Effect on Cardiac Function of Longstanding Juvenile-onset Mixed Connective Tissue Disease: A Controlled Study

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ABSTRACT. Objective. To assess cardiac function in patients with juvenile mixed connective tissue disease (JMCTD) compared to matched controls, and to investigate possible associations between cardiac impairment and disease variables and cardiovascular risk factors.

Methods. Fifty JMCTD patients (86% female) examined median 14.9 (6.6–23.0) years after disease onset were compared with 50 age- and sex-matched controls. Electrocardiogram and echocardiography [including e′ as a marker for diastolic dysfunction and long-axis strain (LAS) and left ventricular (LV) ejection fraction (EF) as markers of systolic function] were performed. LV dysfunction (LVD) was defined as low EF, low LAS, or low e′. Right ventricular function was assessed with tricuspid annular plane systolic excursion (TAPSE). Cardiovascular risk factors and disease variables were assessed.

Results. LVD was found in 16% of patients and 4% of controls ($p = 0.035$). EF and LAS were lower in patients compared to controls (6% lower, $p < 0.001$, and 4% lower, $p = 0.044$, respectively). TAPSE was 8% lower in patients versus controls ($p = 0.008$). No patients had signs of pulmonary hypertension. Patients had longer corrected QT time than controls ($p = 0.012$). LVD was associated with higher levels of apolipoprotein B, higher disease activity measured by physician's global assessment, longer prednisolone treatment, and more organ damage assessed with the Myositis Damage Index.

Conclusion. Patients with JMCTD had impaired left and right ventricular function compared to matched controls after median 15 years disease duration. High disease activity and longer treatment with prednisolone were factors associated with LVD. (First Release March 15 2019; J Rheumatol 2019;46:739–47; doi:10.3899/jrheum.180526)

Key Indexing Terms:
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Mixed connective tissue disease (MCTD) is a rare autoimmune disease with overlapping clinical features from systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis (PM). Common findings include Raynaud phenomenon (RP), puffy hands, arthritis, myositis, and interstitial lung disease. Increased cardiovascular morbidity and mortality in inflammatory autoimmune diseases such as idiopathic inflammatory myopathies (which include PM and dermatomyositis) and rheumatoid arthritis (RA) are well known[1]. The risk of cardiovascular involvement in SLE, such as ischemic heart disease, heart failure, and stroke, is up to 50-fold higher compared to the general population, and more pronounced in young individuals[2,3,4]. A systematic review suggested

that 20% of mortality in MCTD was directly caused by cardiac disease[5].

No systematic studies have assessed cardiac function in MCTD patients with juvenile presentation (JMCTD; 7–23% of all MCTD cases)[6,7]; because of the early onset, these patients may have an increased inflammatory burden with higher risk for development of cardiovascular disease (CVD). Some retrospective studies have shown that cardiac disease in JMCTD is more common than in adult MCTD[8,9], but results are conflicting[7].

Subclinical left ventricular dysfunction (LVD) is a predictor of manifest CVD and heart failure in the general population[10,11]. In adult MCTD and juvenile dermatomyositis (JDM), diastolic LVD has been demonstrated compared to controls[12,13,14]. In juvenile SLE and JDM, subclinical systolic LVD was found in patients compared to controls[15,16]. This was measured by global longitudinal strain (long-axis strain; LAS), which is a more sensitive echocardiographic measure than LV ejection fraction (LVEF) for detecting systolic dysfunction[17].

Possible etiologies behind LVD are hypertension (HTN), coronary heart disease, obesity, dyslipidemia, and exposure to cardiotoxic drugs[18]. Disease activity has emerged as an independent risk factor of LVD in both RA[19] and SLE patients[20]. Also, high early disease activity was independently associated with systolic dysfunction in JDM[16]. However, in MCTD this possible relationship with disease activity has not been examined.

Thus, the aim of our study was to assess cardiac function in a representative JMCTD cohort compared to age- and sex-matched controls from the general population, and to investigate possible associations between cardiac impairment and disease characteristics, activity, and damage, and traditional and disease-related cardiovascular risk factors.

MATERIALS AND METHODS

Patients and controls. This case-control study was performed at Oslo University Hospital (OUH) from March 2013 to June 2015. As previously described in detail[21], different methods were used to search for patients with JMCTD in Norway. The inclusion criteria were (1) fulfillment of the Kasukawa or Alarcón-Segovia and Villareal criteria[22], (2) symptom onset before age 18 years, and (3) a clinical diagnosis confirmed by a rheumatologist or pediatrician. Out of 62 patients who fulfilled the inclusion criteria, 3 were dead, 3 did not want to participate, 1 did not respond, and 3 had developed SLE and were excluded. One patient did not participate in the cardiac assessments and another patient was excluded because of an excluded control. The remaining 50 patients represent our study population.

