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Speckle Tracking Echocardiography for the Early Detection of Subclinical Left Ventricular Systolic Dysfunction in Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis is a chronic systemic autoimmune disease in which cardiovascular complications account for much of the excess mortality reported in affected populations. Heart failure occurs more often than coronary disease alone would predict, and myocardial injury develops silently across years of sustained inflammatory activity. Conventional two-dimensional echocardiography, and the left ventricular ejection fraction in particular, stays within reference limits until damage is advanced, leaving a long interval during which cardiac involvement escapes detection. Two-dimensional speckle tracking echocardiography measures myocardial deformation directly by following acoustic markers within the myocardial wall through the cardiac cycle, and it is not limited by the angle between the ultrasound beam and the direction of fibre shortening. Global longitudinal strain obtained by this method falls in rheumatoid arthritis patients whose ejection fraction is still normal, and the degree of impairment follows disease duration, functional disability and cumulative inflammatory burden.

Keywords: Rheumatoid arthritis; Speckle tracking echocardiography; Global longitudinal strain; Subclinical systolic dysfunction; Left ventricle; Systemic inflammation.

Introduction

Rheumatoid arthritis is a chronic autoimmune disorder in which persistent synovial inflammation leads to progressive joint destruction and loss of function. It affects roughly one per cent of adults, occurs two to three times more often in women, and becomes more frequent with advancing age. Although the joints dominate the clinical picture, the inflammatory process is systemic, and distant organs are drawn into the disease over time. **(1)**

Life expectancy in rheumatoid arthritis is reduced by about ten to fifteen years, and cardiovascular causes account for the greater part of this deficit. Reported cardiac manifestations include accelerated atherosclerosis, pericarditis, myocarditis, conduction disturbance, valvular abnormality and heart failure. Many of these complications begin quietly and are recognised only when symptoms appear, so the clinical difficulty lies in timing rather than in awareness of the underlying disease. **(2)**

The traditional explanation for excess cardiac mortality was ischaemic heart disease arising from accelerated coronary atherosclerosis. Population-based work has shown this account to be incomplete, since heart failure incidence rises rapidly after the clinical onset of arthritis and cannot be attributed to coronary events alone. Non-ischaemic heart failure is disproportionately common, and its occurrence follows the severity and duration of the rheumatoid process. **(3)**

Detecting myocardial involvement before symptoms appear has therefore become an objective of cardiovascular care in these patients. Ejection fraction measured by M-mode or by the biplane method of discs is insensitive to early contractile impairment. Two-dimensional speckle tracking echocardiography addresses this gap by

quantifying deformation of the myocardium from routine grey-scale images, without additional acquisition and without dependence on beam angle. **(4)**

Rheumatoid Arthritis as a Systemic Inflammatory Disease

Rheumatoid arthritis usually begins in the small peripheral joints of the hands and feet, follows a symmetrical distribution, and spreads proximally when treatment is delayed. Sustained synovitis destroys cartilage and produces bone erosions visible radiographically within the first two years in untreated patients. No single laboratory test confirms the diagnosis, so clinical assessment supported by serology and acute-phase measurement remains the basis of recognition. **(5)**

Epidemiological estimates vary between regions, partly through genuine differences in disease frequency and partly through the methods used to identify cases. Reported prevalence is higher in northern and western Europe and in North America than in southern Europe, sub-Saharan Africa and much of southeast Asia. Incidence generally parallels prevalence, which argues that these differences are real rather than an artefact of population ageing. **(6)**

Susceptibility arises from interaction between inherited factors and environmental exposure. Alleles within the class II major histocompatibility complex, and the shared epitope in particular, carry the strongest genetic weight, while cigarette smoking is the environmental factor most consistently linked to disease. Smoking increases citrullination of self-proteins in the lung and raises the likelihood of anti-citrullinated protein antibody formation in genetically predisposed individuals. **(7)**

