Review

The association between rheumatoid arthritis and left ventricular diastolic dysfunction: pathogenesis, predictors and management

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ABSTRACT

Left ventricular diastolic dysfunction (LVDD) plays a central role in the pathophysiology of heart failure with preserved ejection fraction (HFpEF), a major manifestation of heart failure (HF). Low-grade inflammatory reaction is the key mechanism leading to LVDD. Rheumatoid arthritis (RA) is a systemic inflammatory disease and affects 0.5–1.0% of the adult population. Several epidemiologic studies find that the risk of LVDD is increased in RA than in the general population. Since inflammation plays an important role in the pathogenesis of LVDD and RA is a disease characterised by chronic systemic inflammation. RA may be involved in the occurrence and development of LVDD. This review summarises the pathogenesis, predictors, and management of LVDD in patients with RA.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease (1). Although synovitis is the main pathological change of RA (2), there are many comorbidities such as cardiovascular , pulmonary, neurological, gastrointestinal, renal, and haematologic disease in patients with RA (3). Cardiovascular disease (CVD) is the leading cause of death in patients with RA (4). Systemic inflammation mainly contributes to the development of CVD in RA (5). Heart failure (HF) is an emerging public healthcare issue affecting approximately 26 million people worldwide (6). Among patients with RA, HF is one of the main causes of the additional risk of death (7).

The prognosis of HF is severely compromised and one of the leading causes of HF is coronary heart disease (CHD) (8). In patients with RA, HF occurs early and a proportion of them cannot be explained by ischemic heart disease (9). Systemic inflammation has been found to play an important role in the occurrence and development of HF (10). HF with preserved ejection fraction (HFpEF), characterised by systemic inflammation (11), accounts for approximately 50% of HF admissions (12). Currently, there is still a lack of effective treatment for HFpEF (13). Left ventricular diastolic dysfunction (LVDD) plays a central role in the pathophysiology of HFpEF (14). As a preclinical condition, LVDD is defined as the inability of left ventricular (LV) to fill an adequate end-diastolic volume at an acceptable pressure (15). Low-grade inflammatory reaction is the key mechanism leading to LVDD (15).

Hence, RA-related inflammation might be an important driver for developing LVDD. Moreover, growing studies suggest that the prevalence of LVDD may be significantly increased in RA than in the general population (16-32). Other study has shown inconsistent result (33). This may be due to the difference in disease activity. Since inflammation plays an important role in the pathogenesis of LVDD and RA is a disease characterised by chronic systemic inflammation, RA may play an important role in the occurrence and development of LVDD. In this article, we will review the pathogenesis, predictors, and management of LVDD in patients with RA.

Pathogenesis

RA and systemic inflammation

In addition to targeting the synovial joints, RA is also accompanied by high levels of systemic inflammation (6). In this systemic inflammation, cytokines such as interleukin (IL)-17, IL-1β, IL-6, IL-8, tumour necrosis factor

(TNF)-α, interferon (IFN)-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) play important roles (34). Systemic inflammation is involved in the extra-articular manifestations of RA and is an early event in the pathogenesis of CVD (35, 36). Meanwhile, systemic inflammation is the key mechanism leading to LVDD in various diseases such as chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), atrial fibrillation, hypertrophic cardiomyopathy, anaemia, obesity, hypertension, hypercholesterolaemia and diabetes (15, 37, 38). The systemic inflammatory status of RA is also one of the pathogenesis mechanisms of LVDD.

