The clinical implications of left ventricular diastolic dysfunction in systemic sclerosis

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Abstract

Objective

We sought to quantify the burden of left ventricular diastolic dysfunction (LVDD) and heart failure with preserved ejection fraction (HFpEF) in systemic sclerosis (SSc) and assess the progression of LVDD over time and its prognostic importance.

Methods

Two-hundred and twenty-five participants enrolled in the Australian Scleroderma Cohort Study were included and LVDD was assessed according to 2016 ASE/EACVI Guidelines. Logistic regression analyses and generalised estimating equations were performed to evaluate the relationship between LVDD and SSc disease characteristics and symptoms and signs of heart failure, respectively. The relationship between LVDD and mortality was assessed using Kaplan-Meier survival estimates.

Results

Thirty-four (15%) participants were diagnosed with LVDD. A further 89 (40%) participants had indeterminate diastolic function. Older age (p<0.01), hypertension (p=0.02), impaired systolic function (p=0.03) and interstitial lung disease (p=0.01) were all associated with the presence of LVDD. There was no association between the presence of LVDD and clinical signs of heart failure, however, LVDD was associated with more breathlessness and worse functional class (p=0.03). LVDD was observed to progress over time, with significant worsening of parameters of left ventricular filling pressure. There was no significant relationship between LVDD and mortality (p=0.23).

Conclusion

Abnormal diastolic function is a common finding in SSc, progresses over time and is associated with more severe dyspnoea. Whilst patients with LVDD are more breathless, LVDD is not clearly associated with clinical findings of heart failure demonstrating that LVDD may be of importance in explaining symptoms even in the absence of HFpEF in SSc.

Key words
systemic sclerosis, cardiac disease, diastolic dysfunction, heart failure, echocardiography

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Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease of unknown aetiology that causes characteristic skin fibrosis and is associated with multi-system internal organ involvement. More severe organ involvement is associated with reduced patient survival (1) and primary SSc heart involvement (SHI) is a significant contributor to SSc-associated mortality (2, 3). Clinically apparent SHI has a very poor prognosis, with reported mortality rates of up to 72% in those presenting with heart failure, and one third of deaths due to SHI occur within 4 years of diagnosis (4). As such, there has been much interest in the detection of SHI, prior to the onset of heart failure symptoms, to take advantage of any potential therapeutic window of opportunity that may exist for early intervention, prevention of disease progression and improved survival.

Left ventricular diastolic dysfunction (LVDD) has been proposed to be a key mechanism of heart failure with preserved ejection fraction (HFpEF) and is most commonly caused by hypertension, obesity and age-related change (5). Diastolic dysfunction is thought to be an early indicator of SHI. Myocardial fibrosis is the histopathological hallmark of SHI (6, 7) and echocardiographic measures of reduced myocardial compliance are hypothesised to reflect an increasing burden of fibrosis due to progressive SSc and precede the development of clinical heart failure (8). However, a definitive link between diastolic dysfunction and heart failure syndromes and subsequent systolic dysfunction in SSc is yet to be shown. Three studies have evaluated the prognostic implications of LVDD in SSc and suggested an increased risk of death in association with abnormal left ventricular (LV) diastolic function, (9-11) independent of other co-morbidities such as coronary artery disease and pulmonary arterial hypertension (PAH). However, with the inclusion of patients with other cardiac co-morbidities, these studies highlight one of the clinical challenges of HFpEF, namely the attribution of the cause of diastolic dysfunction and whether LVDD and HFpEF are a 'primary' phenomena or secondary to other cardiac and metabolic co-morbidities (5).

Therefore, we aimed to quantify the burden of LVDD in a cohort of patients without co-morbid ischaemic or valvular heart disease or PAH to estimate the prevalence of LVDD due to SSc. We sought to understand the rate of progression of abnormalities of diastolic function attributable to SSc over time. Secondarily, considering the limited data available to understand the symptomatic importance of LVDD and the prevalence of HFpEF in SSc, we examined the association between the presence of LVDD and clinical symptoms and signs of heart failure.

