Prevalence and Correlates of Early Right Ventricular Dysfunction in Sarcoidosis and Its Association with Outcome

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Background: Right ventricular (RV) function has not been systematically assessed in sarcoidosis. The aim of this study was to assess the prevalence and associates of RV dysfunction in sarcoidosis using global longitudinal peak systolic strain (GLS). Furthermore, whether RV dysfunction was associated with clinical outcomes was investigated.

Methods: A total of 88 patients with sarcoidosis (mean age, 54 ± 13 years; 51% men) without known sarcoid-related or other structural heart disease or alternative etiologies of pulmonary hypertension were retrospectively included. RV GLS was measured using two-dimensional speckle-tracking echocardiography, and patients were stratified (using a previously defined cutoff value) as having preserved (RV GLS < −19%) or impaired (RV GLS ≥ −19%) RV function. An age- and gender-matched control group (n = 50) was included. The main outcome was all-cause mortality or clinical heart failure (hospitalization or New York Heart Association functional class ≥ III and/or deterioration by one or more classes).

Results: RV GLS was significantly reduced (−20.1 ± 4.6 vs −24.6 ± 1.8%, P = .001) in patients compared with control subjects. Patients with impaired RV function (n = 41) were older and had worse pulmonary function, worse left ventricular diastolic function, and lower tricuspid annular plane systolic excursion compared with patients with preserved RV function (n = 47). Lower tricuspid annular plane systolic excursion and diabetes were independent correlates of RV GLS. Over a median follow-up period of 37 months, 19 clinical end points occurred. Patients with impaired RV function were more likely to experience the clinical end point (log-rank P = .003).

Conclusions: RV contractile dysfunction, identified using RV GLS, is common in patients with sarcoidosis without manifest cardiac involvement or pulmonary hypertension and is associated with adverse outcome. RV GLS may therefore be useful to detect sarcoidosis-related RV dysfunction at an earlier and potentially modifiable stage. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Sarcoidosis, Right ventricular function, Speckle-tracking echocardiography, Longitudinal strain, Infiltrative cardiomyopathy

Left ventricular (LV) systolic dysfunction is an undisputed harbinger of poor prognosis in patients with sarcoidosis.[1,2] However, less is known about right ventricular (RV) function in these patients, even though RV impairment can arise through multiple mechanisms, including primary involvement of the RV myocardium or as a consequence of pulmonary hypertension. Direct granulomatous infiltration of the myocardium of the interventricular septum and/or the RV free wall not only can manifest as clinical heart failure but also can predispose to lethal bradyarrhythmias and/or tachyarrhythmias that may occur as the first mode of clinical presentation.[1,3] Pulmonary hypertension, regardless of the specific etiology, is also a well-known adverse prognostic factor in patients with sarcoidosis,[4,5] and the development of superimposed RV dysfunction has been shown to further negatively affect outcomes.[5] Therefore, earlier detection of RV contractile impairment, whether primary or secondary, before the development of heart failure or significant pulmonary hypertension, is clinically relevant in this patient population.

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Abbreviations

FWS = Free wall longitudinal strain

GLS = Global longitudinal peak systolic strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

NYHA = New York Heart Association

RV = Right ventricular

TAPSE = Tricuspid annular plane systolic excursion

2D = Two-dimensional

Two-dimensional (2D) echocardiography remains the first-line tool to detect cardiac structural abnormalities in patients with sarcoidosis.[6] However, accurate assessment of RV function by conventional echocardiography is challenged by several factors, most notably the complex geometry of the RV cavity. Meanwhile, longitudinal shortening has been shown to be the most important contributor to RV systolic function.[7] Speckle-tracking strain echocardiography enables the direct assessment of intrinsic RV myocardial function, and RV global longitudinal peak systolic strain (GLS) has been recently validated in both normal subjects and those with RV dysfunction.[8,9] It has also been demonstrated as an independent marker of prognosis in an all-comers pulmonary hypertension population.[10]

Accordingly, the principal aim of the present study was to assess the prevalence and associates of isolated RV dysfunction in sarcoidosis in the absence of overt cardiac involvement or severe pulmonary hypertension using RV GLS as a sensitive, direct parameter of RV function. Second, we sought to investigate whether early identification of RV dysfunction using GLS is associated with clinical outcomes in these patients.