TNF-α and IL-6 is central to the pathogenesis of RA and the serum levels of them are increased in RA patients (39, 40). Both TNF-α and IL-6 can increase the endothelial reactive oxygen species (ROS) production (41), this leads to a decrease in the availability of nitric oxide (NO) (42). Scarcity of NO in turn impairs NO cyclic guanosine monophosphate-protein kinase G (cGMPKG) signal transduction, ultimately leading to the hypertrophy and stiffening of myocardium (43-45). Myocardial hypertrophy and increased myocardial stiffness are the potential pathophysiological mechanisms leading to LVDD (46). Subsequently, rarefaction of cardiac muscle cells occurs with impaired cardiac perfusion and myocardial oxygen release, resulting in diastolic dysfunction (47). The hypophosphorylation of the giant cytoskeletal protein titin plays an important role in the stiffening of myocardium (48). In addition, reduced NO bioavailability promotes proliferation of fibroblasts and myofibroblasts and collagen deposition as its antagonistic effect on the profibrotic action of growth-promoting hormones (endothelin-1, angiotensin II, and aldosterone) decreases (49). Myocardial fibrosis is one of the potential mechanisms of LVDD (50). Furthermore, TNF-α directly decreases sarcoplasmic reticulum Ca2+-ATPase 2a protein (SERCA2a) expression, leading to LVDD (51). In another aspect, TNF-α has a direct effect on cardiac muscle cells, it promotes cardiac muscle cells hypertrophy by binding to TNF receptor 1 (TNFR1) (52).

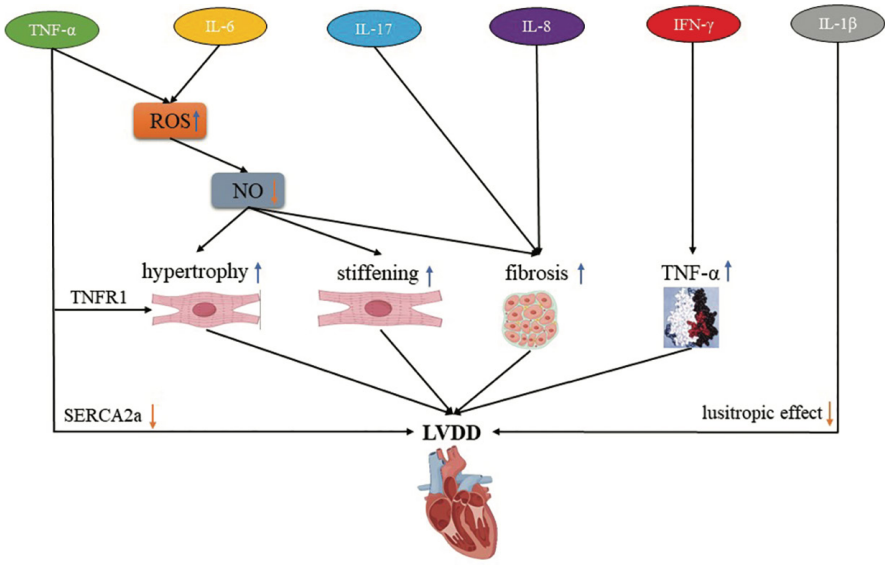

Fig. 1. The pathogenesis of LVDD mediated by systemic inflammation in RA. TNF-α: tumour necrosis factor-α; IL-6: interleukin-6; IL-17: interleukin-17; IL-8: interleukin-8; IFN-γ: interferon-γ; IL-1β: interleukin-1β; ROS: reactive oxygen species; NO: nitric oxide; TNFR1: tumor necrosis factor receptor 1; SERCA2a: sarcoplasmic reticulum Ca2+-ATPase 2a protein; LVDD: left ventricular diastolic dysfunction.

For other systemic inflammatory factors, IL-17 has been shown to be involved in the development of LVDD through myocardial fibrosis and irreversible ventricular remodelling (53). IL-1β also promotes LVDD, likely because of its negative lusitropic effect (54). IL-8, which mediates neutrophil and monocyte/macrophage infiltration and pro-inflammatory mediator production, increases myocardium fibrosis (55). IFN-γ, produced mainly by activated lymphocytes and endothelial cells, mediates LV dilation and dysfunction by high-level cardiac transcription of TNF-α (56). However, another research used IFN-γ deficient mice implies that endogenous IFN-γ plays a protective role in cardiac hypertrophy (56). These discrepancies may be attributed to differences in the experimental objects (57). The pathogenesis of LVDD mediated by systemic inflammation in RA is shown in Figure 1.