One sex- and age-matched control per patient was randomly selected from the National Population Register and invited to participate. Exclusion criteria were a history of autoimmune disease necessitating immunosuppressive medication, and lung or heart disease, except for mild asthma and HTN.

We obtained informed consent from all patients and controls (and their parents if aged < 16 yrs), according to the Declaration of Helsinki. The study was approved by the Regional Ethics Committee for Medical Research (ID 2012/1721).

Clinical examination and cardiovascular risk assessment. In patients, clinical variables from the time of diagnosis during the entire disease course and upon examination were obtained from clinical rheumatological assessment, patient interviews, and medical records. In patients and controls, systolic (SBP) and diastolic blood pressure (DBP) were measured after a 5-min rest in a seated position. Height and weight were measured, and body mass index (BMI) was calculated. Smoking habits and level of physical activity were obtained from questionnaires. Fasting blood samples were collected and analyzed by routine laboratory methods at OUH. Serum levels of anti-RNP were determined with fluorescence enzyme immunoassay. Anti-dsDNA was detected with indirect immunofluorescence technique and fluorescence enzyme immunoassay (EliA).

Disease activity and damage. Because there are no validated criteria for remission in MCTD, we used the criteria for clinical remission in juvenile idiopathic arthritis (JIA)[23], and added the absence of cytopenia, myositis, progressive lung and esophageal manifestations, and progressive sclerodactyly (with or without RP)[21]. Remission was defined as inactive disease with or without medication for a minimum of 6 months, and active disease as the absence of remission.

Disease activity and damage scores developed for SLE, SSc, and JIA were used, including the Systemic Lupus Erythematosus Disease Activity Index[24], Rodnan skin score[25], the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index[26], Myositis Damage Index (MDI)[27], and the Juvenile Arthritis Damage Index (JADI)[28].

Echocardiography and electrocardiogram (ECG). B-mode, M-mode, and Doppler echocardiography, including early and late diastolic filling velocities, were performed by researchers (BNW, TS) blinded to disease characteristics in all participants, as previously described[16]. A minimum of 3 cycles were recorded, analyzed, and averaged. Data analysis (ZB) was done blinded to both clinical information and patient/control identity. Tissue Doppler was performed as previously described[14]. Valvular regurgitation > grade 1 was considered significant.

Low EF, LAS, and e′ were defined as mean – 2SD of the values measured in the matched controls. LVD was defined as low EF, low LAS, or low e′.

Twelve-channel ECG were recorded and accessible in 37 patients and controls aged ≥ 16 years. We assessed rhythm and ST segments, and measured PR interval, corrected QT interval (QTc), and QRS duration. ECG was classified, blinded to information about study participants including disease activity, as normal, borderline, or pathological. Standard criteria for pathological ECG were used, including Cornell voltage criteria for subjects ≥ 16 years of age[29].

Statistical analysis. Differences between patients and matched controls were tested with the paired sample t test, Wilcoxon rank-sum test, or McNemar test as appropriate. Differences between patient groups were tested by the Mann-Whitney U test or the chi-square test/Fisher's exact test as appropriate. Correlations were determined by the Pearson or Spearman correlation coefficient (ϱ), as appropriate. $P < 0.05$ was considered significant. Statistical analyses were performed with SPSS version 24.0 (IBM).

RESULTS

Clinical characteristics. Of the patients, 86% were female, and age at followup was median 27.2 years (interquartile range 19.4–34.1; Table 1).

Active disease was present in 35 (70%) after median 14.9 years (6.6–23.0) of disease duration. At followup, 36 (72%) were taking immunosuppressive drugs. Calcium antagonists were used in 10 (20%; indication RP in 9 and HTN in 1). Two patients reported dyspnea at exertion: a woman aged 54 years with type 2 diabetes, HTN, and coronary artery disease, and a man aged 28 with extensive pulmonary disease. None of the controls reported cardiac-related symptoms. No study participants had known type 1 diabetes, heart failure, cardiac arrhythmias, or cerebrovascular disease.

Table 1. Characteristics of 50 patients with juvenile MCTD.

