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Left Ventricular Systolic Dysfunction in Rheumatoid Disease

An Unrecognized Burden?

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OBJECTIVES This study sought to ascertain whether left ventricular systolic dysfunction (LVSD) is more common among clinic patients with rheumatoid disease (RD) compared with the general population, and to assess the diagnostic utility of brain natriuretic peptide (BNP).

BACKGROUND Patients with RD are at increased risk of ischemic heart disease. However, there are few large echocardiographic studies identifying cardiac dysfunction in RD. We hypothesized that LVSD would be more prevalent in RD patients than in the general population.

METHODS A total of 226 hospital out-patients with RD (65% women) underwent clinical evaluation, electrocardiography (ECG), echocardiography, and plasma BNP assay (218 patients). Prevalence of LVSD was compared with local population estimates.

RESULTS Definite LVSD (left ventricular ejection fraction <40%) occurred in 5.3% of the RD group: standardized prevalence ratio, 3.20; 95% confidence interval, 1.65 to 5.59. Median BNP values were higher in patients with LVSD compared with those without: 16.6 pmol/l versus 8.5 pmol/l, $p < 0.005$, although values between the two groups overlapped. One in nine patients with an abnormal ECG had definite LVSD.

CONCLUSIONS Definite LVSD was three times more common in RD patients than in the general population. Given the prognostic benefits of treating LVSD, echocardiographic screening of RD patients with an abnormal ECG may be worthwhile. (J Am Coll Cardiol 2006;47:1169–74) © 2006 by the American College of Cardiology Foundation

Chronic heart failure (CHF) and left ventricular systolic dysfunction (LVSD) are common conditions with poor outcomes (1–3). Half of patients with LVSD are asymptomatic but are at increased risk (almost five-fold) of developing CHF compared with patients without systolic dysfunction (4). Angiotensin-converting enzyme inhibition in asymptomatic LVSD delays progression to CHF (5), making its identification worthwhile.

Objective evidence of cardiac dysfunction is needed to confirm CHF because of difficulties in clinical diagnosis (6). Echocardiography is a practical confirmatory tool, but community access is currently limited. Brain natriuretic peptide (BNP) distinguishes heart failure from other causes of acute dyspnea (7), but its utility in chronic cases (8) and asymptomatic LVSD (9) is uncertain.

Rheumatoid disease (RD) is associated with increased cardiovascular mortality, probably mediated by ischemic heart disease (IHD) (10,11). Studies have reported an increased risk of developing CHF in RD (12), although they have not documented cardiac dysfunction. Diagnosing CHF in RD patients may be hindered by features of RD itself, e.g., poor mobility.

We hypothesized that LVSD would be more common in a rheumatoid cohort compared with the general population. We examined the predictors of LVSD in this population, and also assessed the potential usefulness of BNP measurement in its identification.

METHODS

Consecutive RD patients (American College of Rheumatology diagnostic criteria [13]) over 40 years old attending a hospital clinic were invited to participate. Participants underwent clinical assessment, 12-lead electrocardiography, echocardiography, and venepuncture (non-fasting).

Electrocardiography. Major abnormalities were pathological Q waves, left bundle branch block, left ventricular hypertrophy, atrial fibrillation or flutter. Other abnormalities were considered minor.

Echocardiography. Patients underwent two-dimensional and Doppler trans-thoracic echocardiography (Powervision 6000, Toshiba, Tokyo, Japan) performed and reported by one investigator (G.S.B.). Left ventricular ejection fraction (LVEF) was assessed visually (14). The LVSD was defined as LVEF <50%: definite and borderline LVSD described LVEF <40%, and between 40% and 50%, respectively. A senior investigator (R.C.D.) reviewed all studies showing LVSD, with agreement for all definite LVSD cases. Pa-

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Abbreviations and Acronyms

BNP = brain natriuretic peptide
CHF = chronic heart failure
CI = confidence interval
ECG = electrocardiogram/electrocardiography
IHD = ischemic heart disease
LVEF = left ventricular ejection fraction
LVSD = left ventricular systolic dysfunction
RD = rheumatoid disease

tients with LVSD without documented coronary disease were offered coronary angiography.

The prevalence of LVSD was compared with that in the general population in the West Midlands (1); R.C.D. was a principal investigator of the previous study, using identical echocardiographic definitions.