RA and renin angiotensin system

Patients with RA have an activation of the renin angiotensin system (RAS), elevated angiotensin-converting enzyme (ACE) levels are found in both synovial fluid and serum of patients with RA(58). In addition to ACE, the RAS system also includes angiotensin II (Ang II) , AT1 receptor and the counter-regulatory composed by angiotensin converting enzyme 2 (ACE2), angiotensin-(1-7) [Ang-(1-7)] and the Mas receptor (59). The activation of RAS has an important role in the RA pathogenesis by enhancing inflammation and osteopenia (60). Besides, in patients with RA, significantly elevated ACE/ACE2 ratio may be associated with CVD (61).

ACE, which is elevated in patients with RA, catalyses the conversion of Ang-1 into Ang-2 and the formation of Ang-2 leads to myocardial hypertrophy and pathological remodelling (62). Ang-2 instigates the production of aldosterone in the adrenal cortex and the aldosterone also induces myocardial fibrosis and LV hypertrophy (63). Myocardial fibrosis and hypertrophy contribute to the pathogenesis and advancement of LVDD (64).

RA and sympathetic nervous system

Increased sympathetic outflow has been found in patients with RA and the heightened sympathetic outflow to the heart can have multiple harmful consequences (65, 66). The enhanced sympathetic activity in patients with RA may be due to disease activity and several environmental factors such as the home environment, working routines, caf-

feine and nicotine, and sleep quality (67). The neurotransmitters of the sympathetic nervous system (SNS) include catecholamines norepinephrine, adrenaline and dopamine (68). There are a large amount of norepinephrine and dopamine in the synovial tissue of RA patients (69, 70). In addition, elevated norepinephrine can also be observed in the serum and heart of RA (71, 72).
Research shows that inhibiting the overactivation of SNS significantly attenuates myocardial hypertrophy and fibrosis and alleviates the progression of cardiac remodelling and dysfunction (73). The mechanism is likely to be related to the baroreflex impairment (74). It is worth noting that LVDD in turn causes an increase in sympathetic nerve activity (75), which will further exacerbate the systemic inflammation in RA (76).

RA and metabolic abnormalities

In patients with RA, the prevalence of metabolic abnormalities is increased, mainly including obesity (77), diabetes (78), dyslipidaemia (79), and hypertension (80). These are associated with increased cardiovascular risk in RA (81). In addition, metabolic abnormalities are associated with a higher prevalence and severity of LVDD (82-84), both in women (85) and men (86).
Research has shown that left ventricle hypertrophy is more common in obese patients (87). In obese patients, myocardial fatty infiltration may affect the cardiac structure and function, leading to the development of LVDD (88). Besides, in patients with obesity, the increase of mitochondrial reactive oxygen species in myocardial cells can lead to stiffness and increased cardiac fibrosis (89). Obese patients express more leptin in their subcutaneous adipose tissue, which is associated with LVDD (90). It is worth noting that successful weight reduction is associated with improved left ventricle diastolic function (91), which suggests that weight control is necessary for patients with RA.
Diabetes is an important risk factor for CVD and is associated with LVDD (92-94). Besides, LVDD is considered an early manifestation of diabetic cardiomyopathy (95). Diabetes mediates LV hypertrophy and stiffness (96, 97).