Methods

Patients enrolled in the Australian Scleroderma Cohort Study (ASCS) at St Vincent's Hospital, Melbourne between January 2007 and July 2017 were eligible for inclusion in this study. Individuals aged ≥18 years were included if they fulfilled the 2013 ACR/EULAR classification criteria for SSc, (12) had data available to define a disease subtype as per LeRoy criteria (13) and had at least one transthoracic echocardiogram (TTE) with ≥2 parameters for the assessment of LVDD, as per the 2016 American Society of Echocardiography (ASE) Recommendations for the Assessment of LV Diastolic Function (14). Patients who were ever diagnosed with ischaemic heart disease or angina, moderate to severe valvular dysfunction detected by TTE or PAH identified by right heart catheterisation with mean pulmonary artery pressure ≥25mmHg and pulmonary arterial wedge pressure ≤15mmHg at any time during follow-up were excluded from all analyses. Ischaemic heart disease was considered present if participants had a history of acute myocardial infarction or coronary angioplasty. Symptoms of angina are recorded at each ASCS annual review. If a patient had ever reported ischaemic chest pain consistent with angina, they were excluded from this study. Ethics approval was provided by the Human Research Ethics Committee at St Vincent's Hospital, Melbourne (HREC-A

020/07) and written informed consent was obtained from all patients prior to the collection of any data. The study was performed in accordance with the Declaration of Helsinki.

Data collection

Demographic and disease-related data were collected prospectively according to a standardised protocol. Autoantibodies were defined as present if ever recorded during follow-up. Disease duration was defined from date of onset of the first non-Raynaud's SSc manifestation. Disease manifestations were considered present if ever recorded during follow-up. The presence of co-morbid ischaemic heart disease and angina were recorded. The presence of diabetes and hypertension were recorded (yes/no) at each annual review, based on history from the patient and medical record review. Smoking status (either current or ex-smoker) was recorded at study entry and at each annual review. In this study, any participant who reported any history of smoking either at baseline or at a subsequent study visit was considered an 'ever smoker'. The presence of any episodes of Raynaud's phenomenon, defined as biphasic or triphasic colour change of the peripheries in response to cold or other stressful stimuli, was recorded at each study visit, based on patients' recall of symptoms. A patient was recorded as ever having had digital ulcers if they reported a history of an area of loss of epithelialisation of the finger, distal to the distal interphalangeal joint at any time during the course of their SSc or such an area of loss of epithelialisation was observed on clinical examination at a study visit. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) at each study visit. Interstitial lung disease (ILD) was identified by the presence of typical findings of pulmonary fibrosis on high resolution computed tomography of the chest (HRCT). Individuals were referred for HRCT if ILD was suspected on the basis of abnormal respiratory function tests or abnormal respiratory system examination findings. Scleroderma renal crisis was defined by the presence of at least two of: new onset hypertension in the absence of alternate aetiology, rising creatinine and new onset microangiopathic haemolytic anaemia. Myositis was defined by a positive muscle biopsy or clinician diagnosis with elevated creatine kinase, electromyographic or magnetic resonance imaging findings consistent with myositis.

Individuals were reviewed annually, with standardised collection of disease-related data and clinical examination, TTE and physician and patient-reported outcomes. Clinical examination included assessment for signs of heart failure including the jugular venous pressure, the presence of pulmonary crepitations on auscultation of the chest and peripheral pitting oedema. At each study visit, the World Health Organisation (WHO) Functional Class was recorded by the physician. Patients were asked to rate their level of breathlessness using the Borg Dyspnoea Scale which rates breathless on a numerical rating scale from 0 to 10 where 0 = no breathlessness to 10 = maximal breathlessness. Patients were also asked "Have you been more breathless in the past month?" which was recorded with a yes/no answer.

