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Posted Date: 17 February 2025

doi: 10.20944/preprints202501.0262.v2

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Article

Uncovering Subclinical Cardiac Involvement in VEDOSS: An Echocardiographic Driven Study

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Abstract: Background: The 2011 Very Early Diagnosis of Systemic Sclerosis (VEDOSS) criteria include patients at risk of progression and those with mild non-progressive forms of SSc. Early diastolic and systolic dysfunction can indicate myocardial fibrosis in SSc patients, yet data on myocardial impairment in the VEDOSS population are limited. **Objectives:** This study aimed to identify subclinical echocardiographic changes and predictive markers of cardiac dysfunction in both very early and mild-longstanding forms of VEDOSS. **Methods:** We conducted a cross-sectional observational study involving 61 patients meeting VEDOSS criteria followed up regularly within our Scleroderma referral center. Patients were categorized as early VEDOSS (e-VEDOSS) or mild-longstanding VEDOSS (ml-VEDOSS) based on disease duration (≥ 10 years). We analyzed clinical and demographic data, focusing on echocardiographic parameters such as the E/A ratio and left ventricular (LV) thickness. Statistical analyses included Chi-square, Fischer exact, and Student's T tests, with a significance threshold of $p < 0.05$. **Results:** ml-VEDOSS patients were older and reported a higher burden of comorbidities. Autoantibody-positive patients exhibited lower E/A ratios and increased left atrial size. Late nailfold videocapillaroscopic pattern patients exhibited increased PWED thickening and aortic valve insufficiency. Notably, patients undergoing vasodilators experienced larger right atrial volume, while patient receiving Renin-Angiotensin-Aldosterone System (RAAS) inhibitors reported reduced E/A ratio. Multivariable analysis confirmed DLCO% as the sole predictor of both diastolic and systolic impairment in VEDOSS population. **Conclusion:** Careful monitoring of cardiac function in VEDOSS patients is crucial as subclinical alterations may occur even in the absence of symptoms. DLCO% emerged as an important predictor of LV diastolic dysfunction.

Keywords: VEDOSS; Systemic Sclerosis; early diagnosis; cardiac involvement; diastolic dysfunction; echocardiography

1. Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by the classical triad of microvascular damage, autoimmune dysregulation and fibrosis of the skin and internal organs [1]. The extensive fibrotic process of vital organs, including the lungs and heart, is significantly associated with a high burden of morbidity and mortality [2]. In this context, it is essential to perform a prompt diagnosis to shape the trajectories of potentially progressive disease [3]. Currently, SSc diagnosis can be oriented by consolidated classification criteria such as those proposed by LeRoy and Medsger in 2001 [4], together with the 2013 ACR/EULAR guidelines [5]. However, it is well recognized that these

classifications do not encompass all patients within the broader scleroderma spectrum, particularly in the earlier stages of the disease [6]. The 2011 criteria for a Very Early Diagnosis of Systemic Sclerosis (the VEDOSS criteria) and their validation in 2021, have enhanced clinicians' ability to identify the disease in its initial phase [7,8].

Thus, while VEDOSS may represent the early stage of SSc, it could also reflect a milder form that remains stable over time and does not progress to clinically established disease. Currently, despite the lack of validated criteria that allow clinicians to differentiate between these two forms, VEDOSS represents a critical stage in the scleroderma continuum, in which it results crucial to identify early organ involvement. [9,10]

Moreover, while some organs, such as the gastrointestinal tract have been investigated in VEDOSS [11], cardiac involvement remains a neglected area. All layers of the heart—endocardium, myocardium, and pericardium—can be affected by the pathogenic processes of SSc, with myocardial fibrosis being the predominant pathological finding in postmortem studies [12]. Subclinical left ventricular (LV) diastolic and systolic impairments represent the initial expression of myocardial fibrosis, which may often be asymptomatic [13]. However, several echocardiographic parameters, such as mitral early diastolic inflow velocity (E wave), mitral late filling peak velocity (A wave), early diastolic annular velocity (E'), as well as the E/A and E/E' ratios may enable the detection of early myocardial involvement in asymptomatic SSc patients. For instance, an E/A ratio less than 1.0 and E/E' ratio ≥ 15 indicate elevated filling pressure and predict the development of diastolic heart failure [14]. Moreover, given that cardiac involvement in SSc is highly predictive of poor prognosis and mortality [15], detecting subclinical echocardiographic signs of systolic and diastolic dysfunction seems to be fundamental even in the VEDOSS population.

The aim of the present study is to identify subclinical echocardiographic alterations in VEDOSS patients by analyzing certain clinical, serological and functional predictive markers of systolic and diastolic dysfunction in both mild-longstanding cases and the very early form of SSc, offering insights into the progression and early detection of cardiac involvement in this patient group.

2. Materials and Methods

2.1. Sample Definition

We conducted a cross-sectional observational study involving a cohort of VEDOSS patients attending the Scleroderma Unit of ASST Ovest Milanese (Italy). Participants were selected based on their fulfillment of the 2011 preliminary VEDOSS criteria [7] while not meeting the 2013 ACR/EULAR and/or 2001 LeRoy and Medsger criteria for a definitive diagnosis of SSc [4,5]. Patients with severe heart failure, a positive history of congenital heart disease, severe chronic obstructive pulmonary disease, pulmonary thromboembolism and individuals who underwent cardiac surgery, percutaneous coronary intervention (PCI) and pacemaker implant were excluded from the study. The presence of other autoimmune disease-related antibodies and/or the fulfillment of additional classification criteria for any systemic autoimmune disease served as further exclusion criteria.

Written informed consent was obtained from each participant, and the study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki, with the ethic protocol number S00125/2023 obtained from the Ethic Committee of Milan Area 3.

2.2. Data Collection

Data collection was conducted by experienced rheumatologists and spanned between June and December 2024. Demographic data including sex, age at enrollment, alcohol consumption or smoking habit, age at the first appearance of Raynaud's Phenomenon (RP) and age at VEDOSS diagnosis were extracted from medical records. Diagnostic delay was calculated as the time interval between the onset of the first VEDOSS symptom and the confirmation of a definitive VEDOSS diagnosis.

Key clinical and anthropometric parameters were recorded at last follow up visit, including height, weight, body mass index (BMI) and body surface area (BSA). The presence of RP and puffy

hands was noted, along with the presence of any gastrointestinal complaints that could be attributed to VEDOSS. Additionally, for the main purpose of the study, the absence of skin fibrosis, sclerodactyly, digital ulcers, pitting scars, calcinosis and telangiectasias was documented. Therefore, clinical evaluation involved a comprehensive physical, functional and radiological assessment for dyspnea and other heart-related symptoms. Data from pulmonary function tests (PFTs), including predicted forced vital capacity (FVC%), predicted diffusing capacity for carbon monoxide (DLCO%), and the FVC/DLCO% ratio, were obtained from the most recent available assessments, along-with chest X-ray which allowed to exclude suspected or established interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) as compelling causes of unexplained dyspnea. Analogously, all patients underwent nailfold Videocapillaroscopy (NVC) at the last follow-up visit, with the NVC results been reported according to Cutolo classification [17].