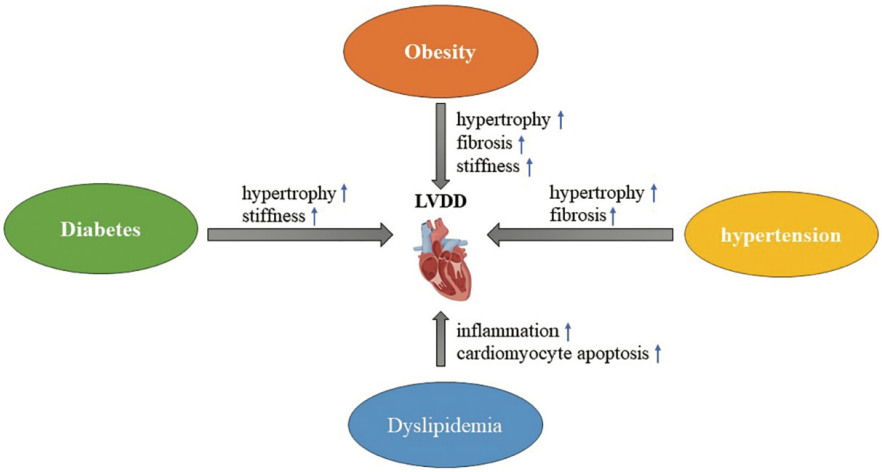

Fig. 2. The pathogenesis of LVDD mediated by metabolic abnormalities in RA.
LVDD: left ventricular diastolic dysfunction.

Otherwise, diabetes patients with cardiovascular autonomic neuropathy are an independent risk marker for the presence of LVDD (98), this is related to the cardiac sympathetic denervation and elevated heart rate (99). The presence of LVDD is significantly related to glycated hemoglobin (HbA1C) levels and the duration of diabetes (100). The future development of LVDD in RA with diabetes could be prevented through good blood glucose control (101, 102).
Dyslipidaemia promotes LVDD even before the development of occlusive coronary artery disease or clinical heart failure (103-106). In patients with RA, dyslipidemia is manifested as decrease total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-c) levels (107, 108). Low HDL-c levels is associated with LVDD (103), increased inflammation in the LV wall and cardiomyocyte apoptosis are possible mechanisms (109). Therefore, the protective effect of statins on LVDD may be achieved by increasing HDL-c levels (110, 111).
Research has found that hypertension is more common in patients with RA than in the general population (112). The risk of hypertension in RA patients is associated with lack of physical activity, systemic inflammation, obesity, diet, alcohol, and medications used to manage RA (113). On the other hand, the prevalence of LVDD in hypertensive patients is 33.8% and LVDD is an early consequence of hypertension-related heart disease (114). LV hypertrophy and fibrosis play an important role (115, 116). In addition, uncontrolled hypertension, longer hypertension disease evolution and smoking are related to the occurrence of LVDD (116). The pathogenesis of LVDD mediated by metabolic abnormalities in RA is shown in Figure 2.

RA and other potential pathogenesis

Endothelial dysfunction has been implicated in the pathogenesis of LVDD through LV hypertrophy and stiffness (117-120). On the other hand, endothelial dysfunction is one of the characteristics of RA (80,121,122). Serum γ-glutamyltransferase (GGT), which has been widely used as an index of alcohol intake and liver dysfunction, induces LVDD through oxidative stress (123). In patients with RA, Serum GGT levels are increased (124). Pericardial fat may be implicated in the pathogenesis of LVDD by disturbing the dilation of the LV and impairing cardiac filling (125). Besides, pericardial fat thickness is higher in patients with RA than in the healthy control (126). Anaemia is associated with an increased risk of LVDD in patients with diabetes, chronic kidney disease and CHD due to LV hypertrophy (127-129). It is worth noting that anaemia is a common extra-articular manifestation of RA (130).

Predictors

Multiple studies have shown that LVDD is related to the duration of RA

(131-134). Chronic cytokine release may be the cause. In addition, higher RA disease activity at baseline is associated with LVDD (135). Disease activity score 28 (DAS28), a clinical and laboratory composite score, is used to evaluate disease activity in RA (136). Research has shown that LVDD is associated with higher DAS28 in patients with RA (137). On the other hand, another study confirms that the prevalence of LVDD in RA patients with continued low disease activity did not differ from that of the control group (138). Besides, with the influence of inflammation, premenopausal women with RA have a threefold increased risk of LVDD when compared to the control group (139).

