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Cardiac Manifestations of Systemic Sclerosis: Unraveling the Role of Exercise Tests in Diagnosis and Staging

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To my son, Xavier

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"The only true wisdom is knowing that you know nothing." (Socrates)

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RESUMO

Contexto: A esclerose sistémica (ES) é uma doença autoimune do tecido conjuntivo, caracterizada por lesão vascular mediada pelo sistema imunitário e fibrose progressiva que afeta múltiplos órgãos, incluindo os pulmões e o coração. As complicações cardiopulmonares, particularmente a hipertensão arterial pulmonar (HAP) e o envolvimento cardíaco primário, constituem as principais causas de morbilidade e mortalidade. A deteção precoce permanece desafiante devido ao início subclínico e à sobreposição de sintomatologia entre estas entidades. Os testes funcionais de exercício, incluindo a prova de marcha de 6 minutos (PM6M) e a prova de esforço cardiopulmonar (PECP), emergiram como ferramentas não invasivas valiosas para avaliar o envolvimento cardiopulmonar, estratificar o risco e orientar a tomada de decisões diagnósticas na ES.

Métodos: Este trabalho integra uma revisão abrangente dos aspetos epidemiológicos, etiopatogénicos e clínicos do envolvimento cardiopulmonar na ES, com foco na HAP associada à ES e na doença cardíaca primária, juntamente com a análise de dados clínicos recentes. Foram considerados dois estudos observacionais:

1. Um estudo transversal que avaliou o desempenho diagnóstico da PECP na exclusão de HAP entre doentes com ES referenciados para cateterismo cardíaco direito (CCD);
2. Um estudo prospetivo que analisou a prevalência e os correlatos clínicos dos diferentes estádios de insuficiência cardíaca (IC) em doentes com ES sem HAP, destacando o papel da PECP e da PM6M na avaliação funcional; e
3. Um estudo transversal que avaliou o desempenho do trabalho miocárdio em detetar disfunção cardíaca subclínica, e a sua associação com marcadores de capacidade funcional.

Resultados: A HAP foi diagnosticada em aproximadamente 26% dos doentes com ES referenciados por suspeita da doença. As variáveis da PECP, nomeadamente o consumo máximo de oxigénio (VO_2 pico), a inclinação da ventilação-minuto em relação à produção de dióxido de carbono (relação

VE/VCO_2) e a pressão parcial de dióxido de carbono no final da expiração ($PetCO_2$), distinguiram doentes com e sem HAP com elevada precisão diagnóstica (área sob a curva (AUC) ≥ 0,80). Os limiares de VO_2 pico ≤ 16 mL/kg/min, relação VE/VCO_2 ≥ 33 e $PetCO_2$ ≤ 33 mmHg demonstraram 100% de especificidade para a exclusão de HAP, podendo reduzir a necessidade de CCD invasivo em até 40% dos doentes. No segundo estudo, cerca de metade da coorte de doentes com ES sem HAP apresentou estádios pré-clínicos de IC (A/B), enquanto 38% exibiram IC sintomática (estádio C). Os estádios mais avançados de IC correlacionaram-se com idade mais avançada, maior carga de doença sistémica e evidência ecocardiográfica de disfunção diastólica (aumento da relação E/e′ e dilatação da aurícula esquerda). Tanto a PM6M como os parâmetros da PECP (redução do VO_2 pico, aumento da relação VE/VCO_2) mostraram associações significativas com a gravidade da IC e com a limitação funcional, sublinhando a sua utilidade na deteção precoce e na estratificação do risco. No terceiro estudo, o índice global de trabalho (GWI) apresentou uma correlação positiva com o $\%VO_2$ previsto (r=0,38; p=0,026), o limiar ventilatório (r=0,43; p=0,04) e o $PETCO_2$ no pico (r=0,45; p=0,006), bem como uma correlação negativa com o $VO2/VCO_2$ no pico (r=-0,40; p=0,016). O trabalho construtivo global (GCW) revelou uma correlação positiva com o limiar ventilatório (r=0,42; p=0,044) e com o $PETCO_2$ no pico (r=0,46; p=0,006), e uma correlação negativa com o VO/VCO_2 no pico (r=-0,44; p=0,007). A distância percorrida no teste dos seis minutos (6MWD) apresentou correlação apenas com a fração de ejeção (FE) (r=-0,34; p=0,033).

Conclusões: A HAP e o envolvimento cardíaco primário constituem manifestações cardiovasculares frequentemente sobrepostas da ES. Os testes funcionais de exercício fornecem informações cruciais sobre a resposta cardiopulmonar integrada, permitindo o reconhecimento precoce de doença subclínica e uma caracterização mais precisa da disfunção estabelecida. A PECP demonstra utilidade na distinção entre HAP e outras causas de dispneia, bem como na decisão de se avançar para testes invasivos, enquanto a PM6M permanece uma medida prática e reprodutível da capacidade funcional e do prognóstico. A insuficiência cardíaca (IC) pré-clínica e sintomática revelou-se

muito prevalente em doentes com SSc. A classificação da IC mostrou estar associada à gravidade da doença, à idade e aos fatores de risco cardiovascular, enquanto os testes de capacidade funcional (PM6M e PECP) apresentam-se como ferramentas para a estratificação do risco de IC. O índice global de trabalho (GWI) e o trabalho construtivo global (GCW) destacaram-se como marcadores sensíveis de disfunção miocárdica precoce em doentes com SSc com envolvimento cardíaco e HAP. Os índices de trabalho miocárdico apresentaram correlações modestas com os parâmetros de desempenho ao exercício, refletindo a natureza multifatorial da limitação funcional nesta população. Estes achados salientam a necessidade crítica de uma avaliação cardiovascular abrangente e de estratégias de gestão direcionadas para mitigar a progressão da IC em doentes com ES.

Palavras-chave: ESCLEROSE SISTEMICA; INSUFICIENCIA CARDIACA; HIPERTENSAO ARTERIAL PULMONAR, TESTE DE ESFORÇO CARDIOPULMONAR, PROVA DE MARCHA DE 6 MINUTOS

ABSTRACT

Background: Systemic sclerosis (SSc) is a autoimmune connective tissue disease characterized by immune-mediated vascular injury and progressive fibrosis affecting multiple organs, including the lungs and heart. Cardiopulmonary complications, particularly pulmonary arterial hypertension (PAH) and primary cardiac involvement, represent leading causes of morbidity and mortality. Early detection remains challenging due to the subclinical onset and overlapping symptomatology of these entities. Functional exercise testing, including the six-minute walk distance (6MWD) and cardiopulmonary exercise testing (CPET), has emerged as a valuable non-invasive tool for assessing cardiopulmonary involvement, stratifying risk, and guiding diagnostic decision-making in SSc.

Methods: This work integrates a comprehensive review of the epidemiological, etiopathogenic, and clinical aspects of cardiopulmonary involvement in SSc, with a focus on SSc-associated PAH and primary cardiac disease, alongside analysis of recent clinical data. Three observational studies were considered:

(1) a cross-sectional study evaluating the diagnostic performance of CPET in excluding PAH among SSc patients referred for right heart catheterization (RHC);

(2) a prospective study assessing the prevalence and clinical correlates of heart failure (HF) stages in SSc patients without PAH, emphasizing the role of CPET and 6MWD in functional evaluation; and

(3) a cross-sectional study evaluating the ability of myocardial work to detect subclinical cardiac dysfunction and its association with functional capacity markers

Results: PAH was diagnosed in approximately 26% of SSc patients referred for suspected disease. CPET variables, namely peak volume of oxygen (VO_2), minute ventilation to carbon dioxide production (VE/VCO_2) slope, and partial pressure of end-tidal carbon dioxide ($PetCO_2$), differentiated PAH from non-PAH patients with high diagnostic accuracy (area under the curve (AUC) ≥ 0.80). Thresholds of peak VO_2 ≤ 16 mL/kg/min, VE/VCO_2 slope ≥ 33, and $PetCO_2$ ≤ 33 mmHg demonstrated 100% specificity for excluding PAH, potentially reducing the need for invasive RHC in up to 40% of patients.

In the second study, nearly half of the SSc cohort without PAH presented preclinical HF stages (A/B), while 38% exhibited symptomatic HF (stage C). Advanced HF stages correlated with older age, greater systemic disease burden, and echocardiographic evidence of diastolic dysfunction (increased E/e′ ratio, enlarged left atrium). Both 6MWD and CPET parameters (reduced peak VO_2, elevated VE/VCO_2 slope) showed strong associations with HF severity and functional limitation, highlighting their utility in early detection and risk stratification. In the third study, the global work index (GWI) shows a positive correlation with %VO2 predicted (r=0.38, p=0.026), ventilatory threshold (r=0.43, p=0.04), PETCO2 peak (r=0.45, p=0.006), and a negative correlation with VO/VCO2 peak (r=-0.4, p=0.016). Global constructive work (GCW) presented a positive correlation with VT (r=0.42, p=0.044), and PETCO2 peak (r=0.46, p=0.006), and a negative correlation with VO/VCO2 peak (r=-0.44, p=0.007). 6MWD only correlates with EF (r=-0.34, p=0.033).

Conclusions: PAH and primary cardiac involvement are often overlapping cardiovascular manifestations of SSc. Functional exercise testing provides critical insight into the integrated cardiopulmonary response, enabling earlier recognition of subclinical disease and more accurate staging of established dysfunction. CPET demonstrates usefulness in distinguishing PAH and other causes of dyspnea, as well as in deciding whether to proceed with invasive testing, while 6MWD remains a practical and reproducible measure of functional capacity and prognosis. Preclinical and symptomatic HF has been shown to be very prevalent in SSc patients. HF staging was linked to disease severity, age, and cardiovascular risk factors, while functional capacity tests (6MWT and CPET) serve as tools for HF risk stratification. GWI and GCW stood out as sensitive markers of early myocardial dysfunction in SSc patients with cardiac disease and PAH. Myocardial work indices correlate modestly with exercise performance parameters, highlighting the multifactorial nature of functional limitation in this population. These findings highlight the critical need for comprehensive cardiovascular assessment and targeted management strategies to mitigate HF progression in SSc patients.

Keywords: SYSTEMIC SCLEROSIS; HEART FAILURE; PULMONARY ARTERIAL HYPERTENSION; CARDIOPULMONARY EXERCISE TEST; 6-MINUTE WALK DISTANCE.