Laboratory detection of antinuclear antibodies (ANA), anticentromere antibodies (ACA), and anti-topoisomerase I antibodies (ATA) was performed using standardized methods during the initial clinical evaluation.

Data on current comorbidities were collected, including cardiovascular conditions such as chronic systemic arterial hypertension and atrial fibrillation, as well as thyroid disorders, pulmonary diseases, gastrointestinal disorders, renal diseases, malignancies, hematological conditions and psychiatric and neurological issues.

Data concerning treatment modalities were registered, encompassing the administration of Iloprost infusions, the use of calcium channel blockers (CCBs) and low-dose aspirin (LDA). Additionally, treatments employed for managing cardiovascular comorbidities with a known influence on microvascular system were documented, such as angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), beta-blockers and diuretics. Immunosuppressive therapies and the use of hydroxychloroquine were also recorded.

2.3. Echocardiography Procedure

Echocardiographic parameters were collected at the last follow-up visit. All selected patients were imaged by transthoracic echocardiography (TTE) in the left lateral decubitus position by experienced cardiologists at the same hospital in accordance with the guidelines of the American Society of Echocardiography (ASE) [18]. All images and measurements were obtained from the standard views with stable Electrocardiograph (EKG). The following parameters were measured: interventricular septum (IVS) thickness (mm), posterior wall at end diastole (PWED) thickness (mm), left ventricular (LV) volumes and diameters in both end systole and end diastole, aorta diameter at sinuses, along with right and left atrial (RA and LA) volumes at end systole in monoplane apical 4 chamber (4CH) view through both Simpson and indexed methods, RA and LA end systolic diameters were measured via monoplane 4CH view in the longitudinal side (superior-inferior) direction as well as RA and LA end systolic area was assessed in cm². Left ventricular (LV) ejection fraction (EF) was measured with the modified biplane Simpson's method from the apical 4CH view [19].

Left ventricular (LV) mass was calculated according to the Devereux formula [20]. Pathological thickening of both IVS and PWED was defined as more than 10 mm and more than 9 mm, respectively. Additionally, the systolic pulmonary artery pressure (sPAP) was estimated using modified Bernoulli's formula [21]. The tricuspid annular plane systolic excursion (TAPSE) was measured by placing the M-mode line at the junction of the tricuspid valve annulus and the RV free wall [22]. Tricuspid regurgitation and the Tricuspid maximum regurgitation pressure gradient were also assessed. Doppler echocardiographic measurements included: Trans-mitral early diastolic inflow velocity (E), trans-mitral late filling peak velocity (A), and E/A ratio measured in the apical 4-CH view [23]. Tissue Doppler imaging was used to measure the early diastolic annular velocity (E'). Left ventricular dysfunction was defined as mitral E/A ratio <1.0 and E/E' ratio ≥15 [24]. Additionally, the presence of mitral, aortic, and tricuspid valve insufficiencies was evaluated by the color Doppler method, along with any noted sclerosis of the aortic and mitral valve leaflets and then reported according to the 2020 ACC/AHA guideline for the management of patients with valvular heart

disease [25]. Lastly, the presence of pericardial effusion was identified by the appearance of an echo-free space between the two layers of the pericardium.

2.4. Statistical Analysis

Patients' data were summarized as mean and standard deviation for normally distributed variables or as median and interquartile range (IQR) for skewed ones. Discrete or qualitative variables were summarized as counts and percentages. Mean differences of continuous variables were assessed using Student's t-test or Mann-Whitney U-test, depending on whether the data followed a parametric or non-parametric distribution. Chi-squared and Fisher's exact tests were used to compare categorical variables based on sample size. ANOVA test served for multiple comparison analysis.

Based on their established relevance on SSc progression and heart involvement, several clinical determinants—such as BMI, age at VEDOSS diagnosis, DLCO% predicted, ACA/ATA positivity, late NVC patterns and puffy hands were included in the multiple general regression model to assess their independent contribution on left ventricular diastolic and systolic dysfunction. E/A ratio, IVS thickness, and PWED thickness served as dependent variables in the multiple general regression model.

A p-value of ≤ 0.05 or a 95% confidence interval not crossing zero were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 27 (IBM SPSS Software, Armonk, NY, USA).

3. Results

3.1. Overall Patients' Characteristics.

The study cohort consisted of 61 participants, with a female predominance (58 out of 61–95.1%). Based on VEDOSS disease duration, patients were distributed into two subgroups: mild longstanding VEDOSS with a disease duration ≥ 10 years (ml-VEDOSS, 24/61– 39.3%) and early VEDOSS group with a disease duration < 10 years (e-VEDOSS, 37/61–60.7%) [Table 1].

Table 1. Patient's main characteristics according to VEDOSS disease duration.

	TOTAL n=61	e-VEDOSS n=37	ml-VEDOSS n=24	p-Value
Female, n(%)	58 (95.1)	36 (97.3)	22 (91.7)	0.56
Male, n(%)	3 (4.9)	1 (2.7)	2 (8.3)	0.56
Age at enrollment, mean \pm SD	58.7 \pm 14.5	55.2 \pm 14.6	64.0 \pm 12.8	0.01
Age at VEDOSS diagnosis, mean \pm SD	49.8 \pm 14.7	51.7 \pm 15.1	47.3 \pm 14.1	0.27
Age at RP onset, mean \pm SD	43.2 \pm 17.1	44.2 \pm 17.4	41.8 \pm 16.9	0.62
Disease Duration of VEDOSS, mean \pm SD	9.9 \pm 7.9	4.9 \pm 2.7	16.8 \pm 7.7	<0.001
Disease duration of RP, mean \pm SD	16.1 \pm 11.6	12.3 \pm 10.9	21.6 \pm 10.4	0.002
Diagnostic delay, mean \pm SD	6.4 \pm 9.5	7.5 \pm 10.6	4.7 \pm 7.4	0.28
Body Mass Index (Kg/m ²), mean \pm SD	23.5 \pm 5.9	22.4 \pm 5.7	25.2 \pm 5.9	0.07
Smoking habits, n(%)	10 (16.4)	8 (21.6)	2 (8.3)	0.29
Alcohol Consumption, n(%)	13 (21.3)	2 (5.3)	1 (4.2)	1.0
Puffy hands, n(%)	18 (29.5)	10 (27.0)	8 (33.3)	1.0
ANA (positive) only, n(%)	21 (34.4)	16 (43.2)	5 (20.8)	0.09
Anticentromere (positive), n(%)	21 (34.4)	9 (24.3)	12 (50)	0.05
Anti-topoisomerase I (positive), n(%)	3 (4.9)	2 (5.3)	1 (4.2)	1.0
Gastrointestinal tract symptoms, n(%)	30 (49.2)	15 (40.5)	15 (62.5)	0.12
COMORBIDITIES, n(%)				
Cardiovascular diseases,	29 (47.5)	13 (35.1)	16 (66.7)	0.02
Dyslipidemia	17 (27.9)	9 (24.3)	8 (33.3)	0.56