Anti-cyclic citrullinated peptide (anti-CCP) antibodies, reference indicator for the diagnosis and prognosis of RA (140). In patients with RA, anti-CCP antibody is an important marker of LVDD (141). Over the past 3 decades, N-terminal proBNP (NT-proBNP) has been an important biomarker for HF (142). On the other hand, with the help of gadolinium-enhanced cardiac magnetic resonance (CMR) imaging, higher NT-proBNP levels in RA correspond to a higher degree of myocardial fibrosis (143). Considering that myocardial fibrosis is one of the initial pathogenic mechanisms of LVDD (143), monitoring NT-proBNP levels in RA patients can help detect LVDD as early as possible. Besides, circulating biomarkers reflecting inflammation such as bone morphogenetic protein 9 (BMP9), pentraxin-related protein 3 (PTX3) and tumour necrosis factor receptor superfamily member 11a (TNFRSF11A) are associated with LVDD (144). Research suggests that immune mechanisms contribute to myocardial fibrosis and leading to LVDD, the high immune response score is strongly associated with advanced LVDD in RA (145). Besides, given the significant elevation of serum TNF-α levels in patients with LVDD(146), a significant increase in TNF-α levels in RA patients may signify the onset of LVDD. It is worth noting that carotid and aortic stiffness are correlated with LV diastolic function in patients with RA(147), carotid artery ultrasound may be considered as a relatively simple test to predict which RA patients may be at greater risk of LVDD.

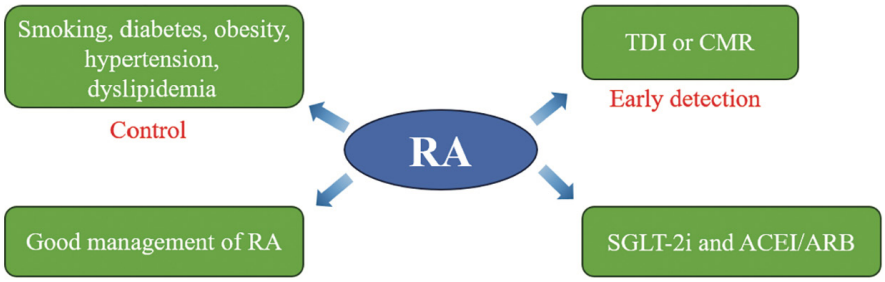

Fig. 3. The management of LVDD in RA.
TDI: tissue Doppler echocardiographic imaging; CMR: cardiac magnetic resonance; RA: rheumatoid arthritis; SGLT-2i: sodium glucose transporter 2 inhibitors; ACEI/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

Management of LVDD in RA

Considering the higher incidence of CVD in RA patients, improving awareness of the increased risk of cardiac complications is crucial for the management of these patients (148). The control of traditional cardiovascular risk factors such as smoking, diabetes, obesity, hypertension and dyslipidaemia is the most basic requirement in patients with RA (149). LVDD may be an early manifestation of RA related cardiomyopathy (150). Besides, LVDD is the risk factor for the development of cardiovascular (CV) events in patients with RA (151). Therefore, the assessment of diastolic function in RA patients is of utmost importance, particularly in those with prolonged disease duration and high levels of disease activity. Early detection of LVDD in RA may help optimise treatment (152). Tissue Doppler echocardiographic imaging (TDI), characterised by feasibility and ease of access, is helpful in detecting the presence of LVDD (153, 154). In TDI, average early diastolic filling flow/early diastolic mitral annular (E/e')>14, septal e' velocity <7 cm s^{-1} or lateral e' velocity <10 cm s^{-1}, tricuspid regurgitation velocity >2.8 m s^{-1} and left atrial volume index >34 mL m^{-2} indicate LVDD (155). However, in RA patients combined with pulmonary hypertension, the application of TDI may be limited due to abnormal Doppler variables (156). CMR has become a promising tool for the non-invasive evaluation of myocardial fibrosis and inflammation in patients with RA and can be used for the assessment of LVDD (157, 158).