Characteristics	Patients, n = 50
Female sex, n (%)	43 (86)
Age at examination, yrs	27.2 (19.4–34.1)
Age at disease onset, yrs	11.6 (9.8–14.4)
Age at diagnosis, yrs	13.6 (11.6–15.8)
Disease duration, yrs	14.9 (6.6–23.0)
SLE-like disease, n (%)	27 (54)
SSc-like disease, n (%)	34 (68)
PM-like disease, n (%)	2 (4)
Anti-RNP, × 10^3 U/l	199 (38–240)
Active disease, n (%)	35 (70)
Current medication	
Any immunosuppressive, n (%)	36 (72)
Prednisolone, n (%)	14 (28)
Antimalarials, n (%)	27 (54)
Methotrexate, n (%)	13 (26)
NSAID, n (%)	11 (22)
Anti-TNF, n (%)	2 (4)
Rituximab, n (%)	1 (2)
Azathioprine, n (%)	5 (10)
Calcium antagonists, n (%)	10 (20)
Prednisolone dose, mg	0 (0–2.3)

Values are median (IQR) unless otherwise stated. MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; PM: polymyositis; NSAID: nonsteroidal antiinflammatory drugs; TNF: tumor necrosis factor; IQR: interquartile range.

Traditional cardiovascular risk factors in patients and controls. No significant differences were found in BMI, smoking habits, level of physical activity, or blood pressure variables between patients and controls (Table 2).

Levels of low-density lipoproteins (LDL) and high-density lipoprotein (HDL) cholesterol were lower in patients compared to controls, with comparable HDL/LDL ratio. Apolipoprotein A-I (ApoA-I) was lower in patients than controls, without significant difference in ApoB/ApoA-I ratio. Fasting glucose, glycosylated hemoglobin, and C-reactive protein (CRP) were not significantly different between the groups, but erythrocyte sedimentation rate was higher in patients (Table 2).

ECG in patients and controls. Pathological ECG was found in 7/37 patients and 2/37 controls (p = 0.090). Pathological ECG in the patients included poor R-wave progression (n = 2), LV hypertrophy signs (n = 4), right-axis deviation (n = 2), and pathological Q-wave (n = 2); in the controls, right-axis deviation (n = 1) and LV hypertrophy (n = 1). Patients had longer QTc compared to controls (417.7 vs 408.7 ms, p = 0.012).

Echocardiographic findings in JMCTD patients and controls. Systolic function measured by EF and LAS were lower in patients compared to controls (6% lower, p < 0.001, and 4% lower, p = 0.044, respectively; Table 3).

Table 2. Traditional cardiovascular risk factors in juvenile MCTD patients and controls.

Variables	Patients, n = 50	Controls, n = 50	p
BMI, kg/m^2, mean (SD)	22.8 (3.5)	23.5 (3.0)	0.279
Height, cm, mean (SD)	166.0 (7.5)	169.6 (8.6)	**0.022**
Weight, kg, mean (SD)	63.0 (12.3)	67.9 (12.4)	0.046
Current smokers, n (%)	7 (14.3)	9 (18.4)	0.785
Daily smokers, n (%)	1 (2.0)	2 (4.1)	1.000
Ever smokers, n (%)	15 (30.6)	17 (34.7)	0.830
Vigorous physical activity, h/week	2.0 (0.8–4.0)	2.0 (0.3–5.1)	0.391
Moderate physical activity, h/week	2.0 (0.8–5.5)	1.3 (0.4–4.6)	0.338
Hypertension, n (%)	1 (2)	0 (0)	1.00
SBP, mmHg, mean (SD)	111.9 (14.5)	114.8 (11.9)	0.233
SBP ≥ 140 mmHg, n (%)	1 (2.1)	0 (0)	0.495
DBP, mmHg, mean (SD)	64.8 (15.0)	67.9 (8.6)	0.177
LDL cholesterol, mmol/l, mean (SD)	2.43 (0.67)	2.83 (0.93)	**0.027**
HDL cholesterol, mmol/l, mean (SD)	1.31 (0.35)	1.65 (0.44)	**< 0.001**
HDL/LDL ratio	0.54	0.58	0.184
TG, mmol/l	0.85 (0.70–1.15)	0.70 (0.60–0.90)	0.115
ApoA-I, mg/l	1.40 (1.10–1.70)	1.60 (1.50–1.80)	**< 0.001**
ApoB, mg/l	0.70 (0.70–0.90)	0.80 (0.70–1.0)	0.158
ApoB/ApoA-I ratio	0.53 (0.46–0.63)	0.50(0.41–0.60)	0.328
Glucose, mmol/l, mean (SD)	4.84 (0.93)	5.06 (0.43)	0.106
HbA1c, %	5.30 (5.10–5.50)	5.20 (4.95–5.45)	0.071
CRP, mg/l (41 pairs)	0.62 (0.50–2.50)	0.60 (0.50–0.90)	0.108
ESR, mm/h	9.0 (5.0–16.0)	4.0 (2.0–7.0)	**< 0.001**