Cardiovascular risk in rheumatoid arthritis is not fully explained by the classical risk factors used in general population scoring systems. Patients develop atherosclerotic and myocardial complications at rates comparable to those seen in diabetes mellitus, and the excess persists after adjustment for smoking, blood pressure, lipids and body mass. Inflammatory activity contributes independently, which has prompted modification of existing risk calculators for this population. **(8)**

Mechanisms Linking Rheumatoid Inflammation to Myocardial Injury

The rheumatoid inflammatory process begins years before joint symptoms, during a preclinical phase marked by circulating autoantibodies and raised cytokine concentrations. Once arthritis becomes apparent, the synovial membrane is infiltrated by macrophages, T cells, B cells and fibroblast-like synoviocytes that sustain a self-perpetuating inflammatory environment. Mediators produced within the joint enter the circulation and act on the vascular endothelium and the myocardium. **(9)**

Tumour necrosis factor, interleukin-1 and interleukin-6 are central to this cascade and each has direct effects on cardiac tissue. These cytokines depress contractility of isolated cardiomyocytes, promote apoptosis, stimulate fibroblast proliferation and alter calcium handling within the sarcomere. Interleukin-6 additionally drives hepatic acute-phase synthesis and contributes to the prothrombotic and dyslipidaemic profile of active disease. **(10)**

Several inflammatory pathways converge on the coronary microcirculation. Endothelial activation increases adhesion molecule expression, reduces nitric oxide availability and impairs vasodilator reserve, which limits perfusion at the level of the small vessels while the epicardial arteries remain patent. Neutrophil extracellular traps release extracellular DNA and granular contents that damage endothelium and promote local thrombosis, changes detectable even in early disease. **(11)**

Chronic exposure to inflammatory mediators produces structural remodelling characterised by interstitial collagen deposition and cardiomyocyte hypertrophy. Fibrosis increases passive stiffness and disturbs the sequence of contraction and relaxation, particularly in the subendocardial layer where longitudinally oriented fibres are concentrated. Because these fibres are most vulnerable to ischaemia and raised wall stress, longitudinal shortening deteriorates before circumferential or radial function is affected. **(12)**

The paradigm developed for heart failure with preserved ejection fraction fits the rheumatoid situation closely. A systemic proinflammatory state induces coronary microvascular endothelial inflammation, which reduces

nitric oxide signalling to adjacent cardiomyocytes, lowers protein kinase G activity and leads to hypophosphorylation of titin with consequent cardiomyocyte stiffening. Fibroblast activation proceeds in parallel, giving a stiff ventricle with preserved emptying but impaired myocardial mechanics. **(13)**

The Spectrum of Cardiac Involvement in Rheumatoid Arthritis

Heart failure occurs more frequently in rheumatoid arthritis than in matched populations with degenerative joint disease, and the difference persists after adjustment for age, sex and conventional risk factors. Comparative work reported an adjusted risk of about four per cent against just over two per cent in osteoarthritis. Patients with rheumatoid disease also present at a younger age and less often report antecedent myocardial infarction. **(14)**

Genetic evidence supports a causal rather than an incidental relationship between the two conditions. Analyses using genome-wide association data and Mendelian randomisation have identified an association between genetically predicted rheumatoid arthritis and increased heart failure risk that is not attributable to shared confounding. This argues against the view that heart failure in these patients is merely a consequence of coexisting hypertension, obesity or coronary disease. **(15)**

Diastolic abnormalities appear early and have been documented in patients maintaining low disease activity on stable therapy. Impaired relaxation, prolonged isovolumic relaxation time and a raised ratio of early transmitral velocity to early diastolic annular velocity are the changes most often reported. Their presence in patients without hypertension, diabetes or coronary disease supports an inflammatory rather than a haemodynamic origin. **(16)**

Longitudinal observation shows that diastolic function deteriorates over time rather than remaining stable. Serial echocardiography has documented progressive worsening of relaxation indices across intervals of a few years, with the rate of change related to inflammatory markers measured during follow-up rather than at baseline. Left atrial enlargement follows the sustained rise in filling pressure, while atrial functional impairment precedes any increase in chamber dimension. **(17)**