METHODS

Patient Population

This was an observational retrospective cohort study. A total of 130 patients with sarcoidosis attending our referral center (Leiden University Medical Center, Leiden, The Netherlands) and undergoing 2D echocardiography at the time of or following their diagnoses were identified using the departmental cardiology information system (EPD-Vision). The diagnosis of sarcoidosis was made in the setting of a compatible clinical picture and the absence of an alternative disease process capable of producing a similar clinical syndrome, with or without histologic confirmation of the presence of noncaseating granulomas.[11] Given that the aim of the present study was to identify the prevalence of RV dysfunction in patients with sarcoidosis independent of manifest systolic LV impairment or other clinical evidence of cardiac involvement, patients with known or suspected cardiac sarcoidosis on the basis of the Japanese Ministry of Health and Welfare diagnostic criteria[12] were excluded ($n = 5$ definite cardiac sarcoidosis, $n = 9$ one major criterion alone). Similarly, those with non-sarcoid-related etiologies of structural heart disease ($n = 16$) were also excluded. Finally, patients with noncardiac conditions associated with pulmonary hypertension were also excluded to avoid possible confounding in the setting of differential causes of afterload-associated RV dysfunction (Figure 1).

Control subjects were identified from the departmental echocardiographic database (EchoPAC version 112.0.0; GE Vingmed Ultrasound AS, Horten, Norway) using a dedicated search code defining the absence of cardiac structural abnormalities[13,14] in subjects without histories of cardiac disease, typically referred for echocardiography in the setting of cardiovascular risk stratification or the finding of a murmur on auscultation. An age- and gender-matched comparator group ($n = 50$) was selected on the basis of published comparability principles.[15]

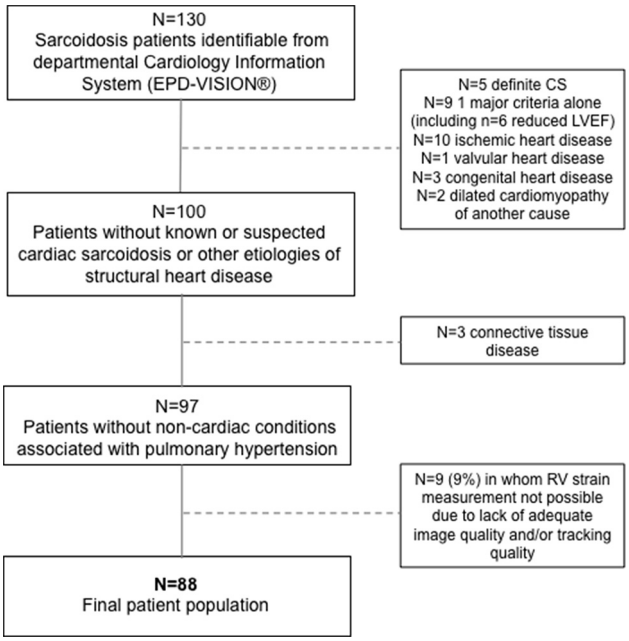

Figure 1 Study flowchart illustrating patient selection process. *CS*, Cardiac sarcoidosis.

The current retrospective evaluation of clinically acquired data was approved by the institutional review board of the Leiden University Medical Center, which waived the need to obtain written informed consent.

Study Protocol and Clinical End Points

Clinical data, including organs involved, mode of diagnosis, serum angiotensin-converting enzyme and lysozyme levels, and results of chest radiography and pulmonary function testing, were recorded for all patients. Pulmonary function parameters were measured according to American Thoracic Society and European Respiratory Society recommendations.[16] RV GLS was measured by 2D speckle-tracking analysis applied to baseline echocardiographic images alongside comprehensive 2D and Doppler analysis in all patients and control subjects. The main outcome measure was prespecified as a composite end point of all-cause mortality or clinical heart failure, defined as heart failure–related hospitalization, New York Heart Association (NYHA) functional class III or IV symptoms, or deterioration of NYHA functional class by one or more classes from baseline.[1] Outcome data were assessed by retrospective review of electronic medical data and the official Dutch National Survival Registry. Follow-up was available for all included patients.

Conventional Echocardiography

Two-dimensional grayscale and Doppler images were acquired with patients in the left lateral decubitus position using a commercially available system (Vivid 7 and e9; GE Vingmed Ultrasound AS) equipped with 3.5-MHz or M5S transducers. Image analysis was performed offline using EchoPAC version 112.0.0. LV chamber and wall thickness quantification were performed according to standard recommendations.[17] LV ejection fraction (LVEF) was derived from LV volumes quantified according to the Simpson biplane method, as recommended.[17] Left atrial volume was also measured using the Simpson biplane