Transthoracic echocardiography

All patients underwent annual TTEs, and all TTEs were performed at St Vincent's Hospital, Melbourne. Ultrasound recordings were performed using GE Vingmed Vivid E9 Ultrasound (GE, Vingmed Ultrasound, Horten, USA). Patients were examined in the left lateral decubitus position and software analyses were performed using Echopac PC v204 analysis software (GE, Horten, USA). All TTEs were re-examined to extract variables of interest. Standard parasternal, apical and subxiphoid windows were used to image cardiac chambers, as well as colour, pulsed- and continuous-wave Doppler measurements. All patients were in sinus rhythm at the time of TTE. Bi-plane LVEF was calculated according to the modified Simpson's rule, and normal LV systolic function was considered LVEF ≥50%. Left atrial volume index (LAVi) was calculated as the average of the volumetric measurement of the left atrium indexed to body surface area. Pulsed-wave Doppler imaging of the mitral valve inflow, measuring peak early diastolic velocity (E) and peak late diastolic velocity (A) to calculate the E/A ratio was used to evaluate diastolic function. Tissue Doppler imaging was used to measure the early diastolic velocity (e') and calculate the average E/e' ratio to estimate LV filling pressures. Tricuspid regurgitant maximum velocity (TRV) was calculated by continuous Doppler. Right ventricular (RV) function was assessed using the tricuspid annular plane systolic excursion (TAPSE). TRV was used to estimate the RV systolic pressure (RVSP) using the modified Bernoulli equation and adding estimated right atrial pressure. LVDD was defined according to the 2016 Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography (14). LVDD was considered present if more than 50% of available parameters met the threshold of abnormal diastolic function, as per ASE guidelines. LVDD was graded according to the 2016 recommendations as grades I, II or III using the E/A ratio and the number of abnormal diastolic parameters (14). If insufficient diastolic parameters were available for grading of LVDD patients were considered to have indeterminate LV diastolic function.

Statistical analyses

Data are presented as number (percentage) for categorical variables and median (interquartile range (IQR)) for continuous variables. The chi-square test was used to compare the frequency of categorical variables and the Wilcoxon rank sum test was used to compare the median values of non-symmetric variables. Wilcoxon signed rank test was used to compare the change between baseline and follow up parameters of LVDD. The associations between LVDD (dependent variable) and SSc disease manifestations (outcome variables) were evaluated using logistic regression analysis. Variables found to have a significant relationship with LVDD or a trend towards significance ($p \leq 0.10$) were included in multivariable logistic regression analysis. Generalised estimating equations (GEE) were used to evaluate any association

Table I. Baseline characteristics.

Patient characteristic	n=225
Female (n, %)	203 (90.2%)
Age at recruitment (years) (median, IQR)	54 (46-64)
Age >60 years at recruitment (n, %)	79 (35.1%)
Disease duration at recruitment (years) (median (IQR))	6.3 (1.8-15.8)
Follow-up (years) (median (IQR))	5.4 (3.0-6.9)
Death (n, %)	12 (5.3%)
Diffuse subtype (n, %)	64 (28.4%)
Anti-centromere antibody (n, %)	101 (45.5%)
Scl70 (n, %)	39 (17.7%)
RNAP III* (n, %)	33 (16.4%)
Interstitial lung disease (n, %)	60 (26.7%)
Scleroderma renal crisis (n, %)	6 (2.7%)
Myositis (n, %)	8 (3.6%)
Raynaud's phenomenon (n, %)	225 (100%)
Digital ulcer (n, %)	113 (50.2%)
Hypertension (n, %)	103 (45.8%)
Body Mass Index (at baseline) (median (IQR))	25.7 (22.6-29.3)
Diabetes (n, %)	13 (5.8%)
Ever smoker (n, %)	90 (40.0%)

*201 patients had RNAP III testing performed.
IQR: inter-quartile range; RNAP III: RNA polymerase III antibody; Scl70: anti-topoisomerase I antibody.

Table II. Baseline echocardiography parameters.

	Whole cohort n=225	LVDD n=34	No LVDD n=191	*p* value
LV diastolic dysfunction (n, %)	34 (15.1%)	-	-	
Indeterminate diastolic function (n, %)	80 (35.6%)	-	-	
LVEF (%) (median (IQR))	60 (60-65)	63.5 (60-67)	60 (60-60)	0.20
LAVi (cm/m^2) (median (IQR))	28.5 (24-34)	35.5 (29-43)	28 (26-30)	0.08
Average E/e' (median (IQR))	8 (7-10)	8 (6-14)	8 (8-9)	0.80
E/A ratio (median (IQR))	1.1 (0.9-1.4)	0.9 (0.9-1.2)	1.1 (1.0-1.2)	0.03
E/A <0.8 (n, %)	38 (17.1%)	8 (23.5%)	30 (15.7%)	0.24
E/A ≥2 (n, %)	14 (6.3%)	1 (2.9%)	13 (6.8%)	0.40
RVSP* (mmHg) (median (IQR))	30 (26-35)	38 (33-42)	30 (28-31)	<0.01
RVSP ≥35mmHg (n, %)	52 (25.5%)	18 (52.9%)	34 (17.8%)	<0.01
TAPSE (mm) (median (IQR))	22 (20-26)	25 (17-33)	22 (21-23)	0.34