Values are median (IQR) unless otherwise specified. Values in bold face are statistically significant. MCTD: mixed connective tissue disease; BMI: body mass index; SBP: systolic blood pressure; DBP; diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; ApoA-I: apolipoprotein A-I; ApoB: apolipoprotein B; HbA1c: glycosylated hemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range.

Table 3. Comparison of echocardiographic variables and 12-channel electrocardiography in juvenile MCTD patients versus controls at examination after a median 14.9 years of disease duration.

Variables	Patients, n = 50	Controls, n = 50	p
B mode			
LV diastolic volume, cm^3	84.9 (19.2)	93.9 (23.4)	**0.036**
LV systolic volume, cm^3	29.2 (8.8)	28.9 (7.3)	0.819
LV ejection fraction, %	65.8 (4.5)	69.6 (4.0)	**< 0.001**
LA area, cm^2	14.9 (2.9)	17.7 (2.5)	**< 0.001**
RA area, cm^2	12.9 (2.7)	14.9 (2.9)	**0.001**
M mode			
IVS diastole, mm	6.72 (1.1)	7.02 (1.0)	0.141
IVS systole, mm	9.06 (1.6)	9.64 (1.5)	**0.045**
LV diastole diameter, mm	48.5 (4.7)	49.1 (4.1)	0.530
LV systole diameter, mm	32.3 (3.8)	33.3 (3.7)	0.159
PW diastole, mm	6.76 (1.0)	7.16 (1.1)	**0.034**
PW systole, mm	11.8 (1.7)	11.9 (2.1)	0.876
MAPSE medial, mm	13.7 (1.9)	14.3 (1.5)	0.094
MAPSE lateral, mm	15.1 (1.7)	16.5 (2.0)	**0.001**
Long axis strain, %	18.7 (1.94)	19.4 (2.07)	**0.044**
TAPSE, mm	22.6 (4.4)	24.4 (3.1)	**0.008**
Doppler			
Resting heart rate, bpm	64.8 (12.0)	55.7 (11.2)	**< 0.001**
MV E velocity, m/s	0.82 (0.12)	0.90 (0.16)	**0.015**
MV E/A ratio	1.95 (0.46)	2.16 (0.56)	**0.029**
MV deceleration time, ms	195.7 (41.1)	186.1 (29.1)	0.108
Cardiac output, l/min	3.80 (0.97)	3.95 (0.76)	0.435
TV max, m/s (46 pairs)	0.55 (0.49–0.65)	0.57 (0.51–0.68)	0.970
e′ (cm/s)	12.38 (1.63)	12.86 (1.79)	0.129
ECG*			
PR, ms	153.0 (20.9)	150.2 (21.4)	0.577
QRS, ms	87.7 (7.9)	93.5 (11.9)	0.088
QTc, ms	417.7 (24.4)	408.7 (23.8)	**0.012**
Pathological, n (%)	7 (19)	2 (5)	0.090

Values are mean (SD) or median (IQR). Values in bold face are statistically significant. * N = 37 pairs. MCTD: mixed connective tissue disease; LV: left ventricular; LA: left atrium; RA: right atrium; IVS: interventricular septum; PW: posterior wall; MAPSE: mitral annular plane systolic excursion; TAPSE: tricuspid annular plane systolic excursion; MV: mitral valve; MV E: early diastolic transmitral flow; MV A: late diastolic transmitral flow; TV: transtricuspidal flow; e′: early diastolic tissue velocity; ECG: electrocardiography; PR: PR interval; QRS: QRS duration; QTc: corrected QT interval; IQR: interquartile range.

None of the patients and controls had clinically pathological LVEF (< 50%). No significant difference in diastolic function measured by e′ was found between the groups. Tricuspid annular plane systolic excursion (TAPSE), a measure for right ventricular (RV) function, was 8% lower in patients than controls (p = 0.008). However, we found no indication of elevated RV pressure in any patients or controls, including normal right atrial size.