LIST OF ABBREVIATIONS

6MWD	Six-minute walk distance
ACR	American College of Rheumatology
ANFPT2	Angiopoietin 2
AT	Anaerobic threshold
ATS	American Thoracic Society
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CIBO	Chronic intestinal pseudo-obstruction
CMR	Cardiac magnetic resonance
CO	Cardiac output
CO_2	Carbon dioxide
Cpc-PH	Combined post- and precapillary PH
CPET	Cardiopulmonary exercise testing
CTD	Connective tissue disease
dcSSc	Diffuse cutaneous systemic sclerosis
DLCO	Diffusing capacity of carbon monoxide
ECG	Electrocardiogram
ECV	Extracellular volume quantification
EF	Ejection fraction
EndoMT	Endothelial to mesenchymal transition
ERA	Endothelin-1 receptor antagonist
ET-1	Endothelin-1
EULAR	European League Against Rheumatism
EUSTAR	EULAR Scleroderma Trials and Research
FVC	Forced vital capacity
FVC/DLCO	Forced vital capacity/diffusion capacity for carbon monoxide
GCW	Global constructive work

GERD	Gastroesophageal reflux disease
GLS	Global longitudinal strain
GWE	Global work efficiency
GWI	Global work index
GWW	Global wasted work
HF	Heart Failure
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
HLA	Human leukocyte antigen
HRCT	High-resolution computed tomography
HR-QoL	Health-related quality of life
hs-cTnT	High-sensitive cardiac troponin T
ILD	Interstitial lung disease
INOCA	Ischemia with no obstructive coronary artery disease
Ipc-PH	Isolated postcapillary PH
IQR	Interquartile range
LA	Left atrium
LAVI	Left atrial volume index
lcSSc	Limited cutaneous systemic sclerosis
LGE	Late gadolinium enhanced
LV	Left ventricle
LVDD	Left ventricle diastolic dysfunction
LVEF	Left ventricle ejection fraction
mPAP	Mean pulmonary arterial pressure
MW	Myocardial work
NO	Nitric oxide
NSVT	Non-sustained ventricular tachycardia
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
O_2	Oxygen
OPN	Osteopontin
$P(A\text{-}a)O_2$	Difference between PAO_2 and PaO_2

PAAT	Pulmonary artery acceleration time
PAH	Pulmonary arterial hypertension
PAO_2	Partial pressure of oxygen in the alveoli
PaO_2	Partial pressure of oxygen in the arterial blood
PASP	Pulmonary arterial systolic pressure
PAWP	Pulmonary arterial wedge pressure
PDE-5i	Phosphodiesterase-5 inhibitor
PET	Positron Emission Tomography
$PetCO_2$	Partial pressure of end-tidal carbon dioxide
PFT	Pulmonary function test
PH	Pulmonary hypertension
PPA	Prostacyclin pathway agent
PVCs	Premature ventricular complexes
PVR	Pulmonary vascular resistance
RBBB	Right bundle branch block
RHC	Right heart catheterization
RNP	Ribonucleoprotein
ROC	Receiver operating characteristic
RP	Raynaud's phenomenon
Scl-70	Topoisomerase I
SD	Standard deviation
sGCS	Soluble guanylyl cyclase stimulator
SIBO	Small intestinal bacterial overgrowth
SMR	Standardized mortality rate
SPRING-SIR	Systemic Sclerosis Progression Investigation group of the Italian Society for Rheumatology
SRC	Scleroderma renal crisis
SSc	Systemic Sclerosis
STE	Speckle tracking echocardiography
TIA	Transient ischemic attack
TPR	Total pulmonary resistance
TR	Tricuspid regurgitation

TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
Vd/Vt	Ratio of physiologic dead space over tidal volume
VE/VCO_2	Minute ventilation to carbon dioxide production
VO2	Volume of oxygen
VT	Ventilatory threshold
WHO	World Health Organization
WU	Wood units

CHAPTER I

The background

SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a chronic autoimmune disease that primarily attacks the body's connective tissues, leading to widespread inflammation and the overproduction of collagen. The distinctive triad of microvascular damage, dysregulated immunity, and generalized fibrosis characterizes this disease in multiple organs (Allanore et al., 2015; Asano, 2018).

Epidemiology

Epidemiologic studies of SSc are scarce and estimates of prevalence and incidence vary widely due to the rarity of the disease, evolving classification criteria, and different study designs. The overall incidence rate of systemic sclerosis ranges globally from 8 to 56 new cases/million/year. The prevalence rate falls between 38 and 443 cases/million (Allanore et al., 2015; Ingegnoli et al., 2018) but presents substantial variation. Research has shown lower estimates of prevalence (<150 cases/million) and incidence (<10 cases/million/year) in northern Europe and Japan. In comparison, higher estimates of prevalence (276–443 cases/million) and incidence (14–21 cases/million/year) have been reported in southern Europe, North America, and Australia (Allanore et al., 2015; Barnes & Mayes, 2012). However, the greatest prevalence (47 in 100 000), was found among the indigenous peoples in Canada (Bernatsky et al., 2009; Calderon & Pope, 2021). Prevalence also differed greatly between sexes. Data from a systematic review and meta-analysis, using 23 studies, present a much greater prevalence of systemic sclerosis among women (28 per 100 000; 95%CI 23.1,33.9; f^2=99%) than among men (6 per 100 000; 95%CI 4.8, 7.5; f^2=97%) (Bairkdar et al., 2021), being also corroborated by Bergamsco *et al*., and others (Allanore et al., 2015; Bergamasco et al., 2019; de Angelis et al., 2022; Ingegnoli et al., 2018). Sources of variation likely reflect differences in population characteristics, case ascertainment, and methodological approaches across studies.

Etiology and Pathogenesis

The exact cause of systemic sclerosis remains unclear however, a permissive genetic background and epigenetic alterations by environmental triggers are likely key factors in the onset of the disease (Jerjen et al., 2022). These conditions trigger a chronic and self-amplifying process involving vascular alterations, inflammation, autoimmunity, and fibrosis, which drive disease progression and manifestations (Allanore et al., 2015).

Environmental agents or acquired genetic factors are probably the triggers for SSc. Environmental and occupational exposures that are demonstrated to be important for SSc, include silica (more frequent in certain occupations), solvents (more widespread, like write spirit, trichloroethylene, aromatic solvents, chlorinated solvents, and ketones), pesticides, epoxy resins, heavy metals, and some virus (Angiolilli et al., 2018; Ingegnoli et al., 2018; Jerjen et al., 2022; Marie et al., 2014; Marie et al., 2017).

It is uncommon for individuals with a family history of SSc to be affected by the disease. This evidence was stressed in a study of twins: Feghali-Bostwick and colleagues demonstrated a low concordance rate for SSc in monozygotic twins, suggesting that genetic factors alone are insufficient to explain disease development. They also showed that the concordance rate for monozygotic and dizygotic twins was similar, suggesting a substantial contribution of non-genetic influences, such as environmental exposures or epigenetic mechanisms to to SSc pathogenesis (Feghali-Bostwick et al., 2003). Nevertheless, accumulating evidence supports a genetic predisposition to SSc, with multiple susceptibility genes identified (Angiolilli et al., 2018). In genetically susceptible individuals, environmental triggers may initiate disease processes by affecting various cell types through direct modulation of intracellular signaling pathways and epigenetic mechanisms, such as DNA methylation, histone acetylation, and the regulation of microRNAs and long non-coding RNAs. These processes collectively promote aberrant immune activation and fibrosis (Allanore et al., 2015; Angiolilli et al., 2018; Asano, 2018; Jerjen et al., 2022). Most SSc susceptibility genes are related to immune regulation and include human leukocyte antigen (HLA) haplotypes and non-HLA immune-related genes, with different alleles associated with the major

autoantibody types (*e.g.* anti-centromere antibodies, topoisomerase-I, and RNA polymerase III) (Angiolilli et al., 2018; Asano, 2018; Jerjen et al., 2022). Still in the category of immune regulation, genes like STAT4, IL21, CD247, or CD226 are involved in T cell differentiation, proliferation, and/or activation. In the inflammation category, IRF5 and IRF8 are regulators for interferon I and II, and Il-6, CTGF, and other cytokines or chemokines that may be linked with fibrosis in SSc (Allanore et al., 2015; Angiolilli et al., 2018; Jin et al., 2014; Sobolewski et al., 2019). Immune regulation and inflammatory genes appeared to be two major categories of SSc. Still, genes involved in transcription regulation (*e.g.*, MECP2, SOX%), kinase activities (*e.g.*, GRB10, CSK), DNA cleavage or repair (*e.g.*, XRCC4, DNASEIL1), and genes that control cell fate and morphogenesis (*e.g.*, NOTCH4, RHOB), are also important in SSc (Jin et al., 2014).

The triggers mentioned above can cause vascular abnormalities through various mechanisms. Platelet activation and increased expression of adhesion molecules can obstruct the blood vessels, leading to ischemia and the production of reactive oxygen species. In response to injury, endothelial cells may undergo apoptosis, endothelial-mesenchymal transition, or become activated to release substances that promote inflammation and fibrosis. Additionally, there is an imbalance between vascular tone mediators promoting vasoconstriction (*e.g.*, endothelin), vasodilation (*e.g.*, nitric oxide), and inflammation (*e.g.*, superoxide anions) (Jerjen et al., 2022). These mechanisms produce two outcomes: (i) vascular injury followed by impaired neovascularization and vascular remodeling, leading to loss of small vessels, stenosis of arterioles and small arteries, and dilation of capillaries; and (ii) vascular activation leading to infiltration of inflammatory cells, impaired coagulation/fibrinolysis system, and endothelial to mesenchymal transition (EndoMT), changes that, adding to tissues hypoxia, promote tissue fibrosis - the hallmark of systemic sclerosis (Asano, 2018).

Nonetheless, the pathogenetic mechanisms underlying the marked female predominance, its heterogeneity and variable outcomes, the nature of environmental triggers and their interplay with the genetic susceptibility, and the extent to which these factors shape disease risk and phenotype remain poorly understood (Allanore et al., 2015).

Clinical Manifestations

Patients with SSc may experience a wide range of signs and symptoms related to the skin, blood vessels, internal organs, and overall health, as the disease is clinically heterogeneous (Jerjen et al., 2022). **Figure 1** summarizes the main manifestations.

Systemic sclerosis is also known as scleroderma. In Greek, the combination form “sclero” means hard, and the word “dermis” means skin, reflecting the primary characteristic of this connective tissue disorder: thickening and tightening of the skin (Odonwodo et al., 2023). Sclerodactyly is the tightening and thickening of skin over the fingers or toes, specifically over the joints closest to the nails but not including the joint that connects the finger bones (Jerjen et al., 2022). Hand involvement can be the first clinical clue of SSc, with patients complaining of edematous or puffy hands, with difficulty making a fist or wearing rings (Pearson et al., 2018). Although reversible, this normally progresses from an initial edematous phase to a fibrotic or indurated phase, and finally to an atrophic phase that may last a lifetime (Jerjen et al., 2022; Pearson et al., 2018). Sclerosis of the fingers can cause flexion contractures, fixing them in a partially bent position, reducing or eliminating the skin folds around the joints (acroosteolysis), and can also result in claw-shaped deformities of the hands and finger disfigurement (Pearson et al., 2018; Sobolewski et al., 2019). Fibrosis of the skin of the face can give typical sharp facial features called “mask-like-face”, like a decreased facial expression (amimia), a pointed, beaked nose, an impaired eye-opening, a radial perioral furrowing, microcheilia (abnormally small size of the lips), microstomia (oral aperture less than 4.5 cm), features that can affect up to 80% of patients, with a significant psychosocial impact (Jerjen et al., 2022; Pearson et al., 2018; Sobolewski et al., 2019). Sclerosis can also affect the eccrine glands, causing xerostomia (dry mouth), present in 60-70% of patients, and reduced tear secretion with resulting sicca syndrome (Jerjen et al., 2022; Pearson et al., 2018). Sclerosis of the lingual frenulum is a rare condition that can affect speech and swallowing abilities (Crincoli et al., 2016; Jerjen et al., 2022). Calcinosis results from insoluble calcified material (hydroxyapatite crystal) deposition within the extracellular matrix of the dermis and subcutaneous tissue,

most found over fingertips, elbows, knees, and shoulders, but may also occur on the trunk or in a more generalized pattern (Jerjen et al., 2022; Pearson et al., 2018). Cutaneous hyperpigmentation is also a condition that could be present in more than 50% of SSc patients, most commonly on the supraclavicular and suprascapular region, but could also affect the scalp, neck, forehead, dorsal hands, and extensor forearms (Pearson et al., 2018). More than 40% of SSc patients also experience pruritus, due to inflammatory irritation of nerves and/or fibrotic nerve-ending entrapment, being particularly debilitating (Jerjen et al., 2022; Pearson et al., 2018). Nail changes can also be present, like onycholysis (when the nail separates from its nail bed), scleronychia (nail thickening), ventral pterygium, brachyonychia (racquet nails), or parrot beak nails (Odonwodo et al., 2023; Pearson et al., 2018).

Additional skin-related manifestations, in the field of vasculopathy, may also be present. These include nailfold capillary changes (enlarged capillaries, capillary loss and microhemorrhages), affecting more than 70% of SSc patients; telangiectasis (superficial dilated cutaneous blood vessels), are typically found on the face, palms and chest in more than 50% of patients (Jerjen et al., 2022); Raynaud's phenomenon (RP), characterized by triphasic color change due to vasospasm, with initial blanching due to vasoconstriction, followed by blue/purple cyanosis (due to deoxygenation of sequestered blood), and resolution with red hyperemia, being present in >95% of patients, typically induced by cold temperatures or strong emotions/stress, localized symmetrically over the fingers (less commonly in the toes, lips, ears and nipples), and often coupled with pain, numbness, tingling and impaired function (Jerjen et al., 2022; Pearson et al., 2018); and digital ulcers and pitting scars, present in 32% to 58% of SSc patients, that may occur due to mechanical or ischemic phenomena, including RP, and may lead do infection, gangrene, and require aggressive medical or surgical treatment, including amputation (Hughes & Herrick, 2019; Ingegnoli et al., 2018; Jerjen et al., 2022; Pearson et al., 2018).