Hyperuricemia	2 (3.3)	0 (0)	2 (8.3)	0.15
Type 2 Diabetes Mellitus	4 (6.6)	2 (5.3)	2 (8.3)	0.64
Thyroid disorders	13 (21.3)	7 (18.9)	6 (25.0)	0.75
Lung Diseases	12 (19.6)	6 (16.2)	6 (25.0)	0.51
Kidney Diseases	8 (13.1)	4 (10.8)	4 (16.7)	0.7
Gastrointestinal diseases	35 (57.4)	17 (45.9)	18 (75.0)	0.03
Hematological disorders	8 (13.1)	2 (5.3)	6 (25.0)	0.04
Malignancies	10 (16.4)	5 (13.5)	5 (20.8)	0.49
Psychiatric disorders	3 (4.9)	2 (5.3)	1 (4.2)	1.0
Neurological disorders	11 (18.0)	5 (13.5)	6 (25.0)	0.32
Comorbidities count, mean±SD	2.7 ± 2.1	2.1 ±1.9	3.6 ± 2.0	0.005
Comorbidities count ≥ 3, n(%)	31 (50.8)	15 (40.5)	16 (66.7)	0.01
NVC PATTERN, n(%)				
Aspecific alterations	7 (11.5)	5 (13.5)	2 (8.3)	0.69
Early pattern	34 (55.7)	23 (62.2)	11 (45.8)	0.29
Active pattern	14 (23.0)	9 (24.3)	5 (20.8)	1.0
Late pattern	6 (9.8)	0 (0)	6 (25.0)	0.002
TREATMENT, n(%)				
Iloprost	44 (72.1)	23 (62.2)	21 (87.5)	0.04
Calcium Channel Blockers	20 (32.7)	8 (21.6)	12 (50.0)	0.03
Low-dose Aspirin	39 (63.9)	23 (62.2)	16 (66.7)	0.78
ACE-I/ARBs	16 (26.2)	6 (16.2)	10 (41.7)	0.04
Beta-Blockers	4 (6.6)	2 (5.3)	2 (8.3)	0.64
Diuretics	1 (1.6)	1 (2.7)	0	1.0
Hydroxychloroquine	20 (32.7)	9 (24.3)	11 (45.8)	0.09
Immunosuppressants	3 (4.9)	1 (2.7)	2 (8.3)	0.56

Acronyms: n=number; %=percentage; SD= Standard Deviation; e-VEDOSS= early very early diagnosis of Systemic Sclerosis; ml-VEDOSS=mild longstanding very early diagnosis of Systemic Sclerosis; RP= Raynaud's Phenomenon; ANA=antinuclear antibodies; ACE-I=Angiotensin Converting Enzyme Inhibitors; Angiotensin Receptor Blockers; ns=not significant; Kg=Kilograms; m²=square meters, NVC= Nailfold Videocapillaroscopy.

The mean age at enrollment was significantly higher in the ml-VEDOSS group compared to the e-VEDOSS group (64.0±12.8 vs 55.2±14.6 years; p=0.01). As expected, the disease durations for VEDOSS and RP were substantially longer in the ml-VEDOSS group (16.8±7.7 vs 4.9±2.7 years; p<0.001 and, 21.6±10.4 vs 12.3±10.9; p=0.002, respectively). Regarding autoimmunity profile, ACA+ patients were more frequently present in the ml-VEDOSS group (50% vs 24.3%, p=0.05).

A greater mean comorbidity count was observed in the ml-VEDOSS group compared to the e-VEDOSS group (3.6±2.0 vs 2.1±1.9; p=0.005), with higher prevalence of patients exhibiting more than 3 comorbidities (66.7% vs 40.5%, p=0.01). Within the same group there was a higher prevalence of cardiovascular and gastrointestinal diseases (66.7% vs 35.1%; p=0.02 and 75% vs 45.9%; p=0.03, respectively), along with hematological disorders (25% vs 5.3%, p=0.04). Furthermore, the late NVC pattern was significantly more common within the ml-VEDOSS group (6 out of 24, 25%; p=0.002).

Similarly, treatment modalities displayed notable variations between the two groups. The administration of vasodilators, such as Iloprost infusion and CCBs, resulted significantly more prescribed in the ml-VEDOSS group (87.5% vs 62.2%, p=0.04 and 50% vs 21.6%, p=0.03, respectively). The use of ACE-Is or ARBs was more common in the ml-VEDOSS group compared to the e-VEDOSS group (41.7% vs 16.2%, p=0.04). Immunosuppressants were prescribed only in 3 out of 61 patients, two of which were receiving methotrexate due to musculoskeletal symptoms, while 1 patient received azathioprine for a concurrent diagnosis of autoimmune hepatitis.

3.2. Subclinical Echocardiographic Findings

Main echocardiographic findings of the entire population are reported in *Table 2*. Specifically, mean E/A ratio was 0.99 ± 0.39 and 37/61 (60.7%) patients exhibited an E/A ratio less than 1, mean PWED thickness was 8.4 ± 1.6 mm and 19 out of 61 (31.1%) presented with a PWED thickening more than 9 mm, while a pathological IVS thickening (> 10 mm) was documented in 17/61 participants (27.9%). A reduced EF% (less than 55%) was reported only in 3/61 patients (4.9%) while the mean value of EF% was $64.5 \pm 4.8\%$. A reduced TAPSE (< 22 mmHg) was reported in 36/61 patients (59%) while only 1 patient exhibited a TAPSE less than 16 mmHg. Mean sPAP of the entire population was 27.2 ± 5.3 mmHg.

Table 2. Echocardiographic findings across the entire population.