LVD was found in 8/50 (16%) of patients versus 2/50 (4%) of controls (p = 0.035; Figure 1A and 1B). Low EF (< 61.6%) was found in 7 (14%) of patients versus 0 of controls (p = 0.006), low LAS (≤ 15.3%) in 2 (4%) of patients versus 1 (2%) of controls (p = 0.500), and low e′ (≤ 9.3) in 1 patient (2%) and 1 (2%) of the controls (p = 1.000).

When comparing echocardiographic findings in patients with active and inactive disease, no significant differences were found (data not shown).

Associations between LVD and patient characteristics, CVD risk factors, and medication in JMCTD patients. When comparing patients with LVD (n = 8) with patients with normal LV function (n = 42), no significant difference in characteristics or antibody profile were found (Table 4). One patient tested positive for anti-SSA, 1 for anti-SSB, and none for myositis-specific autoantibodies. Regarding cardiovascular risk factors, patients with LVD had higher SBP, DBP, and ApoB. Also, patients with LVD had higher disease activity measured by physician's global assessment (PGA), but other measures of disease activity did not differ significantly between the 2 groups. Organ damage assessed with MDI was higher in patients with LVD. Patients with LVD also used calcium channel blockers more often and had used steroids 4.5 times longer than patients with normal LV function (Table 4). In patients, the use of calcium channel blockers showed a positive correlation with RP symptoms assessed with a visual analog scale (ρ 0.35, p = 0.016).

Associations between LVD and early disease variables

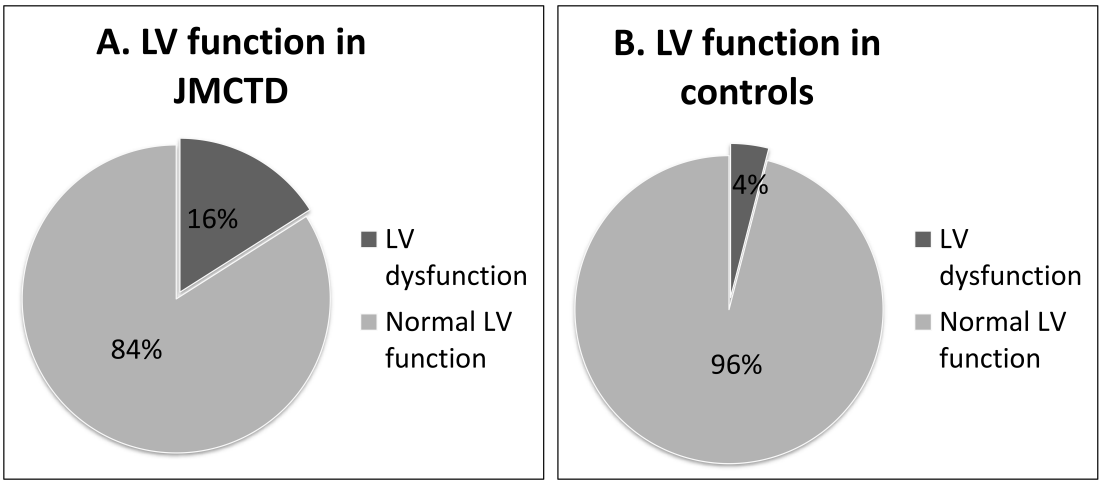

Figure 1. Left ventricular (LV) function in patients with JMCTD after a median 14.9 years of disease duration (A), and in controls (B). JMCTD: juvenile mixed connective tissue disease.

assessed in patients. PM-like disease and muscle weakness at diagnosis was more often found in patients with LVD than in patients with normal LV function after median 14.9 years (Table 5). Also, CRP was higher the first year postdiagnosis in patients with LVD. We found no association with LVD regarding age, typical MCTD symptoms, or signs such as puffy hands, RP, RF positivity, SLE-like disease, and SSc-like disease at diagnosis.

DISCUSSION

In this longterm outcome study of cardiac function in JMCTD, we found impaired LV systolic function measured by EF and LAS in patients compared to controls. Patients with LVD had higher disease activity, more disease damage, and had been treated with steroids for a longer time. Also, we found that PM-like disease, high CRP, or treatment with high doses of steroids at diagnosis were factors associated with LVD after a median 15 years disease duration. To our knowledge, this is the first systematic case-control study on cardiac function in patients with JMCTD.

A strength of our study was that the cohort is believed to be representative of JMCTD patients living in Norway, as previously described in detail[21]. The female predominance and age at diagnosis correspond well with previous studies[30]. Our controls were comparable to the patients regarding BMI, level of physical activity, and smoking habits.