Systemic impairments may also be present, like musculoskeletal manifestations, gastrointestinal manifestations, renal involvement, nervous system manifestations, pulmonary impairment, and/or cardiac manifestations.

Musculoskeletal involvement can be an important and overlooked complication due to the focus on internal organ complications. Systemic sclerosis may affect muscles (weakness, contractures, myalgia, myositis), joints (arthritis, arthralgia), and tendons (tenosynovitis, friction rubs) (Denton & Khanna, 2017; Hughes & Herrick, 2019; Odonwodo et al., 2023; Sobolewski et al., 2019). Gastrointestinal involvement in systemic sclerosis affects the entire digestive tract and is present in 90% of patients. Gastroesophageal reflux disease (GERD) is present in 75% to 90% of SSc patients; in the stomach, gastroparesis is a functional disorder observed in 50% of the cases, and more rarely, gastric antral vascular ectasia ("watermelon stomach"); in the small intestinal bacterial overgrowth (SIBO), malabsorption (steatorrhea) and concomitant nutritional deficiencies can be present; chronic intestinal pseudo-obstruction (CIBO) can occur on large intestine; and anorectal involvement can lead to fecal incontinence, constipation and rectal prolapse (Hughes & Herrick, 2019; Odonwodo et al., 2023; Sobolewski et al., 2019). Approximately 5% of patients with systemic sclerosis may develop scleroderma renal crisis (SRC), which is defined by the development of thrombotic microangiopathy, with a sudden onset of high blood pressure, and progressive acute kidney injury (Denton & Khanna, 2017; Ingegnoli et al., 2018). The same vascular lesions as in Raynaud's phenomenon may develop in the brain and peripheral small vessels that supply peripheral nerves, resulting in symptoms of nervous system involvement, including dizziness, headache, visual disturbances, convulsions, and aphasia. Transient ischemic attack (TIA) and/or other ischemic syndromes, like strokes, peripheral polyneuropathy, trigeminal neuroinflammation, and cranial nerve inflammation, although more rarely, also may be observed (Amaral et al., 2013; Sobolewski et al., 2019).

Pulmonary impairment in systemic sclerosis includes interstitial lung disease (ILD) and PAH, and these are the main causes of morbidity and mortality of SSc (Odonwodo et al., 2023; Sobolewski et al., 2019). ILD is characterized by inflammation and fibrosis of pulmonary parenchyma and appears in the early years of the disease with general stabilization during the first 4-6 years (Denton & Khanna, 2017; Ingegnoli et al., 2018). It is widespread, since up to 90% of SSc patients present evidence of interstitial changes on high-resolution computed

tomography (HRCT) and, at later stages, the most common symptoms are fatigue, breathlessness, dry cough, and dyspnea (Odonwodo et al., 2023; Sobolewski et al., 2019). Damage to the pulmonary vasculature and the development of pulmonary fibrosis contribute to the constriction of blood circulation, culminating in pulmonary arterial hypertension, affecting about 13-15% of SSc patients (Denton & Khanna, 2017; Odonwodo et al., 2023; Sobolewski et al., 2019). The elevated pressure in pulmonary arteries leads to right ventricular insufficiency and ultimately to right heart failure (HF) (Sobolewski et al., 2019). Patients may remain asymptomatic for an extended period. However, the onset of symptoms such as hemoptysis, syncope, and dysphonia signifies a more serious stage of the condition (Odonwodo et al., 2023). Once considered a fatal complication, the prognosis of SSc-PAH patients has significantly improved due to advancements in early detection (like the implementation of the DETECT screening algorithm) and new treatments (Coghlan et al., 2014; Denton & Khanna, 2017; Ingegnoli et al., 2018; Sobolewski et al., 2019).

Cardiac involvement is prevalent, affecting up to 80% of SSc patients. Still, diagnosis and treatment pose challenges, as clinical symptoms (e.g. shortness of breath, fatigue, palpitations, and chest pain) can vary significantly among individuals and are not specific. Moreover, these symptoms often manifest in advanced stages of HF and convey a poor prognosis (Ferri et al., 2005; Moysidou et al., 2023). Heart involvement in systemic sclerosis can occur as a secondary consequence of other organ diseases, such as renal or pulmonary conditions. Alternatively, it may manifest primarily, indicating myocardial fibrosis, autonomic neuropathy, or involvement of the small coronary vessels or pericardial layers (Almeida et al., 2011; Ferri et al., 2003; Lambova, 2014). Depending on the specific structure affected, a spectrum of disorders may manifest, including rhythm irregularities, pericardial effusion, ischemia, hypertrophy, and fibrosis. These are conditions that can occur with and without HF, and are often associated with diastolic dysfunction (Allanore & Meune, 2010; Butt et al., 2019). Cardiac involvement in systemic sclerosis will be further detailed in subsequent sections.

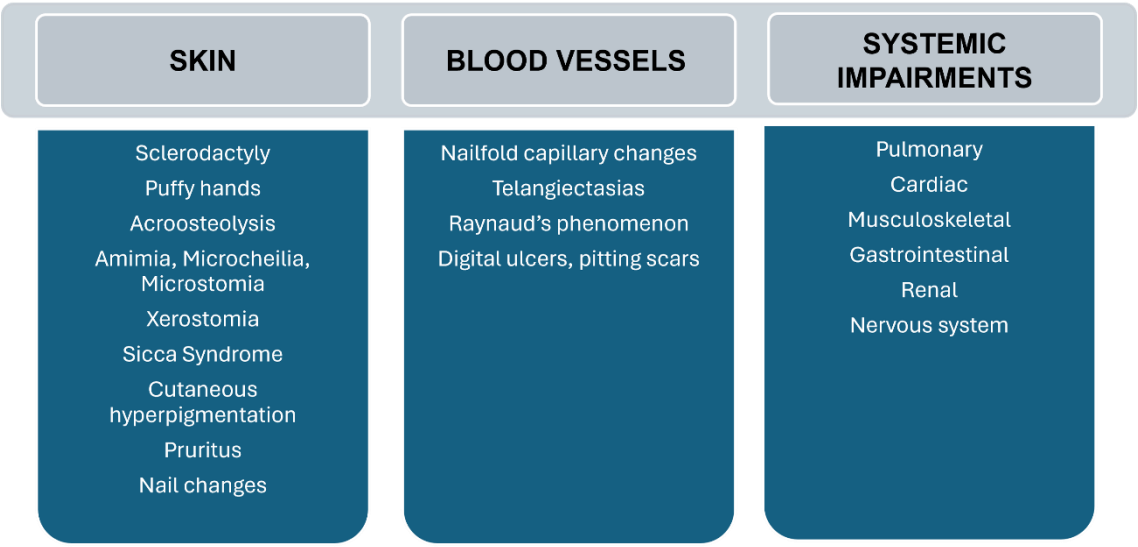

Figure 1 Summary of the main manifestations of systemic sclerosis

Classification of Systemic Sclerosis

In 2013, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) collaboratively formulated the prevailing classification criteria for SSc (**Table 1**). The classification criteria were created for research purposes (to ensure homogeneity among patients with the same clinical entity), and not as diagnostic criteria, although they are a useful aid to clinicians (Hughes & Herrick, 2019; van den Hoogen et al., 2013). These criteria include several assumptions, with different weights/scores, and patients who achieve a total weight/score of ≥9 are classified as having definite SSc. Of these assumptions, one is alone sufficient for classification as SSc: the presence of skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joint. The other assumptions had a weight/score between 2 and 4, and include the presence of some cutaneous (*e.g.*, puffy fingers) and vasculopathy (*e.g.*, RP, digital ulcers) manifestations, the presence of PAH and/or ILD, and SSc-related autoantibodies (*e.g.* anticentromere) (van den Hoogen et al., 2013).

Table 1 The ACR/EULAR criteria for the classification, applicable to any patient considered for inclusion in an SSc study.

Item	Sub-item	Weight or score ǂ
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	na	9
Skin thickening of the fingers (the higher of the two is counted)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the interphalangeal joints)	4
Fingertip lesions (the higher of the two is counted)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	na	2
Abnormal nailfold capillaries	na	2
Lung involvement	PAH and/or interstitial lung disease	2
Raynaud phenomenon	na	3
SSc-related autoantibodies	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

PAH – pulmonary arterial hypertension; na – not applicable

ǂ The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc. *Adapted from (van den Hoogen et al., 2013)*

Taking into account the extent of skin involvement, patients are classified according to the 2001 LeRoy criteria (LeRoy & Medsger, 2001). The limited cutaneous systemic sclerosis (lcSSc) is defined by clinical manifestations of skin fibrosis distal to the elbows, knees, and clavicles, which may include prominent telangiectasia, sclerodactyly, and calcinosis; the primary targets of autoantibodies are the centromere proteins, but Anti-Th/To, Anti-Ui-RNP and Anti-huBF are also common; the lcSSc normally have a slow progression with late development of PAH and frequent severe gut disease; and Raynaud phenomenon may precede other manifestation in this form. CREST (which stands for calcinosis, RP, esophageal involvement, sclerodactyly, and telangiectasia) is considered a synonym for lcSSc (Allanore et al., 2015; Denton & Khanna, 2017; LeRoy & Medsger, 2001; Sobolewski et al., 2019). The clinical

subset of diffuse cutaneous systemic sclerosis (dcSSc) is characterized by skin fibrosis up to elbows and knees, including the trunk, wherein tendon friction rubs may also be present. Normally the skin fibrosis rapidly progresses in this subset, with early manifestation of cardiac, pulmonary, and renal complications. The primary autoantibodies in dcSSc are RNA polymerase III, topoisomerase I (Scl-70), and anti-U3RNP (fibrillarin) (Allanore et al., 2015; Sobolewski et al., 2019).

Nevertheless, a subtype of systemic sclerosis where patients do not present any skin manifestations, although rare (<5% of all SSc patients), is also possible. This subset is called SSc sine-scleroderma, and patients often present clinical features like RP, digital ulcers, nailfold capillary abnormalities, PAH, and SSc-specific autoantibodies (nuclear and centromere proteins), but no skin thickening (Allanore et al., 2015; Denton & Khanna, 2017).

Also, it is not uncommon for systemic sclerosis to coexist with other rheumatological conditions (up to 20% of the patients) (Denton & Khanna, 2017). Patients with SSc overlap syndromes present symptoms of systemic sclerosis combined with clinical signs of other connective tissue diseases (especially Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, polymyositis, and dermatomyositis) (Stochmal et al., 2020). The Anti-PM/Scl, anti-U1-RNP, anti-Ro, and anti-La are the most common antibodies in overlap syndrome, and the disease course is characterized by prominent musculoskeletal involvement, with lung fibrosis and renal crisis being more uncommon (Allanore et al., 2015; Sobolewski et al., 2019).

Diagnosis and Assessment

Currently, there is no definitive test to diagnose systemic sclerosis. The diagnosis depends on the expertise of a clinician, where clinical assessment and the application of a set of classification criteria are typically necessary (Ingegnoli et al., 2018). With the aim of gathering reliable and up-to-date evidence, Asano *et. al*, published guidelines for systemic sclerosis, including diagnostic criteria and severity classification (Asano et al., 2018). The diagnosis determination is based on the criteria present in **Figure 2**.