ECHOCARDIOGRAPHIC PARAMETERS	TOTAL n=61
E deceleration time (m/s), mean \pm SD	244.3 \pm 281.7
E/E' ratio, mean \pm SD	6.9 \pm 1.9
E wave, (m/s), mean \pm SD	0.69 \pm 0.17
A wave, (m/s), mean \pm SD	0.75 \pm 0.19
E/A ratio, mean \pm SD	0.99 \pm 0.39
E/A ratio < 1.0 , n (%)	37 (60.7)
LVED diameter, (mm), mean \pm SD	40.3 \pm 4.8
PWED thickness, (mm), mean \pm SD	8.4 \pm 1.6
PWED > 9 mm, n(%)	19 (31.1)
IVS thickness, (mm), mean \pm SD	9.3 \pm 1.8
IVS > 10 mm, n (%)	17 (27.9)
LVED volume 4CH Simpson, (ml), mean \pm SD	67.7 \pm 16.6
LVES volume 4CH Simpson, (ml), mean \pm SD	25.5 \pm 11.8
LVED volume 4CH AL, (ml/m ²), mean \pm SD	43.4 \pm 8.8
LVES volume 4CH AL, (ml/m ²), mean \pm SD	14.7 \pm 4.3
EF%, mean \pm SD	64.5 \pm 4.8
EF% $< 55\%$	3 (4.9)
Mass ASE, (g), mean \pm SD	123.2 \pm 123.9
Mass/BSA, (g/m ²), mean \pm SD	66.3 \pm 17.3
Relative wall thickness, mean \pm SD	0.44 \pm 0.10
Mass/height, (g/m), mean \pm SD	65.8 \pm 18.2
Aortic diameter, (mm ²), mean \pm SD	29.7 \pm 3.9
LAES area, (cm ²), mean \pm SD	15.6 \pm 3.6
LAES 4CH Simpson, (ml), mean \pm SD	40.4 \pm 13.7
LAES 4CH ind, (ml/m ²), mean \pm SD	24.4 \pm 7.5
LAES diameter sup-inf 4CH, (mm/m ²), mean \pm SD	46.5 \pm 7.6
RAES diameter AL, (mm), mean \pm SD	46.1 \pm 5.8
RAES 4CH Simpson, (ml), mean \pm SD	30.3 \pm 8.9
RAES 4CH ind, (ml/m ²), mean \pm SD	18.5 \pm 5.0
RAES area, (cm ²), mean \pm SD	13.5 \pm 3.1
TAPSE, (mmHg), mean \pm SD	21.5 \pm 3.0
TAPSE < 22 mmHg, n (%)	36 (59.0)
TAPSE < 16 mmHg, n (%)	1 (1.6)
TAPSE/sPAP, mean \pm SD	0.72 \pm 0.32
TAPSE/sPAP < 0.55 , n (%)	1 (1.6)
sPAP, (mmHg), mean \pm SD	27.2 \pm 5.3
Tricuspid maximum regurgitation gradient, (mmHg), mean \pm SD	22.2 \pm 6.5
Mitral Valve Insufficiency, n (%)	42 (68.9)
Mitral Valve Sclerosis, n (%)	25 (40.9)
Tricuspid Valve Insufficiency, n (%)	33 (54.1)
Aortic Valve Insufficiency, n (%)	13 (21.3)

Aortic Valve Sclerosis, n (%)	11 (18.0)
Pericardial Effusion, n (%)	4 (6.6)

Acronyms: SD= Standard deviation. ACA= Anti-centromere autoantibodies; ATA= Anti Topoisomerase I autoantibodies; E wave= early diastolic filling velocity of the left ventricle; E'= early diastolic tissue velocity of the mitral annulus; A=late diastolic filling velocity; LVED= Left ventricular end diastolic; LVES= Left ventricular end systolic; PWED=Posterior wall end diastolic; IVS=Interventricular septum; LAES= Left atrial end systolic; RAES= Right Atrial End Systolic; TAPSE= Tricuspid Annular Plane Systolic Excursion; sPAP= systolic Pulmonary Artery Pressure; 4CH=4 chamber; AL=anterolateral; EF= ejection fraction; %= percentage; BSA=Body Surface Area; ASE= American Society of echocardiography; ind= indexed; sup-inf= superior–inferior; m/s= meter/seconds; mm= millimeters; g= grams; g/m²= grams/square meters; cm²= square centimeters; mmHg= millimeters of mercury.

Since the comparison between e-VEDOSS and ml-VEDOSS group did not reveal any statistical difference on echocardiographic parameters [Supplementary Table S5], we further focused on assessing these findings within three intergroups, by selecting the late NVC pattern, SSc specific autoantibodies positivity and puffy hands as compelling variables [Table 3].

Table 3. Echocardiographic findings among intergroups analysis.

	Late pattern N=6	No late pattern N=55	p-value	ACA/ATA+ N=24	ACA/ATA- N=37	p-value	Puffy Hands N=18	No Puffy hands N=43	p-Value
E deceleration time (m/s), mean±SD	225.2±46.1	246.7±298.9	0.86	213.4±56.2	261.6±349.9	0.55	230.5±52.8	194.4±47.9	0.02
E/E' ratio, mean±SD	7.55±1.37	6.92±1.90	0.52	7.6±1.8	6.7±1.8	0.12	7.0±1.3	6.8±1.9	0.77
E wave, (m/s), mean±SD	0.70±0.22	0.68±0.16	0.86	0.71±0.17	0.65±0.17	0.27	0.68±0.19	0.69±0.16	0.78
A wave, (m/s), mean±SD	0.81±0.17	0.75±0.19	0.46	0.84±0.20	0.70±0.15	0.006	0.79±0.20	0.74±0.18	0.38
E/A ratio, mean±SD	0.92±0.40	1.0±0.39	0.61	0.84±0.27	1.08±0.42	0.02	0.92±0.4	1.02±0.39	0.39
E/A ratio < 1.0, n (%)	3 (50)	34 (61.8)	0.12	18 (75)	19 (51.4)	0.11	10 (55.6)	27 (62.8)	0.77
LVED diameter, (mm), mean±SD	38.5±3.6	40.5±4.9	0.34	39.4±5.6	40.8±4.4	0.45	40.2±6.2	40.4±4.07	0.86
PWED thickness, (mm), mean±SD	8.4±1.5	8.3±1.6	0.89	8.6±1.2	8.2±1.8	0.31	8.5±1.5	8.3±1.7	0.63
PWED > 9 mm, n(%)	4 (66.7)	13 (23.6)	0.04	9 (37.5)	8 (21.6)	0.24	8 (44.4)	9 (20.9)	0.11
IVS thickness, (mm), mean±SD	9.9±1.6	9.3±1.8	0.37	9.9±1.3	8.9±1.9	0.03	9.4±1.6	9.4±2.0	0.90
IVS > 10 mm, n (%)	2 (33.3)	20 (36.4)	0.39	10 (41.7)	12 (32.4)	0.58	6 (33.3)	16 (37.2)	1.0
LVED volume 4CH Simpson, (ml), mean±SD	69.7±22.2	67.5±16.1	0.76	66.9±17.3	68.3±16.4	0.75	24.8±3.5	85.3±363.2	0.49
LVES volume 4CH Simpson, (ml), mean±SD	24.8±9.7	25.6±12.1	0.88	24.0±9.9	26.4±12.8	0.46	68.3±17.8	68.7±16.3	0.93
LVED volume 4CH AL, (ml/m²), mean±SD	41.3±12.4	43.6±8.4	0.88	41.7±10.3	44.3±7.8	0.29	25.7±10.9	26.0±12.7	0.92
LVES volume 4CH AL, (ml/m²), mean±SD	14.8±5.6	14.7±4.2	0.54	14.7±6.2	14.7±2.9	0.92	43.1±10.5	44.3±8.2	0.64
EF%, mean±SD	64.5±6.8	64.6±4.6	0.92	64.9±5.7	64.4±4.3	0.64	15.6±6.2	14.6±3.2	0.42
EF%<55%	1 (16.7)	2 (3.6)	0.27	2 (8.3)	1 (2.7)	0.55	2 (11.1)	1 (2.3)	0.21
Mass ASE, (g), mean±SD	108.3±30.9	124.9±130.8	0.96	129.1±153.4	112±30.3	0.63	63.5±5.7	65.1±4.5	0.26
Mass/BSA, (g/m²), mean±SD	65.5±17.0	66.4±17.0	0.90	68.8±17.4	64.9±17.4	0.42	163.3±217.5	107.3±36.9	0.14
Relative wall thickness, mean±SD	0.48±0.08	0.44±0.1	0.35	0.48±0.09	0.42±0.10	0.04	68.3±19.5	66.5±17.0	0.73
Mass/height, (g/m), mean±SD	69.2±21.8	65.5±17.9	0.64	68.1±20.3	64.7±17.2	0.51	0.45±0.12	0.44±0.09	0.65
Aortic diameter, (mm²), mean±SD	29.7±2.4	29.6±4.1	0.96	29.7±3.7	29.6±4.1	0.94	65.3±20.6	67.5±17.8	0.68
LAES area, (cm²), mean±SD	16.1±2.7	15.6±3.7	0.75	16.7±4.1	15.1±3.2	0.11	28.5±2.5	30.0±4.3	0.19
LAES 4CH Simpson, (ml), mean±SD	41.6±10.5	40.3±14.3	0.83	46.7±18.7	37.2±8.9	0.01	15.4±3.3	16.1±3.8	0.52
LAES 4CH ind, (ml/m²), mean±SD	24.6±5.7	24.4±7.8	0.95	27.7±10.2	22.6±5.1	0.01	42.3±13.2	40.8±14.2	0.73