Our study revealed impaired systolic function measured by LAS and EF in patients with JMCTD compared to controls, despite their young age (median 27.2 yrs). The impairment was subclinical in all but 1 patient. Diastolic function was not significantly different in patients and controls, although the study might be underpowered. In accordance with these results, 2 previous studies have described presence of LVD in adult patients with MCTD[12,13]. However, in contrast to our findings, Vegh, *et al* found a preserved systolic function[12], and both previous studies found impaired diastolic function measured by mitral valve (MV) E/A ratio. Several reasons may contribute to the different findings. First, the other studies involved adult MCTD, while our cohort was JMCTD. Second, we used LAS to reveal systolic dysfunction, which is regarded as a more sensitive and robust marker of systolic dysfunction than EF[31]. Third, we used e′ to assess diastolic dysfunction, a more accurate marker compared to MV E/A ratio, because it is less load-dependent[32]. Although our results in fact did show a slightly lower MV E/A ratio in patients versus controls, in isolation this should not be interpreted as diastolic dysfunction in patients with LVEF > 50%[33]. The fourth reason is the major differences among the study populations: Vegh, *et al* reported 21 of 50 patients having signs of pulmonary arterial HTN (PAH) during the past 2 years and 20 patients had been treated with cyclophosphamide, indicating a patient population biased toward more severe cases compared to ours[12]. LVD has also been shown in juvenile SLE as well as in JDM[14,15]. The prognostic and predictive values of subclinical LVD in JMCTD require further study.

We also found that patients with JMCTD had reduced RV function assessed with TAPSE. In adult MCTD patients with PAH, impairment of RV function has previously been demonstrated, while the patients without PAH had RV function similar to controls[12]. In line with our results, Leal, *et al* reported subclinical RV systolic dysfunction in juvenile patients with SLE, even after excluding patients with PAH[34]. They found that RV dysfunction was associated with antiphospholipid antibodies (aPL). No such association between RV or LV dysfunction and the presence of aPL was found in our patients. None of our patients had elevated right arterial pressure at examination, or other signs of PAH. We have previously reported a frequency of clinically overt PAH

Table 4. Patient and disease characteristics in 50 patients with juvenile MCTD according to left ventricular function.

Characteristics	Normal LV Function, n = 42	LV Dysfunction, n = 8	p
Characteristics at examination			
Female sex, n (%)	37 (88)	5 (63)	0.328
Age, yrs	27.2 (19.0–34.1)	26.2 (20.5–38.4)	0.731
Disease duration from symptom onset, yrs	14.0 (6.5–23.3)	15.2 (12.3–22.9)	0.543
Anti-dsDNA–positive, n (%)	5 (12)	1 (13)	0.962
aPL, n (%)	6 (14)	1 (13)	0.894
Cardiovascular risk factors			
BMI, kg/m^2	22.3 (20.4–23.5)	25.6 (20.8–28.6)	0.144
Never smokers, n (%)	29 (71)	5 (63)	0.644
SBP, mmHg	110.0 (103.3–116.8)	119.5 (112.0–131.0)	**0.032**
DBP, mmHg	65.5 (59.0–71.8)	72.0 (65.8–77.5)	**0.045**
LDL cholesterol, mmol/l	2.40 (2.0–3.0)	2.40 (2.1–2.9)	0.791
HDL cholesterol, mmol/l	1.30 (1.1–1.6)	1.25 (0.9–1.5)	0.465
ApoA-I, mg/l	1.4 (1.1–1.7)	1.5 (1.1–1.7)	0.723
ApoB, mg/l	0.7 (0.6–0.9)	0.8 (0.8–1.0)	**0.023**
ApoB/ApoA-I ratio	0.50 (0.4–0.6)	0.59 (0.5–0.9)	0.193
Triglycerides, mmol/l	0.8 (0.7 –1.2)	1.2 (0.7–1.6)	0.203
Pro-BNP, mmol/l	7.9 (3.7–12.8)	4.7 (2.9–8.1)	0.166
Pathological ECG, n (%)*	7 (23)	2 (33)	0.407
Disease activity at examination			
Active disease, n (%)	28 (67)	7 (88)	0.239
No. active joints	0 (0–0)	0 (0–3.5)	0.159
Anti-RNP, titer × 10^3 U/l	158 (31–240)	223 (68–240)	0.417
ESR, mm/h	8.0 (5.0–14.5)	12.5 (5.0–19.0)	0.707
CRP, mg/l	0.7 (0.5–1.4)	1.3 (0.6–3.5)	0.442
PGA, 10-cm VAS	1.6 (0–5.5)	3.0 (0.4–5.8)	**0.019**
RP, 10-cm VAS	2.9 (1.3–5.4)	6.6 (1.2–7.2)	0.220
Rodnan skin score	0 (0)	0 (0–3.5)	0.172
SLEDAI, median (range)	0 (0–4)	0 (0–4)	0.635
Organ damage			
MDI	1.0 (0–2.0)	6.0 (1.0–3.8)	**0.047**
LROM	0 (0–4.0)	7.0 (0–19.0)	0.218
SLICC	1.0 (0–1.0)	1.0 (0–1.0)	0.929
JADI	0 (0–0)	0.5 (0–13.3)	0.051
Medications at examination, n (%)			
NSAID	10 (24)	1 (13)	0.666
Steroids	11 (26)	3 (38)	0.670
Antimalarials	23 (55)	4 (50)	1.000
Methotrexate	12 (29)	1 (13)	0.662
Azathioprine	3 (7)	2 (25)	0.176
MMF	1 (2)	1 (13)	0.297
Cyclophosphamide	0	0	1.000
Anti-TNF	2 (5)	0	1.000
Rituximab	0	1 (13)	0.160
Calcium antagonists	6 (14)	4 (50)	**0.041**
Current prednisolone dose, mg	0 (0–2.0)	0 (0–6.4)	0.493
Time taking steroids, mos	7.5 (2.0–38.3)	42.0 (24.3–84.0)	**0.015**