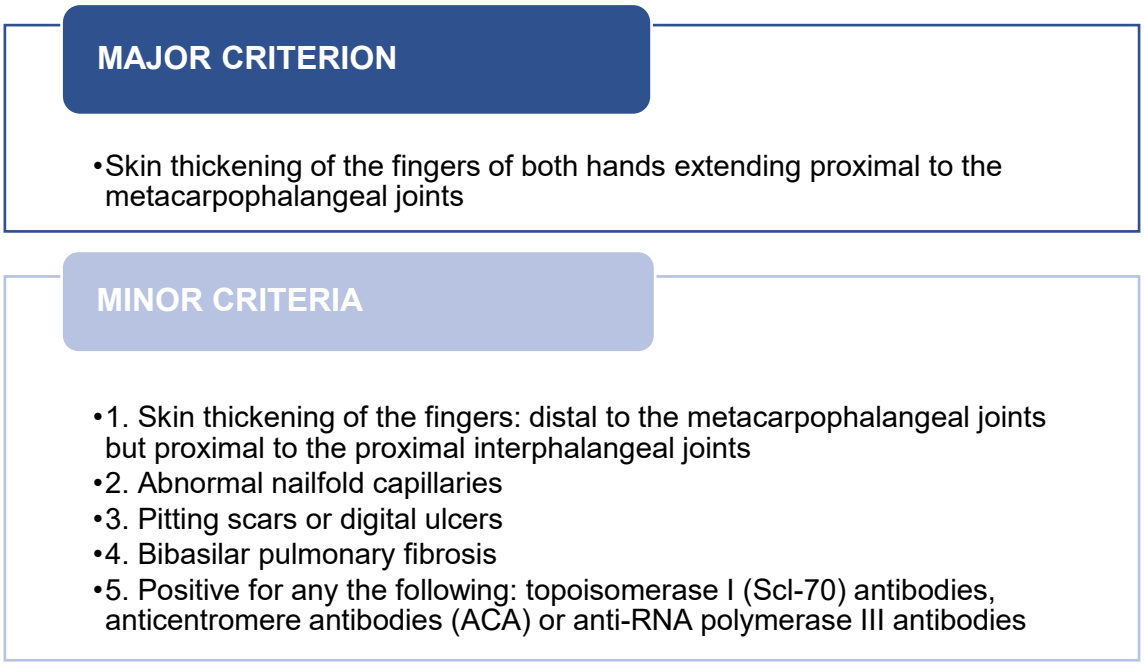

Figure 2 - Criteria for the diagnosis of systemic sclerosis, according to Assano *et. al*.
Patients who meet the major criterion or (1) and at least another minor criterion (2 to 5) are diagnosed with systemic sclerosis.

These diagnostic criteria, although different, have some resemblance to the ACR/EULAR classification criteria, and both are a useful aid to clinicians since a wide range of conditions (e.g. Werner's syndrome, scleroedema, nephrogenic systemic sclerosis, and others) can mimic systemic sclerosis (Hughes & Herrick, 2019; Odonwodo et al., 2023). In order to confirm the diagnosis, clinicians must perform a thorough clinical assessment, which includes conducting some complementary exams such as screening for antinuclear antibodies, nailfold capillaroscopy, transthoracic echocardiography, hand X-ray, DLCO and spirometry, high-resolution computed tomography of the chest, and esophageal manometry. Complementary examinations are also beneficial in detecting any potential systemic complications and should be conducted annually to monitor the patient's health status (Odonwodo et al., 2023).

Treatment and Management

Currently, there is no known cure or treatment available to completely relieve or eliminate SSc. The goal of management of SSc is to alleviate the symptoms and decelerate the progression of the disease (Odonwodo et al.,

2023). Controlling SSc is complex due to the need to inhibit the autoimmune process, manage inflammation, and address organ-specific issues. Considering these aspects, in 2024, the British Society for Rheumatology published guidelines for the management of systemic sclerosis (Denton et al., 2024). The summary of these recommendations, along with the strength of the recommendation/level of evidence, is presented in **Table 2**.

Table 2 Current recommendations for systemic sclerosis treatment

Complication	Medication/treatment	Strength of recommendations/ level of evidence
Raynaud's phenomenon (RP)	Calcium channel blockers and other vasodilators	1B
	PDE5i (effective as 2nd line agent for refractory SSc-RP)	1B
	Prostanoids	1C
Digital ulcers (DU)	Sildenafil (or tadalafil) as 1st line agent in DU healing and secondary prevention and bosentan as second line treatment	1C
	IV prostanoids	1C
Pulmonary arterial hypertension	Treatment initiated by a designated Pulmonary Hypertension Centers	1B
	Anticoagulation is not recommended	1B
Skin	MMF is 1st line treatment for skin fibrosis in dcSSc	1C
	Antihistamines are often used for itch	2C
	Skin camouflage, pulsed dye laser or intense pulsed light therapy (for telangiectasia)	2C
Renal crisis	ACE inhibitors	1A
	Glucocorticoid treatment avoided in adult SSc (increased SRC risk)	1A
	Renal transplantation	1B
Gastrointestinal involvement	PPI and/or H2 receptor antagonists for reflux	1C
	Parenteral nutrition for severe malnutrition	1B
	Intermittent or rotational antibiotics SIBO	1B
	Anti-diarrheal agents or laxatives	2B

Interstitial Lung Disease (ILD)	MMF is recommended as 1sr line treatment with rituximab or cyclophosphamide i.v. as alternative	1B
	Consider adding rituximab or tocilizumab to MMF for progressive disease	2C
	Nintedanib recommended for progressive pulmonary fibrosis	1B
Musculoskeletal	May benefit from immunomodulatory treatments given for other complications	1C
Cardiac	Immunosuppression with MMF when investigation suggests myocardial inflammation	2C
	Glucocorticoids and other bDMARDs may be added if appropriate and/or cyclophosphamide	2C

ACE - angiotensin-converting enzyme; bDMARDs - biological disease-modifying anti-rheumatic drug; dcSSc – diffuse cutaneous systemic sclerosis; DU – digital ulcers; MMF - mycophenolate mofetil; PDE-5 - phosphodiesterase type 5; PPI – proton pump inhibitor; RP – Raynaud's phenomenon; SRC – scleroderma renal crisis; SIBO – small intestinal bacterial overgrowth. Adapted from Denton *et al*., 2024.

Prognosis and quality of life

It is well recognized that SSc is one of the autoimmune systemic diseases with a poorer prognosis in terms of mortality (Ingegnoli et al., 2018; Rubio-Rivas et al., 2014), a fact that is confirmed by a meta-analysis by Rubio-Rivas and colleagues that reported a standardized mortality rate (SMR) between 1.05 and 5.4 in the 17 studies included, with an estimated overall SMR of 2.72 (95%CI 1.93,3.83) (Rubio-Rivas et al., 2014). A few years later, a systematic review reported a SMR in Europe, between 1.3 and 2, and a SMR of 4.7 (95%CI 3.6-5.7) among incident cases in a large cohort study in Canada (Bergamasco et al., 2019). In the same year, a study was published that reported an ever-higher SMR, of 5.73 (95%CI 4.68-6.94), by Pokeerbux *et al.*, in a multicenter, French cohort (Pokeerbux et al., 2019). The primary factors correlated with a higher risk of death include advanced age at diagnosis, male gender, diffuse skin involvement, and visceral complications (e.g. pulmonary, cardiac and renal) (Odonwodo et al., 2023; Pokeerbux et al., 2019).

Systemic sclerosis can exert a substantial, and often overlooked, impact on the quality of life. The health-related quality of life (HR-QoL) in these patients

is frequently compromised, affecting mainly the physical domain with issues like pain, fatigue, limitations in mobility and hand function, and sleep disturbance. Additionally, mental domains are also impacted, including depression, sexual dysfunction, and body image distress from disfiguring changes in appearance (e.g., facial telangiectasias, pigment changes, hand contractures) (Almeida et al., 2015; Hudson et al., 2009; Kwakkenbos et al., 2013). Patients with SSc often have a reduced quality of life, but they frequently do not receive adequate treatment in this area, despite the availability of safe and manageable medicines (Mura et al., 2012).

PAH ASSOCIATED WITH SYSTEMIC SCLEROSIS

Pulmonary arterial hypertension is a severe, life-threatening complication and one of the leading causes of morbidity and mortality in patients with SSc (Erdogan et al., 2024). Pulmonary arterial hypertension, as well as interstitial lung disease and kidney pathology, may contribute to the development of secondary cardiac involvement in SSc (Lambova, 2014; Varga et al., 2017).

Epidemiology

A clear understanding of the prevalence and epidemiological patterns of PAH in SSc is essential to enhance early detection. However, the prevalence of SSc-PAH varies greatly in the literature, since the criteria used to define PAH (pre or post the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension), the studied population, and the method of choice for diagnosis, are not the same among all studies (Saygin & Domsic, 2019). The estimated prevalence of PAH in SSc ranges between 8 and 15%, contrasting with the general population, where the prevalence of PAH is 15-52 cases per million, or 0.00005%, enhancing the high predominance of this condition (Peacock et al., 2007; Saygin & Domsic, 2019). The prevalence of PAH is higher in individuals with limited cutaneous systemic sclerosis (Denton & Khanna, 2017; Odonwodo et al., 2023).

Pulmonary arterial hypertension is a significant contributor to mortality and morbidity in connective tissue diseases (CTDs), especially systemic sclerosis (Sarı et al., 2025). Data from the EULAR Scleroderma Trials and Research (EUSTAR) database, including 5860 patients with SSc, suggests that the presence of PAH diagnosed by echocardiography was associated with increased mortality (HR 2.42, $p < 0.001$), and was also an independent risk factor (Anthony J Tyndall et al., 2010).

Some risk factors have been recognized as being associated with a higher risk of PAH development, namely, male gender and older age at SSc diagnosis. Presence of gastroesophageal reflux disease, calcinosis, more severe Raynaud's phenomenon, decreased nailfold capillary density, and increased

number of telangiectasias are also associated (Morrisroe et al., 2016; Saygin & Domsic, 2019). Also, four main SSc-related antibodies have been linked to an elevated risk of PAH, particularly anti-centromere, anti-Th/To, anti-U1 ribonucleoprotein (RNP), and anti-U3 RNP (Hamaguchi, 2010; Saygin & Domsic, 2019). Alongside recognized clinical and serological risk factors, two validated predictors of SSc-associated PAH have been adopted into clinical practice to guide systematic screening. The analysis of N-terminal pro-B-type natriuretic peptide (NT-proBNP), being strongly correlated with hemodynamic parameters, and also; a decline in diffusing capacity of carbon monoxide (DLCO), and a forced vital capacity (FVC)/DLCO ratio > 1.6, since it has been demonstrated that both have a high positive predictive value of PAH (Allanore et al., 2008; Hamaguchi, 2010; Sarı et al., 2025; Saygin & Domsic, 2019).

Etiology and Pathogenesis

Pulmonary arterial hypertension is a progressive disease characterized by pathologic pulmonary vascular remodeling leading to right ventricular failure and death (Hassoun, 2015; Tuhy & Hassoun, 2023). PAH is a hallmark manifestation of endothelial dysfunction and pulmonary vascular injury in systemic sclerosis. Early vascular alterations (e.g., endothelial apoptosis, activation, inflammatory cell recruitment, intimal proliferation, and adventitial fibrosis) initiate a cascade that promotes vasoconstriction, inflammation, and thrombosis (Humbert et al., 2019). The resultant imbalance between vasodilatory mediators (e.g., nitric oxide, prostacyclin) and vasoconstrictive agents (e.g.,endothelin-1, thromboxane A_2) fosters a procoagulant and proliferative vascular environment, ultimately leading to progressive vessel narrowing and obliteration (Chaisson & Hassoun, 2013; Overbeek et al., 2009). Concomitant activation of fibroblasts and excessive extracellular matrix deposition contribute to vascular stiffening and increased pulmonary vascular resistance. These structural and functional changes culminate in sustained elevation of mean pulmonary arterial pressure (mPAP). Sustained elevation of pulmonary pressures imposes a chronic hemodynamic burden on the right ventricle, driving maladaptive remodeling, dilatation, and eventual right ventricular failure (Allanore et al., 2015; Lechartier & Humbert,

2021; Sobolewski et al., 2019). This sequence of events represents the core pathogenic mechanism underlying cardiac involvement secondary to PAH in SSc.