Considering the significant impact of the duration and disease activity of RA on LVDD (131, 137), good management of RA is the key to preventing the occurrence and development of LVDD. In patients with RA, TNF-α plays an important role in CVD and TNF-α inhibitors have cardiovascular protective effects (159). When circulating TNF-α was blocked by TNF-α inhibitor, a reduction in myocardial fibrosis and LV remodelling can be observed (160). This indicates that TNF-α inhibitors have the potential to prevent LVDD. But there are also studies showing that the administration of TNF-α inhibitors may cause a worsening of LV diastolic function in patients with RA, primarily through the antagonistic action on TNF receptor 2 (TNFR2) and undergoing high-dose treatment (161). TNFR2 has anti-inflammatory activities and protective effect on cardiomyocytes (162). In addition, research has shown that TNF-α inhibition prevent inflammation induced adverse cardiac remodelling, but cannot prevent diastolic dysfunction, this collagen-induced arthritis mouse model suggests that systemic inflammation may affect left ventricular remodelling and diastolic dysfunction through different pathways (163). Tocilizumab, a murine anti-human interleukin-6 (IL-6) receptor antibody, reduces LV hypertrophy and improves LV regional function in RA patients (164, 165). Annexin A1, an endogenous anti-inflammatory modulator (166), corrects the LVDD by regulating of both myocardial fibroblast and inflammatory cell phenotype in RA mice model

(167). Further research is needed in RA patients. In the selection of traditional cardiovascular drugs, sodium glucose transporter 2 inhibitors (SGLT-2i) improve LV diastolic function, which may be more suitable for RA patients with diabetes (168). Besides, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) have been shown to be effective in improving LV diastolic function and are appropriate for the management of RA patients with hypertension (169). However, the impact of other medications, including beta blockers, calcium channel blockers and diuretics, on RA accompanied by LVDD requires further exploration. The management of LVDD in RA is shown in Figure 3.

Conclusion and perspective

In conclusion, patients with RA may have higher incidence of LVDD (16-33), an early manifestation of RA related cardiomyopathy (150). Systemic inflammation plays an important role in this (15, 34, 37, 38). On the other hand, LVDD also indicates the occurrence of CV events in RA (151). Therefore, the increased prevalence of LVDD in RA may have an impact on excess mortality in patients with RA (170). Unfortunately, little is known about the occurrence and development of LVDD in RA patients. More research is needed to reveal the natural history of RA related LVDD. In the existing studies, the main pathogenesis of RA mediated LVDD include systemic inflammation, activation of RAS, overactivation of SNS, metabolic abnormalities, endothelial dysfunction and anaemia (15, 63, 73, 88, 117, 127). It is worth noting that the existing pathological mechanisms are mostly indirect evidence, further research is required to validate these relationships. Given the high prevalence of LVDD in RA patients than those without. It is imperative to conduct a screening for LVDD in patients with RA, especially in the patients with long disease duration and high disease activity (131-135). TDI is most commonly used to detect LVDD (153,154). But in RA patients combined with pulmonary hypertension, CMR may need to be considered (156-158).

Targeted treatment of inflammation and RA activity, as well as additionally addressing traditional CV risk factors, appears to be crucial in avoiding the development of LVDD in patients with RA (151). Biologics have become an effective method for treating RA and help reduce CV risk in RA patients (171-173). Existing studies have demonstrated that TNF-α inhibitors and anti-IL-6 receptor agent have a preventive effect on LVDD in RA patients (160, 164, 165). This may be attributed to the inhibitory effect of biologics on systemic inflammation (174). The effects of other biologics such as interleukin-1 receptor antagonists and Janus kinase inhibitors are still unclear, this would need further study in the future.

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