LAES diameter 4CH, (mm/m ²), mean±SD	50.3±5.8	46.1±8.1	0.27	49.7±5.9	45.0±8.4	0.04	25.6±8.3	24.6±7.3	0.68
RAES diameter AL, (mm), mean±SD	47.2±1.7	46.0±6.1	0.74	47.8±45.4	45.4±5.8	0.22	46.9±6.0	46.7±9.1	0.91
RAES 4CH Simpson, (ml), mean±SD	32.9±9.6	30.0±8.9	0.55	30.1±8.1	30.5±9.5	0.91	44.8±4.5	47.0±6.2	0.27
RAES 4CH ind, (ml/m ²), mean±SD	19.1±5.4	18.4±5.1	0.78	18.5±3.6	18.5±5.6	0.98	28.4±7.9	31.7±9.5	0.33
RAES area, (cm ²), mean±SD	13.8±2.5	13.5±3.2	0.83	14.4±2.9	13.0±3.2	0.12	17.9±4.8	18.9±5.4	0.59
TAPSE, (mmHg), mean±SD	22.0±4.9	21.5±2.9	0.70	21.9±3.7	21.4±2.7	0.61	13.1±2.2	13.8±3.6	0.43
TAPSE < 22 mmHg, n (%)	4 (66.7)	32 (58.2)	1.0	14 (58.3)	22 (59.4)	1.0	12 (66.7)	23 (53.5)	0.40
TAPSE < 16 mmHg, n (%)	0 (0)	1 (1.8)	1.0	1 (4.2)	0 (0)	0.39	0 (0)	1 (2.3)	1.0
TAPSE/sPAP, mean±SD	0.98±0.31	0.69±0.32	0.24	0.71±0.38	0.72±0.29	0.92	21.8±3.3	21.3±2.8	0.59
TAPSE/sPAP < 0.55, n (%)	1 (16.7)	3 (5.5)	0.35	1 (4.2)	3 (8.1)	1.0	1 (5.6)	3 (7.0)	1.0
sPAP, (mmHg), mean±SD	28.0±4.2	27.1±5.5	0.83	26.7±4.4	27.7±6.2	0.63	0.7±±.36	0.69±0.33	0.29
Tricuspid maximum regurgitation gradient, (mmHg), mean±SD	21.9±3.4	22.2±6.7	0.93	22.4±4.8	22.1±7.4	0.88	27.7±3.9	26.8±6.3	0.75
Mitral Valve Insufficiency, n (%)	5 (83.3)	37 (67.3)	0.66	21 (87.5)	21 (56.8)	0.01	12 (66.7)	30 (69.8)	1.0
Mitral Valve Sclerosis, n (%)	3 (50)	22 (40)	0.68	17 (70.8)	8 (21.6)	<0.001	9 (50)	16 (37.2)	0.40
Tricuspid Valve Insufficiency, n (%)	3 (50)	30 (54.5)	1.0	15 (62.5)	18 (48.6)	0.31	10 (55.6)	23 (53.5)	1.0
Aortic Valve Insufficiency, n (%)	4 (66.7)	10 (18.2)	0.02	10 (41.7)	4 (10.8)	0.01	5 (27.8)	9 (20.9)	0.74
Aortic Valve Sclerosis, n (%)	4 (66.7)	9 (16.4)	0.01	9 (37.5)	4 (10.8)	0.02	5 (27.8)	8 (18.6)	0.49
Pericardial Effusion, n (%)	0 (0)	4 (7.3)	1.0	1 (4.2)	3 (8.1)	1.0	2 (11.1)	2 (4.7)	0.57

Acronyms: SD= Standard deviation. ACA= Anti-centromere autoantibodies; ATA= Anti Topoisomerase I autoantibodies; E wave= early diastolic filling velocity of the left ventricle; E'= early diastolic tissue velocity of the mitral annulus; A=late diastolic filling velocity; LVED= Left ventricular end diastolic; LVES= Left ventricular end systolic; PWED=Posterior wall end diastolic; IVS=Interventricular septum; LAES= Left atrial end systolic; RAES= Right Atrial End Systolic; TAPSE= Tricuspid Annular Plane Systolic Excursion; sPAP= systolic Pulmonary Artery Pressure; 4CH=4 chamber; AL=anterolateral; EF= ejection fraction; %= percentage; BSA=Body Surface Area; ASE= American Society of echocardiography; ind= indexed; sup-inf= superior—inferior; m/s= meter/seconds; mm= millimeters; g= grams; g/m²= grams/square meters; cm²= square centimeters; mmHg= millimeters of mercury.