Values are in median (IQR) unless otherwise stated. Values in bold face are statistically significant. * N = 37 (31 with normal LV, 6 with LVD). Includes anticardiolipin antibodies IgG or IgM, and/or anti-β_2 glycoprotein IgG or IgM, and/or lupus anticoagulant. MCTD; mixed connective tissue disease; LV: left ventricular; aPL: antiphospholipid antibodies; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; PM: polymyositis; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ApoA-I: apolipoprotein A-I; ApoB: apolipoprotein B; pro-BNP: pro-brain natriuretic peptide; ECG: electrocardiography; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PGA: physician's global assessment; SLEDAI: Systemic Lupus Erythematosus Activity Index; MDI: Myositis Damage Index; LROM: limited range of motion; SLICC: Systemic Lupus International Collaborating Clinics; JADI: Juvenile Arthritis Damage Index; NSAID: nonsteroidal antiinflammatory drugs; anti-TNF: anti-tumor necrosis factor; IQR: interquartile range; LVD: LV dysfunction; VAS: visual analog scale; RP: Raynaud phenomenon; MMF: mycophenolate mofetil.

Table 5. Variables from time of diagnosis in 49 juvenile MCTD patients according to left ventricular function at examination after a median 14.9 years of disease duration.

Variables Assessed at Diagnosis	Normal LV Function, n = 41	LV Dysfunction, n = 8	p
Age, yrs	14.7 (4.6)	12.3 (2.8)	0.106
Puffy hands	17 (42)	4 (50)	0.710
RP	40 (98)	8 (100)	1.000
SLE-like disease	39 (95)	8 (100)	1.000
Arthritis	36 (88)	7 (88)	0.981
Lymphadenopathy	5 (12)	2 (25)	0.344
Facial erythema	10 (24)	3 (38)	0.422
Cytopenia	5 (12)	3 (38)	0.110
Pericarditis/pleuritis	2 (5)	0	1.000
SSc-like disease	11 (27)	2 (25)	0.944
Sclerodactyly	4 (10)	0	1.000
Pulmonary fibrosis	5 (12)	2 (25)	0.320
Esophagus dysmotility	1 (2)	1 (13)	0.303
PM-like disease	10 (24)	5 (63)	**0.047**
High CK	7 (17)	4 (50)	0.063
Muscle weakness	9 (22)	5 (63)	**0.033**
No. active joints	4.0 (2.0–10.0)	11.5 (4.0–22.3)	0.099
ESR, mm/h	20.0 (12.0–30.5)	23.5 (16.0–48.3)	0.417
CRP, mg/l, n = 41	4.0 (1.9–7.4)	7.0 (4.3–21.8)	0.081
CRP at diagnosis or during 1st yr	4.0 (2.0–7.4)	7.0 (4.3–21.8)	**0.049**
Prednisolone dose, mg	0 (0–13.8)	20.0 (0–45.0)	0.057
RF-positive, n = 42	21 (62)	5 (63)	1.000
RF-positive during 1st yr	23 (56)	5 (63)	1.000
Medications after 1st yr			
Prednisolone	13 (32)	5 (63)	0.230
Antimalarials	20 (49)	4 (50)	1.000
MTX	16 (39)	5 (63)	0.437
NSAID	12 (29)	5 (63)	0.089
Calcium antagonist	5 (12)	2 (25)	0.378