*204 patients had RVSP available for analysis at baseline TTE.
A: average late mitral inflow velocity; BMI: body mass index; E: average early mitral inflow velocity; e': mitral annual early diastolic velocity; IQR: inter-quartile range; LAVi: left atrial volume index; LV: left ventricle; LVDD: left ventricular diastolic dysfunction; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annual plane systolic excursion.

Table III. Associations between signs and symptoms of heart failure and left ventricular diastolic dysfunction.

Clinical feature*	LVDD	
	Odds ratio (95% CI)	*p* value
Borg Breathlessness Index	1.05 (0.9-1.2)	0.59
WHO Functional Class	1.61 (1.1-2.5)	0.03
WHO Functional Class III or IV	2.32 (1.1-5.00)	0.03
Patient-reported worsening breathlessness in past month	1.47 (0.7-3.3)	0.35
Elevated JVP	Perfect prediction	
Pulmonary crepitations	0.85 (0.4-1.9)	0.68
Peripheral pitting oedema	1.71 (0.7-3.9)	0.21

*controlled for presence of interstitial lung disease.
JVP: jugular venous pressure; LVDD: left ventricular diastolic dysfunction; WHO: World health Organisation.

between LVDD and clinical symptoms and signs of heart failure, taking into account the expected correlation that arises when repeated measures are taken from the same individual over time. All GEE analyses were controlled for the presence of ILD, given the significant overlap between symptoms of heart failure and ILD. Kaplan-Meier survival analysis was used to investigate the relationship between LVDD and mortality, with significance tested using the log-rank test. Survival analysis only included those patients with LVDD as per the ASE guidelines compared to those with normal diastolic function. Patients with indeterminate LV diastolic function were excluded from this analysis. For all analyses a p-value <0.05 was considered statistically significant. Statistical analyses were performed using STATA 14.2 software (StataCorp, College Station, TX, USA).

Results

Two-hundred and twenty-five patients fulfilled the inclusion criteria for this study. The median age at recruitment was 54.2 years (IQR 46.3–64.1) and 79 (35.1%) of the participants were aged >60 years at entry to the study. Population characteristics are detailed in Table I.

Burden of diastolic dysfunction

A median of three (IQR 2–5) TTE were performed on each patient, with a median interval of 448 days (IQR 379-539) between TTE. Thirty-four (15.1%) participants fulfilled the ASE criteria for LVDD at any time during follow up and a further 89 (39.6%) participants had indeterminate LV diastolic function. Of those patients with LVDD, 6 had Grade I LVDD, 15 had Grade II LVDD and 2 had Grade III LVDD. Grading of LVDD was not able to be determined for 11 patients. Eight patients (3.6%) recorded a LVEF <50% during the study.

Table II summarises the differences in baseline TTE between those with or without a diagnosis of LVDD at any time during study follow up. The baseline RVSP was higher in those patients diagnosed with LVDD at any time during study (38 mmHg *vs*. 30mmHg, p=0.01). No relationship between LVDD and clinical findings of heart failure (elevated jugular venous pressure, pulmonary crepitations or peripheral pitting oedema) were found. However, diastolic dysfunction was noted to be significantly associated with more severe symptoms and poorer functional status, even in the absence of clinical heart failure (Table III).

Clinical associations of left ventricular diastolic dysfunction

Multivariable analysis demonstrated that LVDD was significantly associated with older age at recruitment, hypertension, reduced LVEF and ILD

Table IV. Clinical associations of left ventricular diastolic dysfunction.

	Odds Ratio (95% CI)	*p* value
Demographic features		
Age >60 years at recruitment	4.22 (1.7-10.6)	<0.01
Co-morbidities		
Hypertension	3.32 (1.3-8.8)	0.02
SSc-specific features		
Interstitial lung disease	3.77 (1.4-10.0)	0.01
LVEF <50%	6.92 (1.2-41.2)	0.03

CI: confidence interval; ILD: interstitial lung disease; LVEF: left ventricular ejection fraction; SSc: systemic sclerosis.