Assessment of Left Ventricular Function and the Limitations of Ejection Fraction

Left ventricular ejection fraction has been the reference measure of systolic function for several decades and still defines the phenotypes used in guidelines and clinical trials. Its position derives from historical trial design rather than physiological accuracy, since the original treatment studies enrolled patients below a threshold of forty per cent. It is a volumetric ratio that says nothing about the behaviour of the myocardium producing the volume change. **(18)**

Current classification divides heart failure into reduced ejection fraction at or below forty per cent, mildly reduced between forty-one and forty-nine per cent, and preserved at or above fifty per cent when symptoms, structural abnormality or raised natriuretic peptides are also present. Roughly half of all patients fall into the preserved or mildly reduced categories, and this phenotype predominates in rheumatoid arthritis. **(19)**

Measurement of ejection fraction is subject to appreciable variability related to image quality, endocardial border definition and the geometric assumptions of the chosen method. The Teichholz formula assumes a symmetrical ellipsoid cavity and is unreliable when regional wall motion abnormality is present, while the biplane method of discs still depends on adequate apical windows. Reported test-retest variability of eight to ten per cent limits interpretation of small changes. **(20)**

A further limitation arises from the compensatory relationship between the three directions of deformation. Longitudinal shortening is generated mainly by subendocardial fibres, whereas circumferential shortening and radial thickening depend on midwall and subepicardial layers and contribute more to volume change. When longitudinal function declines, augmented circumferential shortening maintains stroke volume and holds ejection fraction within normal limits. **(21)**

Principles of Speckle Tracking Echocardiography

Speckle tracking echocardiography derives myocardial motion and deformation from the pattern of acoustic markers seen within the myocardial wall on standard grey-scale images. These markers arise from interference of ultrasound backscattered by structures smaller than the wavelength of the beam. Groups of adjacent speckles form stable patterns that persist between frames and behave as natural acoustic fingerprints of the tissue in which they lie. **(22)**

The technique was developed to overcome the limitations of tissue Doppler imaging, the first echocardiographic method able to measure strain. Tissue Doppler records only the velocity component parallel to the ultrasound beam, so the segment studied must be aligned with the direction of insonation. This restriction confines reliable assessment to a small number of segments, whereas speckle tracking follows displacement in two dimensions without angle dependence. **(23)**

Standardisation has been necessary because vendors use different tracking algorithms, smoothing filters and definitions of the region of interest. A consensus initiative involving manufacturers and professional societies produced agreed definitions for timing reference points, the segmentation model and the reporting of global longitudinal strain. Absolute values still differ between systems, so serial studies in one patient should use the same equipment and software version. **(24)**

Accuracy has been examined against reference standards including sonomicrometry, magnetic resonance tagging and invasive assessment of loading. Experimental work altering ventricular loading in a controlled manner showed that strain analysis tracked the degree of unloading reliably, which supports its use as a measure of myocardial mechanics rather than a derivative of chamber geometry. Reproducibility for global longitudinal strain is better than for ejection fraction. **(25)**

Components of Myocardial Deformation

Strain is a dimensionless measure of deformation expressed as the fractional change in length of a myocardial segment relative to its original length, reported as a percentage. Lengthening or thickening gives a positive value and shortening or thinning a negative one. Strain rate is the first derivative of strain with respect to time, which makes it less load dependent than strain itself but more susceptible to noise. **(26)**

Longitudinal strain describes shortening along the axis running from base to apex and is obtained from the apical four-chamber, two-chamber and long-axis views. Averaging peak systolic values across these views yields global longitudinal strain, the most widely reported deformation parameter. Normal values in healthy adults lie approximately between minus eighteen and minus twenty-two per cent, with values less negative than minus sixteen per cent regarded as abnormal. **(27)**

