The Characteristics of Chronic Heart Failure in Rheumatoid Arthritis

Review Article

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Abstract: In recent times there is an emerging evidence about the increased risk of cardiovascular disease (CVD) and rheumatic conditions. This review has been focused on the multiple relationships between rheumatoid arthritis (RA) and heart failure (HF) features.

Cardiovascular (CV) system involvement is an extra-articular complication of RA and is a major cause of morbidity and mortality. All heart structures may be affected in RA and different clinical manifestations may be seen.

HF is a complex clinical syndrome which represents universal end-stage of nearly every form of heart disease and has a poor prognosis. Patients with RA have almost 2-fold higher risk of HF development than non RA-subjects and this high risk is not explained entirely by traditional CV risk factors. RA patients with HF appear to have a more subtle presentation of HF, compared to HF patients without RA, while mortality from HF is significantly higher. In RA HF mostly is manifested by diastolic dysfunction (DD) which is revealed by echocardiography. In general, brain natriuretic peptide (BNP) is an important clinical and prognostic marker of HF, but there are no final data concerning its screening value in RA-subjects.

Nevertheless, up to date HF is still being poorly revealed in most RA-patients, especially on early stages of the disease, which leads to HF treatment delay, thus contributing to mortality.

These findings emphasize the role and need of further larger studies in this field, which will bring to early identification and treatment of RA-subjects with HF and a decrease in mortality rates.

Keywords: Chronic heart failure, Rheumatoid arthritis, Risk factors, Brain natriuretic peptides, Echocardiography.

INTRODUCTION

In recent years there is a great attention towards the relationships between cardiovascular disease (CVD) and rheumatic diseases. The increased risk of CVD has been described extensively in rheumatoid arthritis (RA) [1-4], systemic lupus erythematosus (SLE) [5-7], ankylosing spondylitis (AS) and psoriatic arthritis [8-13].

RA is a systemic disease of unknown origin, which is characterized by chronic inflammatory process and mainly leading to small and large joints synovial membrane destruction. The prevalence of RA is 0.5-1% in general population of adults and women at reproductive age are 2-3 times higher affected by the disease [14, 15]. RA is an invalidating disease which is associated with life quality changes and decrease in mean duration of life [16]. Furthermore, there is observed high incidence of early mortality after the onset of disease, which particularly can be explained by infective, digestive, renal or pulmonary complications and lung neoplasia (mainly lung cancer and non-Hodgkin lymphoma [17].

Cardiovascular (CV) system involvement is an extra-articular complication of RA and is a major cause of morbidity and mortality. All heart structures may be affected by various pathogenic mechanisms and respectively different clinical manifestations may be seen: valvular heart disease, pulmonary hypertension, rhythm and conduction disturbances, myocarditis/pericarditis, myocardial fibrosis, coronary heart disease (CHD) up to myocardial infarction (MI), and particularly, heart failure (HF) [18].

Moreover, RA is suggested to be an independent risk factor for CHD development similar to type 2 diabetes mellitus (DM) [19].

HF in RA

HF is a complex clinical syndrome which represents universal end-stage of nearly every form of heart disease and has a poor prognosis [20, 21].

Patients with RA have almost 2-fold higher risk of HF development than those without RA and this high risk is not fully explained by traditional CV risk factors [22].

Furthermore, RA patients with HF appear to have a more subtle presentation of HF, compared to HF patients without RA, while mortality from HF is significantly higher [23].

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The increased risk of developing HF in RA is well described [24-26]. In particular, in a population-based incidence cohort of patients with RA over a 40-year period there was observed a higher incidence of HF among patients with RA compared with a cohort of non-RA patients. After adjusting for age, sex, CHD, and traditional CV risk factors, the risk of developing HF (defined by Framingham Heart Study Criteria) in patients with RA was almost twice that of non-RA patients (HR 1.87, 95% CI 1.47-2.39), with an increase in cumulative incidence observed over time. Though higher incidence of HF was seen among all age groups, it tended to be increased in women compared with men (relative risk [RR] 1.9, 95% CI 1.4-2.5 vs RR 1.3 95% CI 0.9-2.0) [22].

Compared with the general population, HF in patients with RA seems to be more frequently associated with diastolic dysfunction (DD) [27, 28]. After adjusting for age, sex, and history of CHD, patients with RA were twice as likely to have preserved LV ejection fraction (EF) (odds ratio [OR] 1.90, 95% CI 0.98-3.67) [29]. When HF with reduced EF does occur in patients with RA, it is seen much more frequently in men (HR 3.7, 95% CI 1.8-7.7) [25]. DD is a predictor for incident HF independent of the traditional CV risk factors (HR 1.81, 95% CI 1.01-3.48) [31, 33]. Echocardiographic findings of DD were associated with an increase in all-cause and cardiac mortality [32-34].