Notably, the prevalence of patients exhibiting PWED thickness >9 mm was significantly greater in the late NVC pattern group (66.7% vs 23.6 %, p=0.04). Furthermore, the presence of aortic valve insufficiency (66.7% vs 18.2%, p=0.02) and sclerosis (66.7% vs 16.4%, p=0.01) were significantly more prevalent in the same group. Moreover, the E/A ratio was significantly lower in the ACA/ATA+ group (0.84±0.27 vs 1.08±0.42, p=0.02) by exhibiting a longer A wave measurement (0.84±0.20 vs 0.70±0.15 m/s, p=0.006). Additionally, IVS thickness was greater in the same group (9.9 ± 1.3 vs 8.9 ± 1.9 mm, p=0.03). Further significant differences were noted in the LA end systolic (LAES) volume, even indexed for BSA, which were significantly higher in the ACA/ATA+ group (p=0.01 for both). Likewise, the LAES diameter (49.7±5.9 vs 45.0±8.4 mm/m², p=0.04) and the relative wall thickness (0.48±0.09 vs 0.42±0.10, p=0.04) were significantly larger in the ACA/ATA+ group. Additionally, ACA/ATA+ group revealed a greater proportion of both aortic and mitral valve insufficiency and sclerosis of valve leaflets. Lastly, in the puffy hands group, E deceleration time was significantly longer compared to the non-puffy hands group (194.4±47.9 vs 230.5±52.8 m/s, p=0.02). Any differences in RV and RA function parameters emerged from the intergroup comparisons of TAPSE, sPAP, and the tricuspid maximum regurgitation gradient, along with RAES volumes and diameters.

Acronyms: ACE-Is/ARBs= Angiotensin Converting Enzyme Inhibitors; ARBs= Angiotensin Receptor Blockers; E/A ratio= ; E'= early diastolic tissue velocity of the mitral annulus/late diastolic filling velocity ratio; LAES= Left atrial end systolic; m2= square meters.

Additionally, patients receiving ACE-Is/ARBs showed a statistically significant reduction in the E/A ratio compared to those who did not receive these treatments (0.81 ± 0.28 vs 1.06 ± 0.4 , $p=0.01$). This treatment group also exhibited a statistically larger LA diameter measured in the superior-inferior direction at end-systole (49.5 ± 5.8 vs 45.3 ± 8.4 mm/m², $p=0.04$) and a greater prevalence of aortic valve leaflets sclerosis (35.3% vs 11.6%, $p=0.03$). [Figure 1]

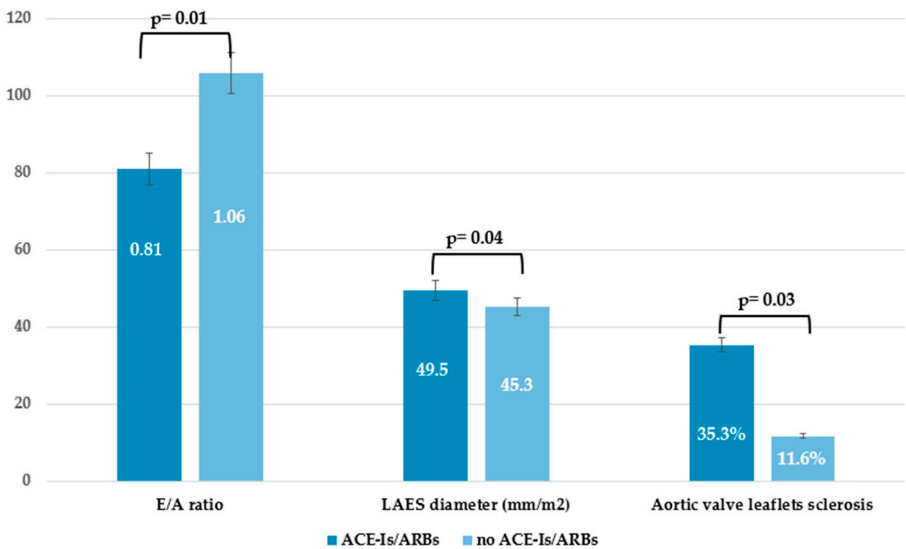


Figure 1. Bar chart showing main echocardiographic findings differences between patients undergoing ACE-Is/ARBs treatment versus patients not receiving ACE-Is/ARBs therapy.

3.3. Subclinical Echocardiographic Findings by Comparing Patients Receiving Current Therapy with Vasodilators

Subclinical echocardiographic alterations in patients receiving vasodilators were further assessed. We exclusively selected Iloprost iv administration and/or calcium channel blockers, as no other vasodilator was administered to our patients. Accordingly, patients were divided into four groups: *Group 1* encompassing patients receiving Iloprost intravenously only (n=25), *Group 2* with patients receiving CCBs orally only (n=8), while *Group 3* included patients undergoing both monthly Iloprost infusion and daily oral CCB (n=18), lastly, *Group 4* encompassed patients receiving no vasodilators (n=13). Our analysis revealed that patients receiving CCBs only exhibited a greater LVES volume measured by Simpson method ($p=0.001$), while reporting a reduced RAES volume compared to each group ($p=0.005$). Moreover, patients undergoing the combination therapy with Iloprost and CCBs exhibited a greater RAES volume measured via Indexed method compared to the other groups ($p=0.01$). [Table 4]

Table 4. Echocardiographic findings across patients undergoing vasodilators compared to those not receiving vasodilators.

Echocardiographic parameters	Iloprost iv N=25	CCBs N=8	Iloprost+CCBs N=18	No Vasodilators N=13	
E deceleration time (m/s), mean±SD	295.0±422.8	176.7±40.7	203.6±62.8	220.9±49.7	0.74
E/E' ratio, mean±SD	7.3±2.1	7.8±2.8	6.8±1.8	6.6±1.1	0.71
E wave, (m/s), mean±SD	0.67±0.18	0.68±0.22	0.68±0.15	0.77±0.23	0.59
E/A ratio, mean±SD	1.08±0.44	0.92±0.35	0.85±0.21	1.0±0.46	0.32
LVED diameter, (mm), mean±SD	40.6±5.1	42.5±7.4	39.6±4.4	40.4±5.0	0.72
PWED thickness, (mm), mean±SD	8.2±1.9	8.7±0.8	8.2±0.9	8.7±2.1	0.75