Circumferential strain describes shortening around the circular perimeter of the ventricle in the short-axis view, and radial strain describes wall thickening towards the cavity centre during systole. Normal circumferential values fall approximately between minus twenty and minus twenty-eight per cent, while radial values exceed thirty-six per cent. Radial strain carries the widest measurement variability because tracking must cross the full wall thickness. **(28)**

Evidence of Impaired Myocardial Deformation in Rheumatoid Arthritis

Deformation imaging has been applied across the autoimmune rheumatic diseases, and rheumatoid arthritis has been the most extensively studied. Reviews of this literature describe a consistent pattern in which global longitudinal strain is reduced relative to healthy controls while ejection fraction, chamber dimensions and left ventricular mass index remain comparable. The same pattern appears in lupus, systemic sclerosis and ankylosing spondylitis, pointing to inflammation as the common factor. **(29)**

Layer-specific analysis has added detail by separating endocardial, midmyocardial and epicardial deformation. Work using this approach in rheumatoid arthritis found reduction across all three layers, most marked in the endocardium, which fits the known vulnerability of subendocardial longitudinal fibres to microvascular

impairment. Strain values were worse with longer disease duration and correlated with composite activity scores and with amino-terminal pro-B-type natriuretic peptide. **(30)**

Studies restricted to patients with entirely normal conventional echocardiography give the clearest evidence of added value. In one such cohort, approximately one third of rheumatoid arthritis patients with preserved ejection fraction had global longitudinal strain below the accepted threshold for normality, whereas no control participant met that criterion. These patients had longer disease duration and higher inflammatory markers than the remainder. **(31)**

Pooled analysis of published cohorts has confirmed the direction and magnitude of these differences. A systematic review with meta-analysis found significantly lower global longitudinal strain and lower global circumferential strain in rheumatoid arthritis than in controls, with heterogeneity reflecting differences in vendor platform, disease duration and treatment rather than disagreement about the presence of an effect. Consistency across regions strengthens the case for a disease-related mechanism. **(32)**

The right ventricle is also affected, although it has been studied less often. Deformation analysis of both ventricles has shown reduced right ventricular free wall longitudinal strain alongside reduced left ventricular global longitudinal strain, with greater impairment in active disease than in remission. Right ventricular involvement is plausible given that the same inflammatory and microvascular mechanisms operate throughout the myocardium. **(33)**

Determinants of Strain Impairment

Disease activity is usually quantified using the composite score calculated from twenty-eight joint counts, an acute-phase reactant and a patient global assessment. The score is interpreted against thresholds defining remission below two point six, low activity to three point two, moderate activity to five point one and high activity above that value. Several deformation studies have reported an inverse relationship between this score and global longitudinal strain. **(34)**

Functional disability, assessed by the self-administered questionnaire covering twenty activities across eight domains of daily living, has proved a strong correlate of impaired deformation. The resulting index ranges from zero to three, with values between zero and one denoting mild to moderate limitation. Higher scores accompany worse global longitudinal strain in several cohorts, and disability integrates disease effects over years rather than at a single moment. **(35)**

The relationship between individual laboratory markers and strain has been less consistent. C-reactive protein is synthesised by hepatocytes in response to interleukin-6 and changes rapidly with inflammatory state, which makes it a sensitive indicator of current activity but a poor summary of past exposure. Several studies found no association between single measurements and strain, while time-averaged values across years showed clearer relationships. **(36)**

Natriuretic peptides occupy an intermediate position between inflammatory and cardiac markers. Concentrations of B-type natriuretic peptide and its amino-terminal fragment are higher in rheumatoid arthritis than in non-inflammatory controls, and the elevation relates to inflammatory activity as well as to ventricular wall stress. This dual determination complicates interpretation, although values still correlate with reduced global longitudinal strain in several cohorts. **(37)**