(Table IV, univariable analysis presented in Supplementary Table S1). Systolic cardiac dysfunction, presumed to be due to SHI given the absence of IHD, valvular heart disease and PAH in the study population, and ILD were the only SSc disease manifestations associated with LVDD.

Progression of left ventricular diastolic function

One hundred and ninety (84.44%) patients had at least two TTE available for analysis. The overall change between baseline and final TTE findings of LVDD are presented in Table V. The median time between baseline and final TTE was 3.45 years (2.2-5.3), with a significant increase in average E/e' ratio and decrease in septal e' velocity observed in the whole SSc population. A progressive increase in LV filling pressures between annual TTEs was noted in those with LVDD compared to those without LVDD, with a significantly higher increase of average E/e' ratio (1.13 *vs*. 0, p=0.01) and increase in TRV (0.04 cm/s *vs*. 0 cm/s, p=0.02) between serial TTEs.

Survival analysis

Kaplan-Meier survival analysis found no significant relationship between a diagnosis of LVDD and mortality. Further analysis was performed evaluating the risk of any diastolic dysfunction (those with either indeterminate diastolic function and LVDD) and death and no significant relationship was observed (see Supplementary material).

Discussion

We have shown abnormalities of diastolic function are highly prevalent in patients with SSc, with a significant negative impact on symptoms and overall function but are not associated with increased mortality, in contrast to previous studies (9-11, 15). In a cohort of patients without IHD, valvular heart disease and PAH, over half of SSc patients were found to have some abnormality of diastolic function, with a cumulative incidence of LVDD as per ASE criteria of 15%. Analysis of parameters of diastolic dysfunction indicate that LVDD in SSc is progressive with worsening of LV filling pressures observed over time. The cumulative incidence of LVDD measured in this study of 15% is lower the incidence rates observed in other studies of LVDD in SSc, (10) however similar to the other studies that apply the 2016 ASE guidelines to cohorts of patients without coronary artery disease or valvular heart disease (11, 16). This lower observed rate is likely reflective of the stringent definition of LVDD applied to this cohort of patients and the exclusion of patients with other cardiac co-morbidities known to contribute to the development of diastolic dysfunction. Co-morbid cardiovascular disease is thought to compound any effects of SSc on the myocardium, accelerating the development of LVDD (16). The absence of other cardiac co-morbidities in this patient population perhaps accounts for the observed difference in survival of patients with LVDD in this study. Exclusion of individuals with coronary artery disease likely selects for a younger, healthier patient population and this cohort is one of prevalent, long-standing SSc, introducing a survivor bias that may further explain the absence of any association between LVDD and mortality.

No study has previously attempted to quantify the burden of HFpEF in SSc by correlating contemporaneous examination findings with LVDD measured by TTE. Our results accord with the observation that heart failure attributable to SHI is an uncommon manifestation of SSc (17). We found no association between TTE findings of LVDD and clinical signs of heart failure and our results suggest that HFpEF is an uncommon manifestation of SSc despite the high prevalence of LVDD. However, that is not to say that isolated LVDD is without clinical consequence; we have

Table V. LVDD parameters at baseline and final follow-up.

	Whole population (n=190)			LVDD only (n=31)		
Variable	Baseline TTE	Final TTE	*p*-value	Baseline TTE	Final TTE	*p*-value
LVEF	60 (60-65)	60 (60-65)	0.81	65 (58-70)	60 (60-65)	0.35
LAVi (cm/m^2)	29 (25-34)	28 (24-33)	0.36	36 (29-43)	33 (29-37)	0.18
Average E/e' ratio	8 (7-10)	9 (8-12)	0.01	7.5 (6-12.5)	12 (10-16)	0.04
Septal e'	7 (5.9-8.8)	6.7 (5-8.1)	0.01	6 (5-6.6)	5.25 (4-6.2)	0.08
TR velocity (cm/s)	2.5 (2.3-2.7)	2.5 (2.3-2.7)	0.61	2.8 (2.5-2.9)	2.9 (2.8-3)	0.03

E: average early mitral inflow velocity; e': mitral annual early diastolic velocity; IQR: interquartile range; LAVi: left atrial volume index; LVEF: left ventricular ejection fraction; LVDD: left ventricular diastolic dysfunction; TR: tricuspid regurgitation; TTE: transthoracic echocardiogram.

detected significantly poorer functional status of patients with LVDD compared to those without LVDD, even in the absence of clinical heart failure.