IVS thickness, (mm), mean±SD	9.3±1.8	8.9±1.4	9.5±1.4	9.3±2.6	0.93
LVED volume 4CH Simpson, (ml), mean±SD	67.5±13.8	54.1±31.5	67.8±15.3	73.8±14.6	0.17
LVES volume 4CH Simpson, (ml), mean±SD	23.7±6.5	47.2±35.1	23.8±6.0	24.6±7.4	0.001
LVED volume 4CH AL, (ml/m ²), mean±SD	42.8±9.8	41.4±8.4	42.1±8.7	46.9±7.1	0.46
LVES volume 4CH AL, (ml/m ²), mean±SD	14.5±3.6	16.5±12.9	14.4±3.5	15.3±4.0	0.84
EF%, mean±SD	64.9±4.4	59.6±6.7	65.1±5.0	65.2±4.2	0.12
Mass ASE, (g), mean±SD	109.3±33.5	95.9±60.3	160.1±217.4	109.1±42.2	0.56
Mass/BSA, (g/m ²), mean±SD	66.1±16.8	71.9±21.4	65.0±13.5	68.1±23.4	0.89
Relative wall thickness, mean±SD	0.44±0.11	0.45±0.10	0.46±0.08	0.44±0.13	0.93
Mass/height, (g/m), mean±SD	67.4±20.8	57.0±21.1	66.9±14.4	66.7±18.9	0.78
Aortic diameter, (mm ²), mean±SD	30.8±2.9	26.9±4.8	28.9±4.7	29.3±4.1	0.27
LAES area, (cm ²), mean±SD	14.4±2.4	15.5±4.1	16.3±3.8	17.0±4.7	0.16
LAES 4CH Simpson, (ml), mean±SD	36.1±8.1	41.0±19.8	44.7±16.3	42.1±16.3	0.26
LAES 4CH ind, (ml/m ²), mean±SD	21.6±4.3	25.5±11.4	26.9±8.3	26.0±9.8	0.14
LAES diameter 4CH, (mm/m ²), mean±SD	45.8±5.9	46.9±5.8	48.5±6.2	44.0±13.7	0.54
RAES diameter AL, (mm), mean±SD	45.1±5.9	40.5±6.1	48.7±5.3	46.2±5.4	0.12
RAES 4CH Simpson, (ml), mean±SD	31.2±8.4	14.1±6.5	26.5±5.4	30.2±9.1	0.005
RAES 4CH ind, (ml/m ²), mean±SD	18.1±5.1	12.4±6.7	21.7±4.5	16.6±2.1	0.01
RAES area, (cm ²), mean±SD	13.4±3.6	12.1±3.0	14.8±3.1	12.6±1.9	0.24
TAPSE, (mmHg), mean±SD	20.8±2.9	20.9±3.1	21.3±2.7	22.9±3.3	0.29
TAPSE/sPAP, mean±SD	0.79±0.33	0.31±0.44	0.76±0.10	0.65±0.39	0.28
sPAP, (mmHg), mean±SD	25.1±4.8	24.5±6.4	29.5±6.1	29.4±3.6	0.21
Tricuspid maximum regurgitation gradient, (mmHg), mean±SD	21.0±4.6	20.4±6.2	24.5±4.9	21.6±11.3	0.23

Acronyms: iv= intravenous; CCB= Calcium Channel Blockers; SD= Standard deviation. E wave= early diastolic filling velocity of the left ventricle; E’= early diastolic tissue velocity of the mitral annulus; A=late diastolic filling velocity; LVED= Left ventricular end diastolic; LVES= Left ventricular end systolic; PWED=Posterior wall end diastolic; IVS=Interventricular septum; LAES= Left atrial end systolic; RAES= Right Atrial End Systolic; TAPSE= Tricuspid Annular Plane Systolic Excursion; sPAP= systolic Pulmonary Artery Pressure; 4CH=4 chamber; AL=anterolateral; EF= ejection fraction; %= percentage; BSA=Body Surface Area; ASE= American Society of echocardiography; ind= indexed; sup-inf= superior –inferior; m/s= meter/seconds; mm= millimeters; g= grams; g/m2= grams/square meters; cm2= square centimeters; mmHg= millimeters of mercury.

3.4. General Multivariable Regression Model

Furthermore, E/A ratio, IVS thickness, and PWED thickness were identified as key descriptors of diastolic and systolic LV dysfunction. A general multivariable regression model incorporating BMI, age at VEDOSS diagnosis, DLCO% predicted, ACA/ATA positivity, late NVC patterns and puffy hands as relevant clinical determinants, revealed that only DLCO% emerged as a significant predictor of both IVS thickening (p=0.034) and PWED thickening (p=0.002). Additionally, ACA positivity was significantly associated with PWED thickening (p=0.004). These findings persisted even when the model was applied exclusively to the e-VEDOSS group.

4. Discussion

The present study provides relevant insights into subclinical echocardiographic abnormalities of patients meeting the VEDOSS criteria. The occurrence of cardiac involvement at the early stage of SSc was previously reported by researchers Gotschy A et al. and De Luca G et al. The former conducted a Cardiac Magnetic Resonance driven study which has proved the presence of myocardial fibrosis in a cohort of 24 VEDOSS patients [26], while the latter described three cases of myocardial involvement, emphasizing the role of vasculopathy, inflammation and fibrosis as major SSc-related pathogenic mechanisms [27].

Our cohort was initially divided into mild longstanding VEDOSS (ml-VEDOSS) and early VEDOSS (e-VEDOSS) groups based on disease duration as suggested by Blaja et al. [9]. The authors stated that subjects fulfilling the criteria for VEDOSS encompass a heterogeneous mixture of patients with both early potentially at risk of progression and long standing, very mild diseases. This observation has important implications, as these two subgroups cannot be easily differentiated based

on clinical phenotype at first presentation and since patients with mild long-standing disease need different frequencies of follow up and therapeutic considerations [9].

The ml-VEDOSS group exhibited a greater comorbidity count compared to the e-VEDOSS group, reflecting the cumulative burden of disease. This observation is consistent with previous research indicating that prolonged disease duration is correlated with prolonged chronic inflammation and prolonged exposure to altered vasoreactivity, ultimately increasing cardiovascular comorbidity [28, 29]. These findings are particularly relevant given that SSc patients account a five-fold increased mortality rate due to cardiac causes and sudden cardiac death occurring in 21%–54% of cases [15, 30]

The intergroup comparisons showed several differences on LV diastolic function parameters. In fact, as demonstrated by Giunta A et al., LV function can reflect heart involvement of SSc more sensitively than RV function [31]. Firstly, VEDOSS patients with late NVC patterns had significantly greater PWED thickness and a higher prevalence of aortic valve insufficiency. This aligns with findings of Markusse IM et al., who confirmed the independent association between advanced NVC pattern and heart/lung involvement [32]. Insightfully, the relationship between macrovascular and microvascular damage in SSc has been largely investigated. Pagkopoulou et al. demonstrated that reduced capillary density was inversely correlated with arterial stiffness. The authors reported also that the Framingham Risk Score, QRISK3, and ASCVD (Atherosclerotic Cardiovascular Disease) were inversely correlated with capillary density [33]. Conversely, Szucs et al. showed that the flow-mediated endothelium-dependent dilation was substantially reduced in SSc patients compared to healthy controls, indicating that impaired endothelium-dependent vasodilation is also present in pre-atherosclerotic stages [34]. Nevertheless, accurately quantifying the roles of intrinsic microangiopathy versus more common atherosclerotic processes in shaping the cardiovascular risk of SSc patients remains challenging.

Our results support these findings, providing additional evidence for the VEDOSS population, revealing that more advanced microarchitectural changes in NVC are related to greater echocardiographic alterations.