Mechanistic work has begun to connect biomarker elevation with specific signalling pathways. A cross-sectional study measuring pro-B-type natriuretic peptide alongside cytokine profiles and components of the nuclear factor erythroid 2-related factor 2 and haem oxygenase-1 pathway found altered signalling in patients compared with controls, together with higher peptide concentrations. The findings support a model in which oxidative and inflammatory stress act together on the myocardium. **(38)**

Influence of Antirheumatic Therapy on Myocardial Deformation

Suppression of inflammation is generally accompanied by improvement in the cardiovascular profile of these patients. Reviews of the available evidence describe lower cardiovascular event rates in patients treated

effectively with conventional synthetic and biological disease-modifying drugs, together with improvement in endothelial function, arterial stiffness and lipid handling. The magnitude of benefit appears to follow the degree of inflammatory control rather than the specific agent chosen. **(39)**

Studies measuring deformation before and after starting therapy give a more cautious picture. Observational follow-up of patients commencing tumour necrosis factor inhibition found no significant change in global longitudinal strain or ejection fraction after six months, despite clinical response in the joints. Six months may be too short for structural myocardial change, and baseline function was relatively preserved, which limits the scope for measurable improvement. **(40)**

Magnetic resonance imaging has addressed the same question with higher spatial resolution. A prospective study in patients starting biological therapy reported improvement in global circumferential, longitudinal and radial strain over the treatment period, with the largest gains in those achieving the greatest reduction in disease activity. The difference from echocardiographic studies may reflect greater precision for regional deformation or longer follow-up. **(41)**

Corticosteroids present a different balance of effects. Their anti-inflammatory action is rapid and reliable, but prolonged exposure promotes hypertension, insulin resistance, dyslipidaemia, fluid retention and direct myocardial remodelling. Several deformation studies have found worse strain values in patients receiving these agents, although confounding by indication is difficult to exclude since they are given preferentially to patients with more severe disease. **(42)**

Clinical Implications, Limitations and Future Directions

The prognostic value of deformation imaging has been addressed by prospective cohort work. Follow-up of a dedicated rheumatoid arthritis cohort found that subclinical left ventricular dysfunction defined by global longitudinal strain carried adverse prognostic implications for major adverse cardiovascular events and heart failure hospitalisation, independent of conventional risk factors and ejection fraction. Traditional activity measures did not predict strain impairment in the same cohort. **(43)**

Incorporating strain into routine cardiac assessment requires attention to methodological detail. Guidance on diastolic assessment recommends a multiparametric approach in which no single measurement is used alone, and the same principle applies to systolic deformation. Image quality determines feasibility, tracking fails in a proportion of patients with poor acoustic windows, and reference values should be drawn from the same vendor platform used for measurement. **(44)**

Several confounders complicate interpretation of the published literature. Body mass index is itself associated with rheumatoid arthritis risk in a dose-dependent manner, and obesity independently reduces measured global longitudinal strain through haemodynamic and technical mechanisms, so cohorts differing in body composition are not directly comparable. Studies also differ in whether patients with any cardiovascular history were excluded. **(45)**

Future work should address these gaps through larger multicentre cohorts with longitudinal follow-up and uniform case definition based on the accepted classification criteria, which combine joint involvement, serology, acute-phase response and symptom duration. Serial deformation measurement linked to time-averaged inflammatory exposure would clarify whether strain impairment progresses or reverses with sustained disease control, and interventional trials would show whether strain-guided management improves outcomes. **(46)**

Conclusion

Cardiac involvement in rheumatoid arthritis develops silently across years of sustained systemic inflammation and is already well established by the time conventional echocardiographic measures become abnormal, since ejection fraction remains within reference limits while longitudinal myocardial shortening has begun to decline. Two-dimensional speckle tracking echocardiography measures this deformation directly, is independent of beam angle, requires no additional image acquisition, and reproducibly identifies reduced global longitudinal strain in patients whose conventional studies are normal, with the degree of impairment following disease

duration, functional disability and cumulative inflammatory burden rather than any single laboratory marker. **(45, 46)**

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