Blood sampling. Routine laboratory assays (including C-reactive protein and erythrocyte sedimentation rate) were performed. Plasma was frozen at −70°C, with BNP immunoassay (ADVIA Centaur, Bayer Healthcare, Newbury, England), performed subsequently in 218 patients by blinded technicians. Serum rheumatoid factor (by latex agglutination: Biokit, Instrumentation Laboratory, Barcelona, Spain) values >30 IU/l defined seropositivity.

RD activity. Disease activity score-28 (DAS-28) was derived from joint examination, subjective symptom severity, and erythrocyte sedimentation rate (15).

Statistical analysis. Comparisons of normally and non-normally distributed data (determined by the Kolmogorov-Smirnov test) were made using the Student *t* test (presented as mean [SD]) and Mann-Whitney test (presented as median [IQR]), respectively. Categorical data were compared using the chi-square test; 95% confidence intervals (CI) for prevalences were calculated. Prevalence of LVSD was stratified by gender, and age-adjusted comparisons were made. Predictors of LVSD ($p < 0.05$ on univariate analysis) were included in a multivariate analysis of overall LVSD using stepwise logistic regression. Receiver operator characteristic curves studied diagnostic performance of BNP. Data were analyzed using SPSS version 10.0 for Windows (SPSS Inc., Chicago, Illinois). The study was approved by the local research ethics committee; all patients gave written informed consent.

RESULTS

Demographics. Of 304 patients initially invited, 226 (74%) patients participated; non-participants were older (mean age, 63.6 years; standard deviation, 8.2). Table 1 illustrates baseline differences between the RD and previously reported comparator populations (1).

RD activity, treatment, and extra-articular symptoms. Table 1 lists RD activity: 161 patients (71%) were seropositive, and examination showed nodules in 27%. Almost one-half of all participants (107 of 226) reported restricted mobility caused by arthropathy, with 16% limited by dyspnea. Median disease duration was 10 years (range, 4 to 16 years); 126 of 226 were taking corticosteroids, and 103 of 226 (45.6%) were taking methotrexate.

Prevalence of LVSD. Table 2 characterizes individuals with LVSD. Definite LVSD was significantly more prevalent in RD ($p < 0.001$): 5.3% (95% CI, 2.4% to 8.2%) versus 1.8% (95% CI, 1.4% to 2.2%). Any LVSD (i.e., definite + borderline) was also more frequent: 10.2% (95% CI, 6.2% to 14.1%) in RD versus 5.3% (95% CI, 4.6% to 6.0%, $p < 0.01$). Most patients with LVSD were male (14 of 23, 61%), and all 23 were white; LVSD was more common in men (14 of 80, 17.5%) than women (9 of 146, 6.2%), $p = 0.01$. Approximately half (11 of 23) had clinical evidence of IHD, but only 8 of 23 had had previous documentation of this. Coronary revascularization had been previously performed in 4 of 23. Only 5 of 19 patients consented to coronary angiography. Significant coronary disease was identified in two cases (Patients #1 and #6, Table 2A), whereas coronary vessels appeared normal in the other three (Patient #9 of Table 2A, and Patients #6 and #10 of Table 2B).

Age-standardized prevalence ratios for LVSD in RD are shown in Table 3. Any and definite LVSD were significantly more frequent in RD, with ratios of 1.92 and 3.20, respectively.

BNP. Median levels (Fig. 1) were significantly higher in those with LVSD, in whom BNP values ranged from 1.1 to 381.0 pmol/l. Receiver operator characteristic curves (not

Table 1. Baseline Demographic and Clinical Differences Between RD and Comparator Populations

Characteristic	RD	General Population	p
Number	226	3,960	
Age band, number (%)			<0.001
<54	45 (19.9)	1,314 (33.2)	
55–64	86 (38.1)	1,194 (30.2)	
65+	95 (42.0)	1,452 (36.7)	
Mean age, yrs (SD)	62.1 (9)	61.0 (11)	NS
Male (%)	80 (35.4)	1,964 (49.6)	<0.0001
Non-white (%)	21 (9.3)	105 (2.7)	<0.0001
Past medical history			
Previous MI (%)	13 (5.8)	211 (5.3)	0.7829
Angina (%)	21 (9.3)	285 (7.2)	0.2392
Hypertension (%)	84 (37.2)	964 (24.3)	<0.0001
Diabetes (%)	19 (8.4)	157 (4.0)	0.0012
Ever smoked (%)	147 (65)	2,284 (57.8)	0.0290
Drug therapy (%)			
ACE inhibitors	22 (9.7)	223 (5.6)	0.0105
Beta-blockers	27 (11.9)	358 (9.0)	0.1414
Calcium blockers	31 (13.7)	345 (8.7)	0.0104
Diuretics	51 (22.6)	515 (13.0)	<0.0001
Aspirin	28 (12.4)	402 (10.2)	0.2811
Disease activity parameter			
Median CRP (mg/l)	14.0 (IQR 16.5)		
Median ESR (mm/h)	20.0 (IQR 25.8)		
Mean DAS-28	3.56 (SD 1.22)		