Risk Factors of CVD and RA

Risk factors of HF range very widely from lifestyle factors to comorbidities, medications, laboratory and genomic markers, *etc.* [35-38]. However, the main risk factors include hypertension, CHD, diabetes mellitus, and obesity. Hypertension and CHD are the most common and strongest risk factors conferring a 2-3 times increased risk [39]. HF risk increases with age and male gender is associated with a higher risk [40]. Valvular heart disease, low physical activity, obesity, coffee consumption, increased salt intake, and low socioeconomic status all have been associated with increased risk [40, 41]. Excessive alcohol intake increases BP, but light-to-moderate consumption lowers the risk of HF [42-44]. Smoking promotes several CVD risk factors associated with HF [40, 45]. Dyslipidaemia, renal dysfunction, some medications (*e.g*. chemotherapeutic agents) and comorbidities (anaemia, microalbuminuria, increased heart rate, *etc.*) are also associated HF [46-49].

Risk factors for RA include female sex, a positive family history, older age, silicate exposure, and smoking [50-52]. Consumption of more than 3 cups of coffee daily (particularly decaffeinated coffee) also may contribute to RA development [53].

Thus, age, smoking and coffee consumption are the same risk factors for the development of both HF and RA.

The increased risk of CVD in RA patients is not entirely explained by an increased incidence of the traditional CV risk factors. Some traditional risk factors in RA may even play a paradoxical role [24, 54, 55].

The influence of age on the CV risk in patients with RA may be even greater than for the general population. In a population-based inception cohort of patients with RA with no prior CVD history the effect of age on CVD risk was almost twice that in the general population in men and more than twice that in women. The impact of age on CVD risk in seronegative patients and in subjects younger than 50 years was similar to that seen in the general population [56].

The prevalence of smoking is higher in patients with RA, but this risk factor alone is unlikely to account for the increased CVD risk [55, 57, 58].

DM, arterial hypertension, dyslipidaemia, and alcohol use/abuse have not been described more frequently in patients with RA when compared with non-RA subjects [22-24, 58].

Obesity and lipids seem to play a paradoxical role in CVD risk in patients with RA, with a lower BMI and lower total cholesterol associated with higher CV risk [58, 59]. Patients with RA with a higher BMI have lower mortality rates than that seen in thinner patients independent of RA onset, age, duration, and smoking status [60].

HDL, LDL and total cholesterol levels may be reduced in patients with untreated RA and later increase with suppression of inflammation via treatment, although the increase in LDL cholesterol associated with RA treatment does not seem to confer a higher CV risk [61-63].

Patients with RA tended to have a lower likelihood of achieving therapeutic LDL levels after statin use. Increased erythrocyte sedimentation rate (ESR) is associated with a lower likelihood of achieving LDL targets, which underscores the importance of disease activity control in risk factor modification [64].

Close relationship between RA and CVD is mainly explained by the similarities in the inflammatory and immunologic responses [65].

Chronic systemic inflammation can promote endothelial cell activation and vascular dysfunction, which leads to decreased blood vessel compliance and atheroma formation, *i.e*. systemic inflammation accelerates development of atherosclerosis and heart disease.

The role of T lymphocytes is crucial in both RA and heart disease [66, 67]. HLA-DRB1, which is the major risk gene for RA, predisposes to RA by promoting the selection and survival of auto reactive CD4+ T cells. HLA-DRB1 alleles are also associated with increased risk of MI and various forms of non-RA-associated heart disease [68, 69]. As in heart disease, T lymphocytes isolated from the joints of RA-subjects have enhanced production of interferon-γ and interleukin-17, which presumably mediate chronic inflammation [70, 71].

Structural and Functional Changes of Myocardium in RA

Patients with RA are more likely to have abnormal LV geometry (higher LV mass and LV hypertrophy) than healthy people without RA. These abnormalities are associated with an increased risk of CVD. There is a strong association between increased LV mass (seen in patients with RA) and incident HF (HR 1.4 per 10% increment, $P<0.0001$) [72, 73].

Patients with RA with abnormal LV geometry are also significantly more likely to have LV concentric remodelling (OR 4.73, 95% CI 2.85-7.83), which is associated with a higher risk of incident CHD [72, 74].

Speckle-tracking echocardiography is an advanced echocardiographic modality for detection of myocardial changes during contraction and relaxation (*i.e*., myocardial strain) [75, 76]. According to the results of a population-based study in 87 patients with RA speckle-tracking echocardiography revealed a reduction in LV and right ventricular strain in RA patients when compared with the general population, which correlated with markers of disease severity [77].

Relationships between RA Characteristics, Duration and CVD

The RA disease characteristics seem to have an impact both on the risk of CVD development and CV mortality, with rheumatoid factor (RF) positivity and disease severity conferring the greatest risk [78, 79].

Positive RF is a significant predictor of CV events including HF all-cause and CV mortality among the general population, suggesting a role for antibodies in the pathogenesis of CVD [79, 80]. Among RF-negative subjects, after adjusting for age, sex, CHD, and CV risk factors, the increased risk of HF was no longer significant in a population-based cohort study but remained significant with a 2.5-fold increased risk among RF-positive subjects (adjusted HR 2.59, 95% CI 1.95-3.43) [22]. Severe extra-articular manifestations of disease are associated with a higher likelihood of developing HF (HR 3.1, 95% CI 1.9-5.1) even after adjustment for CV risk factors [25]. The presence of rheumatoid lung disease and RA vasculitis, as disease severity markers, has also been associated with a greater likelihood of CV death [78].