Accurate attribution of LVDD in SSc as a primary phenomenon of SHI rather than a sequela to other disease manifestations or co-morbidities remains a near-impossible task. By comparison to aged-matched populations, patients with SSc are observed to have higher rates of LVDD (9, 16, 18), and autopsy studies have shown excess myocardial fibrosis at a young age in SSc (7). However, in the absence of specific biomarkers of SSc-associated fibrosis, or without endomyocardial biopsy, it is not possible to definitively show that diastolic abnormalities are due to SHI rather than other co-morbidities such as hypertension or pulmonary vascular disease. We have again demonstrated that advancing age and hypertension are strongly associated with LVDD, in keeping with the epidemiology of LVDD in the general population as well as other studies of diastolic dysfunction in SSc (5, 9, 10, 15, 16). It is also very challenging to differentiate LVDD due to SHI from that due to right heart dysfunction and pulmonary vascular disease (10). Patients with idiopathic PAH are noted to have a high prevalence of LVDD (19) and pulmonary vascular disease is highly prevalent in patients with SSc and some degree of lung parenchymal change is a near-universal finding in SSc. Our results suggest that a burden of right heart dysfunction may contribute to a diagnosis of LVDD as we have observed a significant association between LVDD and ILD as well as RVSP, despite the exclusion of all patients diagnosed with PAH at any time during follow up. The complexity of defining the pathological mechanisms of cardiac and pulmonary vascular disease have been recently highlighted in a single-centre study that evaluated consecutive SSc patients with PAH using advanced cardiac imaging and right heart catheterisation. This study showed that left heart disease can be commonly detected in patients with PAH, however multi-modal imaging in combination with invasive measures of pulmonary arterial wedge pressure and clinical evaluation are likely required to detect the concurrent presence of both pulmonary vascular and left heart pathology (20). Therefore, we feel it reasonable to only attribute LVDD to primary SHI cautiously, and arguably this should only be done so in young patients, in the absence of any other cardiovascular co-morbidities, including hypertension, and significant pulmonary disease.

These results should be interpreted within the limitations of the study design. This data was retrospectively analysed and TTE data was re-evaluated for this study, and prior to 2016 TTE data was not routinely collected in strict accordance with the 2016 ASE guidelines for the assessment of LV diastolic function. Additionally, this study did not have a non-SSc control group, therefore no firm conclusions could be drawn about the contribution of co-morbidities such as advancing age or hypertension to the rates of LVDD observed in our study population. We observed relatively few events of either death or LVDD over the course of follow-up, limiting the conclusions that can be drawn about the prognostic implications of LVDD in SSc. Additionally, the low number of patients meeting criteria for LVDD in this study meant it was not possible to perform subgroup analyses to explore the effects of hypertension, diabetes, age and ILD on the development and subsequent progression of LVDD. Furthermore, biomarkers of cardiac disease and heart failure such as troponin and B-type natriuretic peptide (BNP) were not routinely collected in the ASCS. Correlation of LVDD with biomarkers may aid the identification of patients with HFpEF as well as assisting in the stratification of patients into high and low risk groups. Elevated troponin and BNP have both been shown to be useful prognostic markers in SSc, identifying those patients with cardiac abnormalities at increased risk of death and poor cardiac outcome (21, 22).

Conclusion

Abnormalities of diastolic function are common findings in SSc and LVDD is a progressive pathology, with worsening parameters of LV filling pressure noted over time. As a counterpoint to other studies suggesting LVDD is associated with increased mortality in SSc, in the absence of other cardiac co-morbidities, we have not found a link between LVDD and increased mortality. We have for the first time linked contemporaneous clinical and TTE findings showing that LVDD is not associated with signs of heart failure but is associated with dyspnoea and poorer functional status.

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