)      | 24 (39.3)   | 19 (34.5)        | 0.593   |
| Tricuspid Regurgitation, n (%)   | 28 (45.9)   | 7 (12.7)         | 0       |
| Pulmonary Regurgitation, n (%)   | 6 (9.8)     | 0 (0.0)          | 0.017   |

Figure 1. Correlations between HDL-C, EF%, prevalence of LVH and mitral regurgitation with hs-CRP or ESR. HDL-C and EF% were negatively correlated with hs-CRP. (A, B). The prevalence of LVH and mitral regurgitation shows positive correlations with ESR (C, D).
Correlations have established between RA inflammation and left ventricular remodeling. Impairment of cardiac systolic and diastolic function is commonly found in patients with RA. Increased left ventricular (LV) mass in patients with RA has been found to be parallel with the risks of cardiovascular morbidity and mortality. Study suggested that the thickness of LV relative wall is independently associated with RA disease activity. The “gold standard” for left ventricular hypertrophy (LVH) is left ventricular mass index (LVMI) on echocardiogram in our study, to exclude the influence of individual differences and accurately reflect the degree of hypertrophy, LVMI was adopted to evaluate left ventricular remodeling. Our results showed that 50.8% ACS patients with RA had LVH, which was significantly higher than those without RA (29.1%). Moreover, the prevalence of LVH exhibited a positive correlation with ESR in RA patients.

Vácular abnormalities mainly involving the mitral and aortic valve with mild to moderate regurgitation in RA patients, the mechanisms might be due to the chronic inflammatory process and fibrosis of the cardiac valves. Our results showed that the prevalence of mitral regurgitation was slightly more than that of the control group, but the difference was not significant between 2 groups, we found the prevalence of mitral regurgitation was correlated with ESR in RA patients. The proportion of patients with RA who had tricuspid and pulmonary valve regurgitation was significantly higher than that of the control group. This finding has not been reported in past research, and the mechanism is unclear and needs further exploration.

In RA patients, the asymptomatic reduction in cardiac systolic function is about 3 times more than non-RA population. Study has suggested that RA patients with reduced LVEF% are less likely received antirheumatic drugs such as methotrexate and corticosteroids. Our results showed the mean value of EF% significantly lower in patients with RA, and negatively correlated with hs-CRP. Moreover, patients with RA were more likely to present with diastolic cardiac dysfunction, LV diastolic dysfunction is reported in 76% of RA patients. In this study, 96.7% of the patients with RA showed decreased diastolic function, which was significantly higher than the control group (63.6%). Diastolic dysfunction in RA patients is mainly due to LV hypertrophy, interstitial fibrosis and ischaemia, but not to RA disease activity. The results described above indicate that RA aggravates cardiac systolic and diastolic dysfunctions in patients with ACS.

Cardiac morphology and function can be changed in patients with ACS complicated with RA. The mechanism of the cardiac function impairment, however, has not been clearly explained yet. It is currently considered that these changes may contribute to the chronic inflammatory state of RA and CRP, interferon (IFN) –α, and tumor necrosis factor (TNF)-α may participate in the pathological process of left ventricular remodeling in patients with RA. Administration of TNF-α antagonist can significantly improve cardiac remodeling in patients with RA. It has been revealed in genetic studies that the RA-related gene HLA-DRB1 positively is related with the increasing risk of coronary events. It was further indicated in this present study that RA has adverse effects on cardiac morphology and function in patients with ACS.

The main limitation of this study is that it is a retrospective cross-sectional study, most of patients were hospitalized in the department of cardiology. The DAS28 score of each RA patient cannot be calculated. In this study, we evaluated the correlations between laboratory and ultrasonic parameters of cardiac morphology and function with hs-CRP or ESR in the patients with ACS complicated with RA.

In conclusion, Patients with ACS complicated with RA are more likely to be afflicted with left ventricular remodeling, cardiac systolic and diastolic dysfunctions and cardiac valve involvement. Therefore, early intervention for controlling the inflammation of RA may play a significant role in preventing and alleviating the cardiac morphological and functional changes in patients with ACS.

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**Author Contributions**
L.P. conceived of the study, performed the statistical analysis and drafted the manuscript. Tian Wang participated in the design of the study which is a part of a series of investigations for cardiovascular risks of connective tissue diseases directed by Tian Wang, helped to revise the manuscript. All authors read and approved the final manuscript.

**Additional Information**

**Competing Interests:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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