It seems that the increased CVD risk in RA may predate the clinical manifestations of the disease, with evidence of atherosclerosis and CHD predating the diagnosis [81]. After the RA diagnosis, the relationship between the disease duration and CVD outcomes is less clear. The risk of DD in RA patients may be associated with the duration of disease: in population-based cohort studies there was shown that after adjusting for CV risk factors, there was a significant association between the duration of the disease and DD (OR 3.2, 95% CI 1.8-5.4) [82, 83].

Clinical Manifestations of CVD in RA Patients

It was shown that RA patients are less likely to have angina pectoris as a manifestation of CHD (OR 0.58, 95% CI 0.34-0.99), more likely to have silent MI (OR 5.86, 95% CI 1.29-26.64) compared with the general population, and less likely to have typical ECG changes at presentation [54, 84].
The difference in clinical presentation may contribute to delays in the recognition and treatment of patients with RA and emphasizes the importance of a high index of suspicion in these patients.

Typical clinical features of HF are less likely to be evident at presentation in patients with RA. Studies showed that they are less likely to have dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea at presentation. Patients with RA in this study were also more likely to have rales compared with non-RA subjects and less likely to have elevated BP at presentation [23].

The Role of Laboratory Markers: Brain Natriuretic Peptide (BNP) and Cardiac Troponin (cTn)

BNP is an important and prognostic biomarker of HF which is released mainly in heart ventricles and atria as a result to an increase in volume or pressure in heart chambers. Herewith, it was shown that BNP release has no circadian rhythm [29].

In general population BNP is used as a screening tool for LV DD detection, *i.e*. it may reveal asymptomatic patients with HF [85, 86].

There is no definite approach for BNP use in HF during RA. Harney SMJ *et al.* showed that BNP may be a potential beneficial method for HF screening [87]. Nevertheless, there is a need in larger studies to confirm this observation.

There is evidence that patients with no CVD history had higher BNP levels than healthy control subjects. Patients with active RA had higher levels of BNP than those with moderate or no activity, which suggests possibility of direct cardiodepressive effect of inflammatory cytokines [88].

In patients without clinical CVD, those with RA were more likely to have elevated BNP levels than non-RA subjects (16% vs 9%, P<0.001). Patients with RA with abnormal BNP are more likely to have LV DD compared with those with normal BNP, but the specificity compared with non-RA patients (89% vs 94%, P=0.02) and the positive predictive value (25%) of elevated BNP in patients with RA is low (25%) and is, therefore, not a good screening tool [89]. The duration of RA and CRP levels is independently associated with N-terminal proBNP [90].

In RA patients without HF high sensitive cTn-I is elevated independently of CV risk profile and inflammatory markers, which may suggest subclinical, silent damage of myocardium in these patients [91].

Prognosis and Outcome

The prognosis in RA patients with HF is worse than in those subjects without RA. In a community-based cohort study by Davis JM 3rd *et al.*, the 30-day mortality rate following the onset of HF was higher for RA compared to non-RA subjects (at 15.5% vs 6.6%, respectively (p=0.001)). The 1-year mortality rate following HF remained higher for RA compared to non-RA subjects at 35% vs 19.3%, respectively (p=0.01). After adjusting for age, sex, and calendar year, RA subjects experienced a 2.39-fold higher risk of death 30 days following onset of HF compared to non-RA subjects (HR 2.39, 95% CI 1.36-4.18). At 1 year, this mortality difference was similar but less pronounced (adjusted HR 2.02, 95% CI 1.40-2.90). After also adjusting for use of CV medications and CHD, the excess 1-year mortality was similar (HR 1.89, 95% CI 1.26-2.84). Among those who survived the first year after onset of HF, there was no difference in overall survival between RA and non-RA subjects with HF in the subsequent years [23].

RA patients with HF seemed to have less aggressive control of HF and CV risk factors. In particular, these patients were administered first-line medications for HF treatment (ACE-inhibitors and β-blockers) less frequently compared to non-RA subjects: ACE inhibitors (15% vs 30%) and β-blockers (10% vs 23%) [23].

SUMMARY

CV system involvement is an important co-morbidity in rheumatic conditions which is accompanied by high mortality rates. In particular, HF is best described in RA and mostly is manifested by DD. In patients with RA the risk of HF is almost 2 times higher than in general population, and this risk is not explained entirely by traditional CV risk factors.

Speckle-tracking echocardiography can be useful in detecting early myocardial changes in RA-subjects.

BNP is an important clinical and prognostic marker of HF, but there are no final data concerning the screening value of BNP in patients with RA and HF. In patients with RA the typical clinical manifestations of HF differ from that in general population and have some features which are not well studied.

Both prognosis and outcome of RA patients with HF are worse than in non-RA subjects.

Summarizing all these key points it becomes clear, that up to date there is no definitely understanding of HF features in RA, identification and early detection of which will improve the prognosis of these patients via early treatment. And there is still a need in further and larger studies in this field.

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