Clinical manifestations

Patients with SSc-PAH are predominantly female, reflecting the general trend in SSc. Men tend to be diagnosed at an older age, often presenting with more severe disease and experiencing poorer outcomes (Tuhy & Hassoun, 2023). SSc patients with PAH present nonspecific symptoms, such as dyspnea on exertion and fatigue, which are often attributed to SSc global functional impairment. In fact, in the early stages of the disease, SSc-PAH patients typically show no symptoms or only symptoms associated with other organ involvement (Lechartier & Humbert, 2021). Syncope, dysphonia, and hemoptysis are signs of seriousness (Odonwodo et al., 2023). Most patients with PAH are diagnosed late with advanced symptoms (Erdogan et al., 2024).

Right heart catheterization is the gold standard for the diagnosis of PAH. According to the most recent published consensus on the condition, RHC should evaluate pulmonary vascular resistance by measuring cardiac output (Humbert et al., 2022). This is reflected in the definition of PAH. The criteria for the diagnosis of PAH are presented in **Table 3**. Pulmonary hypertension is classified by the World Health Organization (WHO) in a five-group structure. PAH is group 1, as we defined in **Table 3**. Patients with SSc may also develop pulmonary hypertension due to left-sided heart disease (Group 2), chronic lung disease (Group 3), or other less common causes, which may coexist in the same individual (Hudson et al., 2025; Humbert et al., 2022).

Table 3 Criteria for the diagnosis of pulmonary arterial hypertension

Pulmonary arterial hypertension documented on right heart catheterization, requiring the concomitant presence of all of the following criteria:
1. Mean pulmonary artery pressure (mPAP) > 20 mmHg;
2. Pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg; and
3. Pulmonary vascular resistance (PVR) > 2 Wood units.

Adapted from Hudson *et al*.

Management and therapeutic options

Approved medications for treating PAH have been shown to improve functional class, exercise capacity, hemodynamic parameters, right heart function, and levels of BNP / NT-proBNP, among other outcomes (Chin et al., 2024). Recent advancements in target therapy development and risk assessment have led to a major improvement in the management of CTD-PAH. At the moment, there are four key pathways for management of PAH: endothelin 1 (macitentan, ambrisentan, bosentan), prostacyclin (treprostinil, epoprostenol, iloprost, selexipag), nitric oxide (sildenafil, tadalafil, riociguat) and more recently, activin/TGF-β (sotatercept) (Alturaif & Alduraibi, 2025; Chin et al., 2024). At the 7th World Symposium on Pulmonary Hypertension, the current treatment algorithm for CTD-PAH was suggested. This treatment algorithm begins with risk assessment, using functional class, 6MWD and natriuretic peptides, hemodynamics, RV imaging and others. If the patient is not at high risk, a combination of endothelin-1 receptor antagonist (ERA) and phosphodiesterase-5 inhibitor (PDE-5i) is recommended. Additionally, a prostacyclin pathway agent (PPA) may be considered if severe hemodynamics and/or poor RV function were present. If the patient was considered at a risk, initial triple therapy (ERA + PDE-5i + PPA) must be initiated, and transplant referral should be considered in selected patients. The risk stratification should be performed within 3-4 months and periodically thereafter. If the patient continues at low risk, initial therapy should be maintained. If the patient is at an intermediate-low risk, it is recommended adding an activin-signaling inhibitor and oral or inhaled PPA. Switching PDE-5i to a soluble guanylyl cyclase stimulator (sGCS) can be considered. With patients at intermediate-high risk, intravenous/subcutaneous PPA or activin-signaling inhibitor should be added. Transplant referral should also be considered for intermediate-high risk patients. In patients who have become high risk, intravenous/subcutaneous PPA must be added (1st choice if not on), or activin-signaling inhibitor. Patients at persistent intermediate-high or high risk, should have a 4-drugs maximal prescription: PPA, ERA, PDE-5i or sGCS, and activin-signaling inhibitor; with lung transplantation being the final step, in patients with severe functional impairment and inadequate clinical response (Chin et al.,

2024; Lechartier & Humbert, 2021). Treatment algorithm for SSc-PAH is represented in **Figure 3**. Despite therapeutic advances and the growing diversity of treatment options, the prognosis of SSc–associated PAH remains poor and continues to represent a major determinant of mortality in this population (Legendre & Mouthon, 2014).

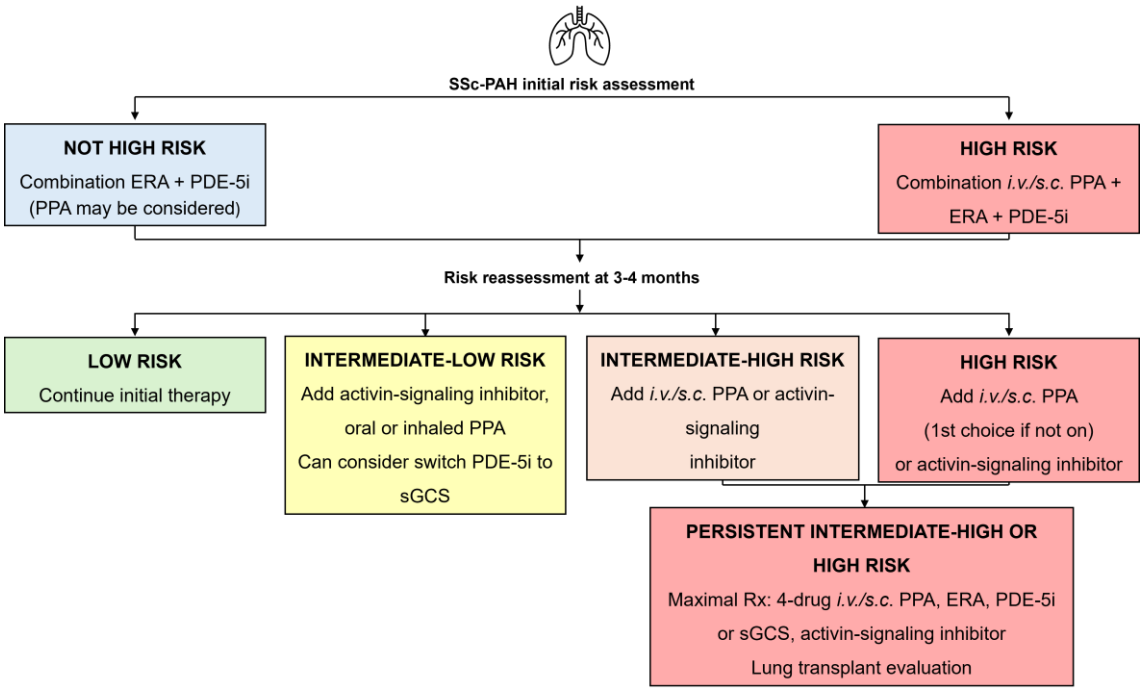

Figure 3 Treatment algorithm for SSc-PAH. PAH: pulmonary arterial hypertension; ERA: endothelin-1 receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitor; i.v.: intravenous; s.c.: subcutaneous; PPA: prostacyclin pathway agent; sGCS: soluble guanylyl cyclase stimulator; Rx: prescription. Adapted from Chin *et al*. (Chin et al., 2024)

PRIMARY CARDIAC INVOLVEMENT

Cardiac involvement in SSc is a serious and potentially life-threatening aspect of the disease. A systematic review and meta-analysis involving 14,813 participants showed that SSc was significantly associated with a higher risk of cardiovascular disease (HR 2.36, 95% CI 1.97-2.81) (Cen et al., 2020). Cardiac involvement in SSc could be primary, as a direct consequence of SSc, or secondary, as a consequence of other complications. Primary cardiac involvement can manifest as myocardial abnormalities, microvascular disease,

conduction abnormalities, pericardial disease, and, less commonly, valvular disease (Lambova, 2014; Varga et al., 2017).

Epidemiology

Understanding the prevalence and epidemiological trends of heart complications associated with SSc is crucial for effectively managing and allocating resources within healthcare systems. Determining the prevalence of cardiac involvement in SSc is challenging because it can manifest in a variety of different ways. (Lambova, 2014; Mohameden et al., 2024; Parks et al., 2014).

Primary cardiac disease is reported in both diffuse and limited SSc; however, the literature suggests that it might be more severe and prevalent in the diffuse subtype than in the limited form of systemic sclerosis (Allanore & Meune, 2010; Fernandez-Codina et al., 2017; Mohameden et al., 2024). The prevalence of the diverse types of cardiac involvement in SSc in the literature is scarce. In 1999, a study published that 14% of a cohort of 77 SSc patients had a significant pericardial effusion, but the data were not corroborated by Meune et al. years later (Handa et al., 1999; Meune et al., 2008). Hachulla et al. reported a prevalence of 75% (39/52 patients) for at least one cardiac abnormality on MRI (*e.g.*, thinning of LV myocardium, pericardial effusion, LV kinetic abnormalities) (Hachulla et al., 2009). Regarding ventricular dysfunction, most studies have reported a low prevalence of reduced left ventricle ejection fraction (LVEF), varying between a prevalence of 1.4% (in a French multicenter study, with 570 patients evaluated) to 12% (Norwegian cohort of 277 patients) (Butt et al., 2019; De Groote et al., 2008; Tennøe et al., 2019). Comparatively, diastolic dysfunction has a higher prevalence, ranging from 17.7% to 30%, corroborating the frequent presence of diastolic dysfunction in patients with SSc (De Groote et al., 2008; Fontes Oliveira et al., 2022; Meune et al., 2008). Thus, the prevalence of cardiac involvement in SSc can reach 70% to 100%, with most cases being subclinical (Mohameden et al., 2024; Varga et al., 2017). The estimated clinically overt cardiac involvement rate is around 30% (Mohameden et al., 2024).

The cumulative risk of death for cardiac involvement in SSc, has been reported to be around 3.15, analogous to PAH, ILD, or renal involvement, and it

can account for 20 to 30% of all premature deaths (Fernandez-Codina et al., 2017; Komócsi et al., 2012). Cardiac involvement increases mortality, and it is also known that it occurs at a higher rate, especially during the first year after SSc onset (Fernandez-Codina et al., 2017).

Etiology and Pathogenesis

The underlying cause of this condition is multifaceted. Multiple risk factors for primary cardiac involvement in SSc have been identified, including specific autoantibodies such as anti-U3-RNP and anti-Scl-70, skeletal muscle involvement, rapid skin thickness progression, older age, obesity, pre-existing coronary artery disease, and also dyslipidemia and hypertension (Butt et al., 2019; Hinze et al., 2022; Mohameden et al., 2024; Osgueritchian et al., 2025). Cardiac involvement in SSc, specifically diastolic dysfunction, was also independently associated with reduced diffusion capacity for carbon monoxide (DLCO ≤ 60% of predicted), longer disease duration, and a history of scleroderma renal crisis (Hinze et al., 2022; Jones et al., 2025).

The main cause of cardiac fibrosis and ventricular dysfunction is believed to be an abnormality of the coronary microcirculation, characterized by vasospasm and recurrent ischemia-reperfusion injury, primarily driven by cardiac Raynaud's phenomenon, which is associated with microvasculopathy, inflammation, and tissue damage (Dorniak et al., 2025; Varga et al., 2017). Vascular dysfunction is thought to arise from initial damage to endothelial cells, which may be secondary to a disruption in immune tolerance following exposure to an environmental trigger (Jones et al., 2025). This cascade ultimately leads to the production of autoantibodies targeting vascular antigens and the release of proinflammatory cytokines and chemokines, which facilitate the recruitment of immune cells, including neutrophils, macrophages, dendritic cells, and T lymphocytes. The resulting endothelial damage further amplifies cardiac injury through mechanisms such as the dysregulated secretion of nitric oxide (NO) and endothelin-1 (ET-1), promoting a vasoconstrictive environment, enhanced immune cell infiltration into myocardial tissue, and the release of profibrotic mediators that drive cardiac fibrosis. Collectively, these interconnected processes contribute to

cardiovascular remodeling and the development of heart failure in systemic sclerosis (Jones et al., 2025).

Clinical manifestations

Patients with SSc exhibit complex cardiac manifestations due to the often nonspecific and subclinical nature of their symptoms, which may include chest pain, dyspnea, palpitations, exercise intolerance, shortness of breath, lightheadedness, dizziness, or even syncope (He et al., 2023; Osgueritchian et al., 2025; Varga et al., 2017).