ACE = angiotensin-converting enzyme; CRP = C-reactive protein; DAS = disease activity score; ESR = erythrocyte sedimentation rate; IQR = interquartile range; MI = myocardial infarction; RD = rheumatoid disease; SD = standard deviation.

Table 2. Characteristics of Subjects With Definite and Borderline LVSD

Patient	Age (yrs)	Gender	Past Medical History	ECG Findings	BNP (pmol/l)	Symptoms/Signs
A. Definite LVSD						
1	55	M	Ex-smoker	SR inferior Q_waves	11.0	Dyspnea on moderate exertion
2	72	F	BP DM ex-smoker COPD	SR anterior Q_waves LVH	119.9	Dyspnea on walking uphill LVH, S4 gallop
3	66	F	BP	SR LBBB	22.5	Dyspnea on walking uphill
4	73	F	BP smoker On loop diuretic	SR poor R-wave progression	381.0	Dyspnea on mild exertion Fluid overload evident
5	76	M	Ex-smoker COPD On loop diuretic	SR lateral T-wave inversion	16.6	Dyspnea on mild exertion, PND Fluid overload evident
6	56	M	BP DM chol ex-smoker PVD On ARB	SR lateral T-wave inversion	3.3	Limited by intermittent claudication
7	72	M	MI chol ex-smoker On loop diuretic and ACEI	SR LBBB	105.8	Dyspnea on walking uphill S4 gallop, fluid overload evident
8	71	F	MI-CABG chol On ACEI	SR dominant R-wave anteriorly lateral T-wave inversion	37.4	Dyspnea on walking uphill Fluid overload evident
9	66	F	Ex-smoker	SR LBBB	8.3	Dyspnea on walking uphill
10	77	F	MI PVD ex-smoker On loop diuretic and ACEI	SR anterior Q_waves RBBB	54.0	Mobility restricted by arthralgia
11	72	M	BP smoker COPD On loop diuretic and ACEI	SR LVH	NA	Dyspnea on walking uphill Fluid overload evident
12	63	M	CABG ex-smoker COPD	SR bifascicular block	15.3	Dyspnea on mild exertion, PND Fluid overload evident
B. Borderline LVSD						
1	61	M	Previous coronary angioplasty ex-smoker Pulmonary fibrosis On beta-blocker	SR LBBB	3.1	Limited by angina Dyspnea on mild exertion
2	65	M	BP AF ex-smoker On beta-blocker	AF LVH	14.7	Fatigue
3	55	F	Smoker Asthma	SR LBBB	20.6	Dyspnea on moderate exertion, relieved by bronchodilators
4	59	M	Nil of note	SR	NA	Limited by arthralgia
5	61	M	Smoker	SR inferior Q_waves	31.7	Limited by arthralgia
6	52	M	Ex-smoker Pulmonary fibrosis	SR anterior T-wave inversion	1.1	Limited by arthralgia Dyspnea on walking upstairs
7	58	F	Paroxysmal AF smoker	SR	5.9	Limited by dyspnea/fatigue
8	56	M	Aortic dissection repair Angina BP chol On ARB, beta-blocker	SR LBBB LVH	25.8	Limited by dyspnea, angina
9	64	M	MI chol ex-smoker	SR inferior Q_waves	20.4	Dyspnea on mild exertion
10	48	F	Nil of note	SR LBBB	8.7	No symptoms
11	67	M	MI CABG PVD chol ex-smoker On loop diuretic, ACEI, beta-blocker	SR	11.4	Limited by intermittent claudication

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; BP = hypertension; CABG = coronary artery bypass graft; CAD = coronary artery disease; chol = hypercholesterolemia; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; L/RBBB = left/right bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; NA = not available; PVD = peripheral vascular disease; SR = sinus rhythm; other abbreviations as in Table 1.