Values are in n (%) or median (IQR). Values in bold face are statistically significant. MCTD: mixed connective tissue disease; LV: left ventricular; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; PM: polymyositis; CK: creatine kinase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; NSAID: nonsteroidal antiinflammatory drugs; IQR: interquartile range; RP: Raynaud phenomenon; MTX: methotrexate.

of 3.4% in the present JMCTD cohort[21]. However, one of the 2 patients had died before inclusion, and the other had reversible symptoms and normal cardiac function at the time of examination. Thus, the present echocardiographic results support our previous finding that the occurrence of PAH in an unselected JMCTD cohort is low, in accordance with reports in adult MCTD[35]. Further, our data suggest that subclinical RV impairment in JMCTD is unlikely to be due to PH.

Possible mechanisms behind LVD in patients with autoimmune diseases are many, and among them, dyslipidemia is known to play a role. Our JMCTD cohort had lower HDL and ApoA-I compared to controls, and both variables have been shown to be inversely related to the risk of CVD[36,37]. In line with our results, lower ApoA-I in adult patients with MCTD compared to controls has been reported[38]. However, they found similar HDL and LDL levels in patients and controls. Unexpectedly, we found lower LDL in patients compared to controls; however, in patients with RA or JDM, a so-called lipid paradox has previously been described, with lower levels of LDL and total cholesterol, but still an association with higher CVD risk or cardiac dysfunction[39,40].

Additionally, we found that patients with LVD had higher ApoB levels compared to those with normal cardiac function. We found no significant differences in HDL, LDL, ApoA-I, or triglycerides levels, which might be due to a type 2 error, and/or the complex relationship between dyslipidemia, inflammation, and CV risk in MCTD.

Inflammation plays a significant role in CVD[41,42]. Our data show a similar relationship in JMCTD, because patients with LVD had higher disease activity according to PGA, longer treatment with corticosteroids, and a trend toward a higher CRP and number of active joints early in the disease course. Also, the increased MDI and borderline increased JADI in patients with LVD possibly reflects a longer active inflammatory disease course, causing irreversible joint and organ damage, and possibly cardiac damage. In RA, higher disease activity has been shown to be associated with reduced LV function independently of cardiovascular risk factors[19],

and in juvenile SLE, higher disease activity contributed to myocardial impairment[15], which is in line with our findings.

The majority of patients with LVD at examination had PM-like disease with muscle weakness at diagnosis, and we also found an association between PM-like disease and pathological ECG. It is known that patients with JDM have both diastolic and systolic dysfunction after longterm followup[14,16]. Although the sample size is too small to draw conclusions, it might be that the subset of JMCTD patients with PM-like onset has similarities in pathogenesis with JDM patients.

No valvular abnormalities were observed, as opposed to what has been reported in adult-onset MCTD[5]. However, this was similar to findings in other juvenile CTD[43,44], and might be explained by the young age of the cohort.

A limitation of our study is the relatively small sample size of patients and controls, which may underestimate differences between the groups. The comparisons between patients with and without LVD must be interpreted with care, because the group with LVD comprises only 8 patients and p values could be due to chance alone. However, the relationships are interesting and should be assessed in future studies. Assessing disease activity and damage in MCTD is difficult, because there are no validated scores available for the disease. Thus, we had to use surrogate measures to record the broad spectrum of disease activity and damage seen in MCTD as comprehensively as possible.

To our knowledge, our present study is the first to systematically examine cardiac manifestations in an unselected cohort of patients with JMTCD. The patients have a long followup time despite young age, and the case-control design is well suited to detect subclinical manifestations. We used state-of-the-art methods, such as strain imaging of both the RV and LV, to detect subclinical cardiac dysfunction. This method is more accurate and sensitive than LVEF measurements[31].

In this longterm study, we found that patients with JMCTD had impaired LV systolic function and RV function, but preserved diastolic LV function compared to matched controls after a median 15 years of disease duration. Factors associated with LVD were high disease activity, longer treatment with prednisolone, and PM-like disease at diagnosis. Cardiac manifestations in our JMCTD cohort were mostly subclinical. Further prospective studies are needed to evaluate the prognostic implication of subclinical LVD in JMCTD.

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