Signs of primary cardiac manifestations in SSc are also very varied, including pericardial diseases (*e.g.*, pericardial effusion, cardiac tamponade, pericardial fibrosis, constrictive pericarditis), and myocardial fibrosis, that may lead to fibrosis of the conduction system (leading to bradyarrhythmias, bundle branch and atrioventricular blocks), tachyarrhythmias, valvular dysfunction, asymptomatic diastolic or systolic dysfunction, and symptomatic heart failure (Fernandez-Codina et al., 2017; He et al., 2023; Osgueritchian et al., 2025; Varga et al., 2017).

Heart failure is, indeed, the major complication of cardiac involvement in SSc. It can occur secondary to PAH or renal impairment, or as a consequence of primary myocardial involvement (Jones et al., 2025). Diastolic dysfunction is a very common functional finding in these patients and often precedes the clinical diagnosis of HF with preserved ejection fraction (HFpEF) (Tennøe et al., 2018). HF with reduced ejection fraction (HFrEF) is rarer in SSc. Later stages of the disease are characterized by apoptosis and fibroblast proliferation, which result in HFrEF and LV remodeling (Jones et al., 2025; Zagouras et al., 2021). Criteria for cardiac involvement in systemic sclerosis are shown in **Table 4**.

Table 4 Criteria for cardiac involvement in systemic sclerosis

Any of the following 10 findings in any of the 4 categories:
1. Clinical evidence of left-sided heart failure, confirmed by a physian,
OR
2. Myocardial dysfunction, any one of:

a) LV systolic dysfunction with LVEF < 50% or preserved LVEF and decreased LV longitudinal strain on echocardiogram;
b) Diastolic dysfunction with elevated LV filling pressures on echocardiogram or cardiac MRI;
c) Myocardial fibrosis or inflammation (widespread, patchy) on cardiac MRI or myocardial biopsy

OR

3. Cardiac conduction system dysfunction, any one of:
    a) Second- or third-degree heart block on electrocardiogram or ambulatory monitoring;
    b) Frequent premature ventricular contractions on ambulatory monitoring; or
    c) Supraventricular or ventricular tachycardia on electrocardiogram or ambulatory monitoring

OR

4. Pericardial disease, any one of:
    a) Pericarditis: pericardial pain by patient history and pericardial rub on physical examination confirmed by a physician;
    b) Pericardial effusion: greater than trace amount on echocardiogram or cardiac MRI; or
    c) Pericardial fibrosis on echocardiogram or MRI.

Adapted from Hudson *et al*. (Hudson et al., 2025)

Management and therapeutic options

Diastolic or systolic heart failure, arrhythmia, and conduction abnormalities are examples of clinically obvious cardiac involvement, which carries a high death rate, and the treatment of these patients should be carried out with the appropriate participation of a cardiologist. As first line, it is important to optimize the care and control of additional related co-morbidities like systemic hypertension, high cholesterol, diabetes, and renal disease. All patients should be encouraged to change their lifestyles, including their nutrition and smoking habits (Bissell et al., 2017).

The British Society for Rheumatology and British Health Professionals in Rheumatology, although recognizing that the publish evidence is scarce, recommended immunosuppression with or without pacemaker; implantable cardioverter-defibrillator; and angiotensin-converting enzyme inhibitors and β-

blockers, in case of systolic heart failure. In presence of HFpEF, the recommendation involves diuretics (including spironolactone and furosemide); and calcium channel blokers (Denton et al., 2016). Transplantation in end-stage systolic dysfunction is currently used in the general population and could be considered for patients with SSc (Bissell et al., 2017). Lastly, the majority of specialists would advise vigorous cytotoxic therapy until troponin negative is attained in patients who present with acutely worsening heart failure and persistent troponin leakage, which is suggestive of active myocarditis (Kahan et al., 2009).

When arrhythmias are present, the same principles applied to the general population should be used in SSc patients. Pharmacotherapy should be started, paying particular attention to the possible side effects of some anti-arrhythmic medications (such as the vaso-spastic effects of β-blockers and the possible lung fibrotic impact of amiodarone). Implantable cardioverter-defibrillator should be vonsidered for life-threatening arrhythmias (Bissell et al., 2017).

For SSc patients with proven coronary artery disease, prognostically favorable medication (aspirin, statin, angiotensin-converting enzyme inhibitor, and a cardioselective beta-blocker) and intervention as indicated should be the standard of care. Programs for cardiac rehabilitation should also be taken into account (Bissell et al., 2017).

When Myocardial fibrosis and inflammation are present, immunosuppressive therapy (e.g., cyclophosphamide, mycophenolate mofetil) may be considered, although evidence is still evolving (Ferlito et al., 2022).

Diagnostic approaches

The diagnosis of cardiac involvement in SSc remains a significant clinical challenge; however, all appropriate diagnostic methods must be used, as early myocardial involvement, if not detected, can lead to irreversible fibrosis and should be seen as an early sign of poor prognosis.

- Biomarkers

Understanding whether biomarkers can help stratify patients at risk of cardiac complications is a question that continues to drive research. The cardiac biomarkers most studied in SSc are the natriuretic peptides, BNP and NT-proBNP; however, although these biomarkers can diagnose overall cardiac involvement, they cannot be used for screening for primary or secondary cardiac involvement in SSc (Allanore et al., 2009; Desai et al., 2011). Levels higher than the study thresholds (NT-proBNP ≥ 125 pg/ml and BNP ≥ 60 pg/ml) could be a sign of cardiac involvement in SSc; however, it cannot be forgotten that several conditions, cardiac and non-cardiac, can influence these natriuretic peptide values, and therefore their interpretation must be done with caution within the clinical context (Desai et al., 2011; Osgueritchian et al., 2025). The role of high-sensitive cardiac troponin T (hs-cTnT) is also controversial, but may have special importance when accompanied by left ventricular (LV) systolic dysfunction on echocardiography, elevated serum levels of NT-proBNP, the presence of right bundle branch block (RBBB) on electrocardiogram (ECG), and also when the clinical subset of dcSSc is present (Bosello et al., 2019; Jones et al., 2025; Osgueritchian et al., 2025). While these biomarkers are ineffective for screening preclinical or asymptomatic cardiac involvement, they seem to serve as indicators of severity and prognosis, as NT-proBNP and hs-cTnT correlate with mortality risk. (Bosello et al., 2019; Jha et al., 2022; Osgueritchian et al., 2025).

Some emerging biomarkers, like angiopoietin 2 (ANFPT2), osteopontin (OPN), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), galectin-13, and growth differentiation factor-15 (markers of inflammation, fibrosis, cardiovascular stress, and are associated with heart failure, all features well describe in SSc) are promising yet not suitable for practical application, since additional research are required to assess the specificity and sensitivity of these biomarkers in predicting outcomes in SSc (Jones et al., 2025; Lui et al., 2025; Osgueritchian et al., 2025).

- Imaging modalities

Autonomic dysfunction, conduction disorders, and arrhythmias are common in SSc, resulting in an estimated annual sudden cardiac death rate of 1.0–3.3%, which is a tenfold higher risk than in the general population (Osgueritchian et al., 2025). In fact, in a systematic review and meta-analysis, Fairley et al., noted that on ambulatory electrocardiogram, arrhythmias such as non-sustained ventricular tachycardia (NSVT) and frequent premature ventricular complexes (PVCs) are common, even among individuals without known or suspected SSc-cardiac involvement. (Fairley et al., 2023). The Systemic Sclerosis Progression Investigation group of the Italian Society for Rheumatology (SPRING-SIR) identified, using echocardiography and ECG, a prevalence of cardiac involvement in 25% of a large cohort (149 of 600 SSc patients), with LV diastolic dysfunction, conduction blocks, and arrhythmia being the most common alterations reported (Tonutti et al., 2025). Echocardiography stands out as an essential, affordable, and radiation-free tool with high specificity and predictive value, playing a pivotal role in screening and early detection of diverse pathologies, even in asymptomatic SSc patients, as well as in forecasting unfavorable outcomes (Jones et al., 2025; Osgueritchian et al., 2025; Weber et al., 2023). Two-dimensional (2D) echocardiography offers crucial information on cardiac function and size, valvular and pericardial disease, it can also provide important information that helps determine the type of pulmonary hypertension when present. In fact, regarding pulmonary hypertension, it is known that some parameters assessed by echocardiography (tricuspid annular plane systolic excursion, tissue Doppler S' velocity, and fractional area change) have predictive value for mortality in SSc-PAH (Farrell et al., 2021; Weber et al., 2023). Three-dimensional (3D) echocardiography, especially for volumetric evaluation of right ventricular ejection fraction, is being increasingly employed in clinical practice to assess therapy response due to its strong association with cardiac magnetic resonance (CMR) techniques in pulmonary hypertension (PH) (Weber et al., 2023). Speckle tracking echocardiography (STE) provides a sensitive approach to assess cardiac involvement and may reveal early cardiac changes in SSc patients. A systematic review and meta-analysis showed that SSc patients (*vs.*

healthy controls) have a lower strain for the majority of STE parameters, revealing the presence of subclinical cardiovascular abnormalities in SSc patients (Qiao et al., 2023). Myocardial work (MW) is a recently validated non-invasive method that accounts for myocardial deformation and afterload (via blood pressure) to evaluate LV performance (Manganaro et al., 2020; Marzlin et al., 2023; Russell et al., 2012). In SSc, myocardial work is in its early stages. Magda et al., and Zhang et al., describe the values of MW in SSc cohorts (versus matched controls), and compared to the most traditional/accepted parameters to assess LV function (e.g. LVEF and GLS). Even when standard echocardiography measurements were normal, they both conclude that MW deteriorated in SSc patients, indicating subclinical myocardial dysfunction and implying that MW might be used as a screening parameter to identify patients at increased risk of cardiac disease (Magda Ș et al., 2024; Zhang et al., 2025).

This data underscores the necessity of an annual ECG and echocardiography to enable early detection and timely intervention for potential cardiac complications in SSc patients. Nonetheless, while echocardiography offers substantial advantages in terms of accessibility, safety, and diagnostic value, its ability to characterize microvascular dysfunction or detect myocardial fibrosis remains limited, highlighting the need for complementary imaging modalities such as cardiac magnetic resonance.

For assessing cardiac involvement in SSc, cardiac magnetic resonance remains the ideal non-invasive imaging technique, as it can provide data not only about cardiac function and structure, but also allows the assessment of myocardial perfusion and deep tissue characterization (Jones et al., 2025). In fact, according to the consensus of World Scleroderma Foundation/Heart Failure Association, it is acknowledged that CMR can reveal abnormalities even in entirely asymptomatic patients, and functions as a surrogate modality for the gold standard, endomyocardial biopsy (Bruni et al., 2023). Native T1 mapping and extracellular volume quantification (ECV) are more sensitive than conventional CMR techniques, allowing the detection of low-grade and diffuse myocardial inflammation, while using late gadolinium enhanced (LGE) images detect replacement myocardial fibrotic tissue (Mavrogeni & Pepe, 2024; Weber et al.,

2023). Knight, D.S *et al*., show us, in a cohort of 260 symptomatic patients, that native myocardial T1, was an independent predictor of mortality, even after adjustment for age and the presence of PH (Knight et al., 2023). A study on a cohort of 20 SSc European patients, with any nonspecific symptoms and/or signs suggestive of possible heart involvement, demonstrated significantly lower LVEF, higher LV end-systolic volume index, higher ECV, and longer T1 and T2 relaxation times as compared to healthy controls (Dorniak et al., 2025). It was also reported that CMR detected cardiac tissue damage in 15% of patients with normal ECG and echocardiographic findings, and provided additional tissue characterization in 20% of patients with borderline, nonspecific echocardiographic abnormalities (Dorniak et al., 2025). This data corroborates the fact that CMR reveals even subtle morpho-functional alterations, playing an important role in early diagnosis of myocardial involvement in SSc.

Despite its demonstrated advantages, the utilization of CMR remains limited by high cost and restricted availability, particularly outside academic centers. In addition, the technical complexity of both image acquisition and interpretation poses further challenges, rendering it less broadly applicable than echocardiography (Jones et al., 2025).