Table 3. Age-Standardized Prevalence Ratios for LVSD in RD Stratified by Gender

	Standardized Prevalence Ratio (95% CI) in RD
Definite LVSD	
Men	2.41 (0.89–5.25)
Women	4.74 (1.74–10.3)
Men and women	3.20 (1.65–5.59)
Any LVSD	
Men	2.36 (1.29–9.95)
Women	1.48 (0.68–2.81)
Men and women	1.92 (1.22–2.88)

CI = confidence interval; LVSD = left ventricular systolic dysfunction; RD = rheumatoid disease.

shown) for BNP across the whole RD population showed an area under the curve for any LVSD of only 0.69 (95% CI, 0.55 to 0.83), whereas that for definite LVSD was 0.78 (95% CI, 0.62 to 0.95).

Electrocardiographic findings and LVSD. Of 226 RD patients, 108 (48%) had electrocardiographic (ECG) abnormalities. All 12 with definite LVSD, and 8 of 11 with borderline LVSD had ECG abnormalities (sensitivity, 87%). Of those with LVSD, 14 of 23 (61%) had major abnormalities. Table 4 lists the performance of ECG in identifying LVSD.

Predictors of LVSD. Factors associated with any LVSD among RD patients are shown in Table 5. On multivariate analysis, only abnormal ECG (odds ratio, 8.778; 95% CI, 1.901 to 40.530; p = 0.005), previous myocardial infarction (odds ratio, 4.939; 95% CI, 1.046 to 23.316; p = 0.044), and BNP (odds ratio, 1.030; 95% CI, 1.001 to 1.059; p = 0.043) were independent predictors.

DISCUSSION

The prevalence of echocardiographic LVSD was significantly higher in the RD cohort compared with the general population, supporting recent epidemiologic data (12), and also providing a likely mechanism for CHF. The prevalence of definite LVSD (LVEF <40%) was three times more frequent in RD. This is important given the reduced survival associated with LVSD, and the fact that many therapeutic studies for LVSD used a definition of LVEF <40%.

Previous echocardiographic studies have been smaller, have recruited younger patients, and have excluded those with cardiac risk factors (10). Most have shown no differences in systolic function between RD patients and control patients.

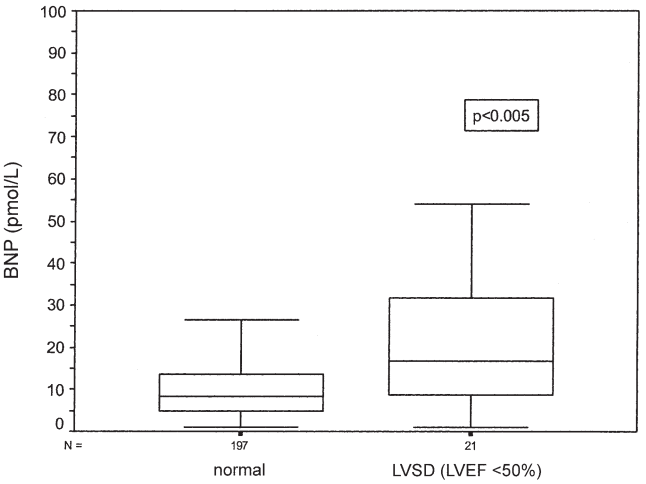

Figure 1. Box plots showing median plasma brain natriuretic peptide (BNP) levels **(horizontal bars)** for normal left ventricular (LV) function versus left ventricular systolic dysfunction (LVSD). Median BNP = 8.5 pmol/l (interquartile range, 8.8) in those with normal LV function versus 16.6 pmol/l (interquartile range, 26.1) in those with LVSD. LVEF = left ventricular ejection fraction.

We have presented data from older patients in a real-world setting. Clearly, important demographic differences existed between the two cohorts. The RD cohort was mostly female (65%), reflecting the typical excess in women. Male gender was associated with LVSD, and a higher proportion of males would have increased its overall prevalence. There were also significantly higher rates of hypertension, diabetes, and tobacco use among the RD group, which clearly could have effected the increased prevalence of LVSD. The increased prevalence of these factors in RD is noteworthy. For example, higher rates of hypertension in RD may be treatment related (16). Furthermore, tobacco use may increase the risk of developing RD itself (17), possibly underlying some increased susceptibility to IHD.