Additionally, it is worth mentioning that the ongoing process of endothelial dysfunction also affects coronary microvasculature [35]. Due to abnormal vasoreactivity, patients with SSc may experience repeated cycles of myocardial ischemia-reperfusion, potentially contributing to the development of myocardial fibrosis, even in the absence of significant heart-related symptoms.

Furthermore, we observed that VEDOSS patients with specific SSc autoantibody positivity exhibited a reduced E/A ratio, greater modifications in LAES area, valve dysfunction and, an increased PWED thickness, positioning with previous research that has shown a relationship between specific autoantibodies and cardiac involvement [36]. Despite the causal relationship between autoantibodies and myocardial fibrosis is not yet fully understood, Henault et al. demonstrated that ATA can directly bind to fibroblast surfaces, inducing their activation and proliferation in endothelial tissue [37]. Moreover, Shen et al. found that ACA and ATA antibodies could induce vascular endothelial cell senescence via mechanisms distinct from the classic p53-p21 pathway in vitro, as observed in the sera of patients with Raynaud's phenomenon [38].

Moreover, Bellando-Randone et al. stated that autoimmunity plays a crucial role in shaping the progressive trajectories of VEDOSS patients, highlighting that SSc-specific antibodies are the most significant isolated predictor of progression from VEDOSS to definitive SSc, whereas negativity for antinuclear antibodies (ANA) at baseline has a strong negative predictive value [39].

Interestingly, by comparing patients undergoing vasodilators to patients not receiving such treatment, the former reported a greater percentage of enlarged RA, potentially reflecting an increased pressure or volume load on the RV. However, our echocardiographic findings did not show any discrepancies in RV functionality, as reported by the similar values of TAPSE, sPAP and Tricuspid maximum regurgitation gradient.

Our intriguing data did not allow easy interpretation. On one hand, our observation suggests that vasodilators may exert detrimental effects on right atrial enlargement, without causing

detectable changes in RV measurements. On the other hand, patients in the VEDOSS cohort could be characterized by an overall greater disease severity due to more severe microvascular involvement, which encompasses RA abnormalities, and vasodilators may simply be insufficient to detain the damage progression.

As demonstrated by Guedón et al., in a prospective three-years survival analysis, Iloprost administration did not show any effect on reducing nor increasing the occurrence of diastolic dysfunction and PAH, while Sildenafil demonstrated a potential protective role in preventing the progression toward diastolic dysfunction and heart failure with altered EF [40]. The authors also emphasized the need for a comprehensive analysis of the potential benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin and dapagliflozin, on diastolic dysfunction in patients with SSc. These medications have demonstrated beneficial effects in patients with heart failure and preserved EF [41]. However, we have no evidence regarding their efficacy in the VEDOSS population, as the present study focused on detecting subclinical echocardiographic changes in patients without heart-related symptoms.

Nevertheless, the increased use of both ACE-Is and ARBs in ml-VEDOSS points to a proactive approach in mitigating cardiovascular risk in patients experiencing a longer disease duration. This strategy is supported by evidence implying that these medications can improve cardiovascular and renal outcomes in the general population. In fact, ACE-Is and ARBs encompass the same Renin-Angiotensin-Aldosterone System (RAAS) inhibitors group although exerting different mechanisms of action, including increased bradykinin levels, potentiated bradykinin response and stimulated nitric oxide production with ACE-Is [42]. Moreover, the reduced E/A ratio in RAAS inhibitors group could reinforce the theory of their usage in more at-risk individuals, potentially mitigating the occurrence of major cardiac events and mortality. However, the preventive role of RAAS inhibitors in the early stages of SSc is still debated and their usage should be practiced with caution. In fact, as reported by Bütikofer L. et al. in an EUSTAR cohort analysis, ACE-Is in SSc patients with concomitant arterial hypertension display an independent risk factor for the development of Scleroderma Renal Crisis (SRC) but they still represent the first choice in SRC treatment. This study advocates that ARBs might be a safer alternative than ACE-Is, yet the overall safety of alternative antihypertensive drugs needs to be further investigated [43].

Furthermore, the multivariable analysis, indicating that DLCO% was the only significant predictor of IVS and PWED thickening, supported the role of pulmonary function in uncovering subclinical cardiac changes within our population. As recently described by He H. et al. in a magnetic resonance guided study, the DLCO% values are inversely correlated with myocardial native T1 values in SSc patients, suggesting that DLCO might be a potential indicator for subclinical myocardial fibrosis [44].

Although the present study adds new evidence on the underexplored occurrence of subclinical cardiac involvement in VEDOSS, it is limited by several factors. The relatively limited sample size of 61 participants may impact on the robustness of our conclusions. However, this small sample size primarily stems from the low prevalence of systemic sclerosis, as well as the even lower prevalence of VEDOSS. Therefore, multicenter studies involving larger cohorts are necessary to enhance the validity of these findings. Furthermore, inter-operator variability in the echocardiographic technique should be considered, although standardized protocols in accordance with the 2020 ACC/AHA guidelines were implemented to minimize its impact, as detailed in the methods section. Additionally, since the study was conducted at a single center in Italy, the generalizability of these findings may be limited. Due to the cross-sectional nature of the study, causal inferences cannot be made. To address this limitation, we strongly recommend conducting further multicenter prospective studies.

In conclusion, we demonstrated that various subclinical echocardiographic alterations occur in both early and mild-longstanding form of VEDOSS, however, we excluded patients initially classified as VEDOSS who further developed an established SSc. Future research is warranted to detect early differences in echocardiographic parameters between progressive and stable forms.

5. Conclusions

This study highlighted critical echocardiographic changes among patients fulfilling VEDOSS criteria. The associations between pulmonary function, cardiac structure, specific autoantibodies profile and microvascular damage underscored the complexity of VEDOSS and the need for comprehensive management strategies. Timely detection of heart involvement, especially in patients with advanced microangiopathy and features of SSc-related autoimmunity, is crucial for predicting disease progression and mortality.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: *Echocardiographic findings comparison between e-VEDOSS and ml-VEDOSS*.

Author Contributions: E.C.: Conceptualization, Software, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Writing—review & editing. E.Z.: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing—review & editing. I.S.: Resources, Data curation. A.L.: Resources, Data curation. L.C.: Resources. Data curation. E.M. Resources. Data curation. D.B.: Resources. Data curation. A.T.: Resources. Data curation. M.I.: Methodology. Supervision. M.S.C.: Methodology. Supervision. A.M.: Conceptualization, Validation, Resources, Supervision. Project administration. P.F.: Conceptualization, Validation, Resources, Writing—review & editing, Supervision. Project administration.

Funding: This research received no external funding.

Institutional Review Board Statement: “The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of ASST OVEST MILANESE.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data supporting this study’s findings are available from the corresponding author upon reasonable request. The data is not publicly available due to ethical restrictions.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflicts of interest.

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