ROLE OF EXERCISE TESTS IN DIAGNOSIS AND STAGING

- 6-Minute Walk Distance (6MWD)

The official statement of the American Thoracic Society (ATS) about the 6MWD, back in 2002, says that this test is practical and simple (only requires a 30-meter hallway, no exercise equipment, nor advanced training for healthcare providers), and evaluates the global and integrated responses of all the systems involved during exercise, assessing the submaximal level of functional capacity ("ATS statement: guidelines for the six-minute walk test," 2002). The same document also tells us that the strongest indication to perform this test is measuring the response to medical interventions in patients with moderate to severe heart or lung disease, but it has also been used as a single measurement of functional status on heart failure patients, as well as a predictor of morbidity

and mortality in heart failure and pulmonary hypertension patients, diseases that as we already describe, that are highly prevalent in systemic sclerosis and predictors of poor outcomes ("ATS statement: guidelines for the six-minute walk test," 2002; Ingegnoli et al., 2018; Komócsi et al., 2012). Since then, several studies have been published addressing the use of the 6MWD test in SSc. In 2018, using a small cohort of 56 patients, Pugnet *et al*. showed, within a follow-up of 2 years, a correlation between a distance covered of less than 80% of the predicted, with the presence of pulmonary and cardiac disease, which is a sign that 6MWD effectively correlates with SSc severity, confirming the utility of 6MWD to assess the overall prognosis of SSc patients (Pugnet et al., 2018). One year later, with a much larger cohort of 625 patients, Pokeerbux *et al*. found a negative correlation between 6MWD and survival in SSc patients, recognizing the 6MWD as an additional prognostic factor (Pokeerbux et al., 2019). Regarding the use of the 6MWD for screening cardiopulmonary involvement in SSc, a systematic literature review of three studies concludes that SSc patients with PAH walk a shorter distance in the test than patients without PAH, with one of the three studies also showing that exercise-induced desaturation (oxygen (O_2) <92%) was an independent predictor of PAH development (Hsu et al., 2014; Madigan et al., 2024; Phung et al., 2009); another recent study by Ahmed S. *et al*., shows that cardiopulmonary involvement (myocardial involvement, PAH, ILD or a combination) was significantly and independently associated with 6MWD and with the occurrence of desaturation during exercise (Ahmed et al., 2025). Therefore, the 6MWD emerges as a valuable diagnostic tool, as it not only enables the early detection of cardiopulmonary involvement in SSc patients but also provides significant prognostic information regarding disease progression.

- Cardiopulmonary exercise test (CPET)

Cardiopulmonary exercise testing is a comprehensive, standardized method and relatively non-invasive objective test, that evaluates the integrative response of the cardiovascular, respiratory, metabolic, and muscular systems during physical exertion (Pritchard et al., 2021). It is based on the principle that the system (e.g. cardiovascular, pulmonary, or muscle-energetic) failure typically

happens while the system is under stress. Thus, in a controlled way, the supporting system are “forced” normally over their tolerable range, which allows uncovering abnormalities that may remain undetected at rest (Palange et al., 2007). Nowadays, CPET is used to assess a wide spectrum of diseases, including heart failure, pulmonary hypertension, interstitial lung disease, and chronic obstructive pulmonary disease.

As we have already discussed, cardiac involvement, PAH, ILD, or a combination of these characteristics are frequently linked to SSc. Exercise intolerance is a frequent side effect, and depending on the underlying cause, SSc patients exhibit various gas exchange patterns (Boutou et al., 2016; Giubertoni et al., 2025). CPET allows a differential diagnosis of cardiovascular causes of functional impairment in these patients. Several studies have published data that may help distinguish between the various causes of exercise intolerance. In 1996, Schwaiblmair *et al*., using a cohort of 78 SSc patients (43% with symptoms of exertional dyspnea), concluded that CPET findings differ between diffuse and limited skin involvement, and that SSc patients with lung disease, the ratio of physiologic dead space over tidal volume (Vd/Vt) and the difference between the partial pressure of oxygen in the alveoli (PAO_2) and the partial pressure of oxygen in the arterial blood (PaO_2) [$P(A\text{-}a)O_2$], increased during exercise (Schwaiblmair et al., 1996). Later, in 2010, Cuomo *et al*., in a cohort study with 46 SSc patients (plus controls), discovered that these patients' cardiovascular and respiratory parameters are noticeably impaired during exercise, with a lower VO_2, a decrease O_2 pulse, a reduced ventilatory volume, and a significant lower anaerobic threshold (AT) compared to the predicted VO_2 peak. They also reported significant correlations between exercise intolerance and the severity of heart involvement, the LV diastolic dysfunction, and the severity of lung involvement (Cuomo et al., 2010). In the same year, Walkey *et al*., using a small cohort of 19 SSc patients, and adding right-heart catheterization to CPET, attempted to differentiate the various sources of exercise intolerance, presenting 5 different types, with their main characteristics gathered in **Table 5** (Walkey et al., 2010).

Table 5 The 5 types of exercise intolerance in SSc patients, proposed by Walkey *et al*.

Pulmonary vasculopathy	LV dysfunction	Ventilatory limitation	Cardiovascular limitation	Deconditioning
● ↓ VO_2 peak at AT ● ↑ VE/VCO_2 ● PCWP < 18 mmHg	● ↓ VO_2 peak at AT ● ↑ VE/VCO_2 ● PCWP ≥ 18 mmHg ● DPG ≤ 5 mmHg ● EF ≥ 50%	● ↓ VO_2 peak ● ↓ BR	● ↓ VO_2 peak, without signs of pulmonary vascular, LV, or ventilatory impairment at CPET or RHC ● Abnormalities in a resting echo	● ↓ VO_2 peak, without signs of pulmonary vascular, LV, or ventilatory impairment at CPET or RHC

VO_2 - volume of oxygen; AT - anaerobic threshold; VE/VCO_2 - minute ventilation/carbon dioxide production; PCWP - pulmonary capillary wedge pressure; DPG – diastolic pulmonary gradient; EF – ejection fraction; BR - breathing reserve; LV – left ventricle; CPET – cardiopulmonary exercise test; RHC – right heart catheterization.

More recently, Boutou *et al*., assessed the potential causes of exercise intolerance in a population of 78 SSc patients with perceived exertional dyspnea or reduced physical performance, proposing 4 groups: normal exercise capacity or subnormal exercise capacity, respiratory limitations, patients with LV dysfunction, and those with pulmonary vasculopathy (Boutou et al., 2016). Their main characteristics are presented in **Table 6**.

Table 6 Categorization of the different causes of exercise intolerance, proposed by Boutou *et al*.

Pulmonary vasculopathy	LV dysfunction	Respiratory limitation	Normal or subnormal exercise capacity
● peak VO2 < 80% predicted ● AT < 75% predicted ● VE/VCO_2 at AT < 34 ● decreasing $\Delta PetCO_2$ or	● peak VO2 < 80% predicted ● AT < 75% predicted ● normal or high VE/VCO_2 at AT ● increasing or neutral ΔPetCO2	● BR < 11 liters	● peak VO2 ≥ 80% predicted or peak VO2 < 80% predicted ● AT ≥ 75% predicted ● BR ≥ 11 liters ● VE/VCO_2 at AT < 34

● peak VO2 ≥ 80% predicted ● AT ≥ 75% ● VE/VCO_2 at AT ≥ 34 ●decreasing $\Delta PetCO_2$	● no resting and no exercise-induced hypoxemia		● rest SaO_2 ≥ 95% ● rest SaO_2 - peak SaO_2 ≤ 4%

VO_2, oxygen consumption; AT, anaerobic threshold; BR, breathing reserve; VE, minute ventilation; VCO_2, volume of exhaled carbon dioxide; $PetCO_2$, end-tidal partial pressure of carbon dioxide; $\Delta PetCO_2$, change of $PetCO_2$ from rest to AT; SaO2, arterial oxygen saturation; CPET, cardiopulmonary exercise testing; SSc, systemic sclerosis.
Adapted from Giubertoni *et al.* (Giubertoni et al., 2025).

Both studies aim to differentiate the underlying mechanisms of exercise intolerance, but they approach the classification with slightly different emphases. Walkey *et al*., besides CPET, incorporate invasive hemodynamic data and non-invasive findings from echocardiography; while Boutou *et al*., focused the analysis only on CPET-derived parameters. The two authors overlap in highlighting reduced VO_2 peak, low AT, and elevated VE/VCO_2 as markers of pulmonary vasculopathy or left ventricular dysfunction, with Boutou *et al*., suggesting that the differentiation between this two causes of exercise intolerance, should be done by observing a decrease in $PETCO_2$ from rest to AT (Boutou et al., 2016; Giubertoni et al., 2025; Walkey et al., 2010). Regarding ventilatory limitation, both approaches emphasize the reduced breathing reserve, and, while Walkey *et at*., make a differentiation between cardiovascular dysfunction and deconditioning, Boutou *et al*., preferred to include these patients on the normal or subnormal exercise capacity group (Boutou et al., 2016; Walkey et al., 2010). Thus, while Walkey *et al*. takes a more mechanistic and integrative approach by combining CPET, echocardiographic, and hemodynamic data, Boutou *et al.* focuses on standardized CPET thresholds, making it potentially more practical for uniform application in clinical and research settings.

CPET also assumes greater importance when screening for PAH, which accounts for around 30% of deaths in SSc patients (Anthony J Tyndall et al., 2010). The gold standard for diagnosing and classifying pulmonary hypertension is right heart catheterization. In cases of suspected pulmonary hypertension, even in asymptomatic patients, echocardiography is the primary non-invasive

diagnostic investigation, serving as the initial line of assessment, but its diagnostic accuracy alone is suboptimal (Humbert et al., 2022). With the goal of an earlier and more accurate screening of PAH in these patients, the DETECT algorithm emerged, adding other tests, such as respiratory function tests, ECG, serum biomarkers, and the current/past present of telangiectasias. (Coghlan et al., 2014; Humbert et al., 2022) The DETECT algorithm is highly sensitive in screening for PAH but lacks specificity (only 35%), often leading to unnecessary invasive procedures, such as RHC (Hao et al., 2015; Young et al., 2021). CPET could have a particular diagnostic utility when PAH is suspected since these patients display an abnormal cardiorespiratory response to exercise due to a reduced ventilatory efficiency and an increased right ventricle afterload (Dumitrescu et al., 2017; Weatherald et al., 2019). There are few, and heterogeneous, studies looking at the CPET diagnostic performance in SSc patients. Dumitrescu *et al*. concluded that particularly a VE/VCO_2 ratio of 45.4 is strongly predictive of PAH, whereas a peak oxygen uptake (VO_2) >18.7 mL/min/kg was found to be the most accurate parameter for excluding PAH in 100% of the patients (Dumitrescu et al., 2017). Santaniello and colleagues combined CPET with the DETECT algorithm and demonstrated that the addition of the VE/VCO_2 slope measurement into the DETECT algorithm could reduce unnecessary RHC without compromising its sensitivity (Santaniello et al., 2020). A study from 2022 looked at PAH screening in a small sample of 52 SSc patients using CPET. The study suggested PAH in 16 patients, in which resting RHC confirmed PAH in 5 patients, while exercise RHC confirmed it in an additional 7 patients (Sánchez-Aguilera Sánchez-Paulete et al., 2022). With that, the authors show that when CPET was used with both rest and exercise RHC, the diagnostic sensitivity was 100%, contrasting with a sensitivity of 70% by the DETECT algorithm in the same patients (Sánchez-Aguilera Sánchez-Paulete et al., 2022). In conclusion, CPET represents a comprehensive tool in PAH, as it supports early diagnosis by identifying abnormal pulmonary vascular responses to exercise.