Etiology of LVSD. Reported myocardial infarction was an independent predictor of LVSD. We found clinical evidence of IHD in almost 50% of cases; unfortunately, not all patients without documented coronary disease accepted coronary angiography. Interestingly, however, three patients who did consent had angiographically normal coronaries. This raises the possibility of underlying myocarditis (18) or microvascular disease. Myocardial biopsy data

Table 4. Performance of the ECG in Identifying LVSD in RD Patients

Characteristic	Any LVSD (LVEF <50%)	Definite LVSD (LVEF <40%)
Sensitivity, % (95% CI)	20/23, 87.0 (73.2–1.00)	12/12, 100
Specificity, % (95% CI)	115/203, 56.7 (49.8–63.5)	118/214, 55.1 (48.5–61.8)
Positive predictive value, % (95% CI)	20/108, 18.5 (11.1–25.8)	12/108, 11.1 (5.2–17.0)
Negative predictive value, % (95% CI)	115/118, 97.5 (94.6–100)	118/118, 100

CI = confidence interval; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; RD = rheumatoid disease.

Table 5. Features Associated With LVSD in RD Patients on Univariate Analysis

Variable	Odds Ratio	95% Confidence Interval	p
Presence of ECG abnormalities	8.3	2.4–28.9	0.001
Reported MI	6.8	2.0–22.9	0.002
Reported angina	4.4	1.5–12.9	0.006
Restricted mobility caused by dyspnea	3.4	1.3–8.9	0.011
Peripheral edema evident	3.4	1.4–8.6	0.009
Male gender	3.2	1.3–7.8	0.010
Hemoglobin	1.4	1.0–2.0	0.035
Glucose	1.2	1.0–1.4	0.022
Brain natriuretic peptide	1.04	1.02–1.07	0.001

Abbreviations as in Table 4.

or, less invasively, positron emission tomography or cardiac magnetic resonance imaging would be of interest here.

Adding to epidemiologic data associating RD and IHD, interesting pathophysiological similarities between rheumatoid and atherosclerotic inflammation exist (19). However, studies detailing the coronary anatomy and nature of lesions in rheumatoid patients with IHD are surprisingly scarce, yet would be most valuable.

ECG as a predictor of LVSD. The presence of ECG abnormalities independently predicted LVSD. As in the general population, the absence of major abnormalities makes definite LVSD unlikely (negative predictive value, 97%), whereas a completely normal ECG virtually rules out the possibility of definite LVSD (negative predictive value, 100%). Thus, when confronted by RD patients with possible heart failure, rheumatologists should make ECG a first-line investigation.

BNP—a useful test? The BNP values overlapped in RD patients with and without LVSD despite a significant difference between median values. Receiver operator characteristic curve analysis indicated poor performance in identifying any LVSD. Elevated BNP levels are not specific for LVSD, and may be reduced by concomitant diuretic and angiotensin-converting enzyme inhibitor therapy, limiting sensitivity.

Screening for LVSD. Identifying patients at risk of developing CHF attributable to LVSD is important given the benefits of angiotensin-converting enzyme inhibitors. Furthermore, some patients could benefit from further investigation and therapy (e.g., prognostic revascularization).

However, community echocardiographic screening is costly, and should probably be restricted to high-risk groups. Given the overall prevalence of LVSD reported, evaluating a screening strategy might be worthwhile in RD patients. According to our data, one in nine RD patients with any ECG abnormality, and almost one in six with a major abnormality, would be expected to have definite LVSD. The BNP assay—less widely available—would not have any advantage over ECG in targeting RD patients for echocardiography.

Study limitations. We acknowledge the difficulties in comparing clinic and community populations; RD patients treated solely in the community may be expected to have less severe disease and fewer co-morbid illnesses. However, with earlier implementation of disease-modifying medication (and surveillance for side effects), most patients with proven RD may now be under hospital supervision. Therefore, our findings are especially applicable to this setting.

CONCLUSIONS

Prognostically relevant LVSD is common in hospital clinic patients with RD. A normal ECG effectively rules out LVSD, and ECG should be the first-line investigation for patients with suspected heart failure. A role for BNP is less clear in this setting. Echocardiographic screening for LVSD among RD patients with abnormal ECG results is likely to be valuable and warrants further evaluation.

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