Multiple studies have shown that CPET also holds prognostic significance for patients with SSc. Ewert and colleagues, following a cohort of 210 SSc

patients (52 with PH, of whom 38 had PAH) for 10 years, concluded that peakVO_2 (< 15.6 mL/Kg/min), VE/VCO_2 slope (>35), and 6-MWD (<413 meters), and the presence of PAH, were all negative prognostic predictors and can predict survival (Ewert et al., 2019). In 2021, with a smaller cohort of 29 SSc patients, and a shorter follow-up of 3.7 years, Hemelein *et al*., reported some correlations suggesting that CPET parameters might discriminate between SSc patients with or without adverse outcomes, namely baseline VO_2 and VE/VCO_2 correlated with a reduction in forced vital capacity; AT was linked to the development of digital ulcers, while VE/VCO_2 was linked to increases in pulmonary arterial pressure (Hemelein et al., 2021). More recently, a study including 62 SSc patients without baseline PH, with a follow-up of 10 years, found that a lower baseline VO_2 peak was associated with a higher risk of death (0.861, 95% CI: 0.739–1.003, p = 0.054), and was also capable of predicting pulmonary function test (PFT) deterioration, highlighting the value of CPET to predicted prognosis and mortality risk in this population, even in the absence of PH (Bournia et al., 2022; Giubertoni et al., 2025).

Overall, CPET seems to offer a thorough assessment and is a potential tool for pathophysiology evaluation, SSc patient follow-up, risk stratification, complication screening, and even the provision of useful endpoints for therapeutic trials.

- Stress echocardiography

Stress echocardiography has emerged as a valuable tool in the assessment of SSc, providing insights into early cardiovascular involvement that may not be detected by conventional methods. Nagel and colleagues found that, to detect PAH in SSc patients, stress echocardiogram improved the sensitivity from 72.7% on resting echocardiogram to 95.2% on exercise, with a specificity of 84.9%, using a PASP of 40 mmHg at rest and 45 mmHg during low exercise (Nagel et al., 2015). Rallidis *et al*., using a cohort of 49 patients with SSc who underwent treadmill exercise echocardiography, reported that a post-exercise tricuspid regurgitation (TR) velocity >3.4 m/s had a sensitivity of 90.5%, a specificity of 80% and an accuracy of 84% in detecting PAH, being also positively

correlated with sPAP and mean PAP obtained by RHC (Rallidis et al., 2021). Knowing that the right ventricular capacity to adapt to increased afterload is the main determinant of outcome in pulmonary hypertension, Mukherjee *et al.*, prospectively enrolled 56 SSc patients, submitting them to a supine bicycle echocardiography, coupled with RV longitudinal systolic strain. They found that the speckle tracking abnormalities in RV contractile response to exercise were not detectable by conventional measures, and demonstrated the effect of resting loading conditions on RV contractile response to exercise, in which the RV chamber differentially dilates with no further augmentation in contractility in those with elevated RVSP at rest, suggesting subclinical impairments on RV reserve in SSc that may be missed by resting echocardiography (Mukherjee et al., 2021).

Patients with systemic sclerosis often experience left ventricular diastolic dysfunction and HFpEF, which is linked to high mortality (Arase et al., 2021). Stress echocardiography can detect the early stages of these conditions in SSc patients with normal resting hemodynamics, potentially influencing their prognosis. In a cohort of 140 SSc patients who underwent 6MWD stress echocardiography, Arase and colleagues reached that conclusion, with their data revealing impaired LV cardiac reserve in patients with normal hemodynamics, and also an independent association between LV cardiac reserve and clinical worsening in SSc, providing incremental prognostic utility (Arase et al., 2021). In conclusion, stress echocardiography is a sensitive non-invasive method for detecting subclinical myocardial dysfunction and pulmonary vascular involvement in systemic sclerosis, potentially enhancing risk stratification and timely intervention in this population.

- Invasive hemodynamic exercise test

Right heart catheterization is the gold standard method to assess pulmonary hemodynamics at rest and during exercise (Kovacs et al., 2017). A recent study analyzed the results of rest and exercise RHC in 19 patients with SSc, concluding that 95% of patients presented an mPAP > 30 mmHg during exercise, with 68% showing an abnormal pulmonary pressure-flow relationship

> 3 mmHg/l/min, finding also that 7 out of 9 patients without PH at rest, had exercise-induced PH (Andersen et al., 2024). Mohri and colleagues, in a cohort of 45 SSc patients with normal hemodynamics at rest, also found occult LV diastolic dysfunction during exercise RHC, defined by a PAWP ≥ 25 mmHg, in 29% of patients (Mohri et al., 2022). These findings highlight the importance of exercise RHC in unveiling subclinical cardiopulmonary involvement in systemic sclerosis.

With the aim of investigating the prognostic value of exercise hemodynamics measured during RHC in SSc patients, we highlight two studies. The first study by Stamm et al., reported in a cohort of 72 SSc patients, found that 28 (39%) presented with exercise-induced pulmonary hypertension, defined by mPAP ≥ 30 mmHg and mPAP/cardiac output (CO) > 3 mmHg/l/min at maximal exercise. They also reported that the mean survival without transplantation in this subgroup was 5.2 years, compared to 9.5 years in the subgroup without pulmonary hypertension. The second study, by Zeder and colleagues, followed a cohort of 80 SSc patients with resting mPAP < 25 mmHg for 10.4 years (interquartile range (IQR) 8.5-11.8). They found that pulmonary vascular resistance (PVR) (p=0.006; HR: 2.20 [95%CI 1.26–3.87]), total pulmonary resistance (TPR) at peak exercise (p=0.026; HR: 1.56 [95%CI 1.06–2.29]), mPAP/CO slope (p=0.047; HR: 1.14 [95%CI 1.002–1.286]), and TPG/CO slope (p=0.034; HR: 1.34 [95%CI 1.02–1.76]) were significantly associated with mortality. They also reported an area under the receiver-operating-characteristics curve for exercise PVR to predict 10-year mortality of 0.917 [95%CI 0.797–1.000] (Zeder et al., 2021). All of these results highlight how exercise hemodynamic parameters measured by RHC offer strong prognostic data, making it possible to identify SSc patients who are more likely to experience negative outcomes even when their resting values are acceptable.

REFERENCES

Ahmed, S., Liem, S. I. E., Ciaffi, J., Hoekstra, E. M., Schouffoer, A. A., Bergstra, S. A., Ueckert, D., Ninaber, M., Bruni, C., Jordan, S., Distler, O., Huizinga, T. W., Vliegen, H., & De Vries-Bouwstra, J. (2025). Value of the 6 min walk test in detecting cardiopulmonary involvement in patients with systemic sclerosis. *RMD Open*, *11*(3).

Allanore, Y., Avouac, J., Zerkak, D., Meune, C., Hachulla, E., Mouthon, L., Guillevin, L., Meyer, O., Ekindjian, O. G., Weber, S., & Kahan, A. (2008). High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis and rheumatism*, *58*(1), 284-291.

Allanore, Y., & Meune, C. (2010). Primary myocardial involvement in systemic sclerosis: evidence for a microvascular origin. *Clinical and experimental rheumatology*, *28*(5 Suppl 62), S48-53.

Allanore, Y., Simms, R., Distler, O., Trojanowska, M., Pope, J., Denton, C. P., & Varga, J. (2015). Systemic sclerosis. *Nature Reviews Disease Primers*, *1*, 15002.

Allanore, Y., Wahbi, K., Borderie, D., Weber, S., Kahan, A., & Meune, C. (2009). N-terminal pro-brain natriuretic peptide in systemic sclerosis: a new cornerstone of cardiovascular assessment? *Annals of the rheumatic diseases*, *68*(12), 1885-1889.

Almeida, C., Almeida, I., & Vasconcelos, C. (2015). Quality of life in systemic sclerosis. *Autoimmunity Reviews*, *14*(12), 1087-1096.

Almeida, I., Faria, R., Vita, P., & Vasconcelos, C. (2011). Systemic sclerosis refractory disease: from the skin to the heart. *Autoimmunity Reviews, 10*(11), 693-701.

Alturaif, N., & Alduraibi, F. K. (2025). CTD-PAH: an updated practical approach to screening, diagnosis, and management. *Therapeutic Advances in Respiratory Disease*, *19*, 17534666251385674.

Amaral, T. N., Peres, F. A., Lapa, A. T., Marques-Neto, J. F., & Appenzeller, S. (2013). Neurologic involvement in scleroderma: a systematic review. *Seminars in arthritis and rheumatism*, *43*(3), 335-347.

Andersen, M. J., Husted, A., Clemmensen, T. S., Olesen, A. B., Baumgartner, J., & Mellemkjær, S. (2024). Pulmonary vascular dysfunction in systemic sclerosis. *JHLT Open*, *3*, 100024.

Angiolilli, C., Marut, W., van der Kroef, M., Chouri, E., Reedquist, K. A., & Radstake, T. (2018). New insights into the genetics and epigenetics of systemic sclerosis. *Nature Reviews Rheumatology*, *14*(11), 657-673.

Arase, M., Kusunose, K., Morita, S., Yamaguchi, N., Hirata, Y., Nishio, S., Okushi, Y., Ise, T., Tobiume, T., Yamaguchi, K., Fukuda, D., Yagi, S., Yamada, H., Soeki, T., Wakatsuki, T., & Sata, M. (2021). Cardiac reserve by 6-minute walk stress echocardiography in systemic sclerosis [Article]. *Open Heart*, *8*(1), 9, Article e001559.

Arena, R., Lavie, C. J., Milani, R. V., Myers, J., & Guazzi, M. (2010). Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. *The Journal of Heart and Lung Transplantation*, *29*(2), 159-173.

Asano, Y. (2018). Systemic sclerosis. *J Dermatol*, *45*(2), 128-138.

Asano, Y., Jinnin, M., Kawaguchi, Y., Kuwana, M., Goto, D., Sato, S., Takehara, K., Hatano, M., Fujimoto, M., Mugii, N., & Ihn, H. (2018). Diagnostic criteria, severity classification and guidelines of systemic sclerosis. *The Journal of Dermatology*, *45*(6), 633-691.

ATS statement: guidelines for the six-minute walk test. (2002). *American Journal of Respiratory and Critical Care Medicine*, *166*(1), 111-117.

Bairkdar, M., Rossides, M., Westerlind, H., Hesselstrand, R., Arkema, E. V., & Holmqvist, M. (2021). Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. *Rheumatology (Oxford)*, *60*(7), 3121-3133.

Barnes, J., & Mayes, M. D. (2012). Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Current opinion in rheumatology*, *24*(2), 165-170.

Bergamasco, A., Hartmann, N., Wallace, L., & Verpillat, P. (2019). Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. *Clinical Epidemiology*, *11*, 257-273.

Bernatsky, S., Joseph, L., Pineau, C. A., Belisle, P., Hudson, M., & Clarke, A. E. (2009). Scleroderma prevalence: demographic variations in a population-based sample. *Arthritis and rheumatism*, *61*(3), 400-404.

Bissell, L.-A., Anderson, M., Burgess, M., Chakravarty, K., Coghlan, G., Dumitru, R. B., Graham, L., Ong, V., Pauling, J. D., & Plein, S. (2017). Consensus best practice pathway of the UK Systemic Sclerosis Study group: management of cardiac disease in systemic sclerosis. *Rheumatology*, *56*(6), 912-921.

Bosello, S., De Luca, G., Berardi, G., Canestrari, G., de Waure, C., Gabrielli, F. A., Di Mario, C., Forni, F., Gremese, E., & Ferraccioli, G. (2019). Cardiac troponin T and NT-proBNP as diagnostic and prognostic biomarkers of primary cardiac involvement and disease severity in systemic sclerosis: A prospective study [Article]. *European Journal of Internal Medicine*, *60*, 46-53.

Bournia, V. K., Kallianos, A., Panopoulos, S., Gialafos, E., Velentza, L., Vlachoyiannopoulos, P. G., Sfikakis, P. P., & Trakada, G. (2022). Cardiopulmonary exercise testing and prognosis in patients with systemic sclerosis without baseline pulmonary hypertension: a prospective cohort study. *Rheumatology International*, *42*(2), 303-309.

Boutou, A. K., Pitsiou, G. G., Siakka, P., Dimitroulas, T., Paspala, A., Sourla, E., Chavouzis, N., Garyfallos, A., Argyropoulou, P., & Stanopoulos, I. (2016). Phenotyping Exercise Limitation in Systemic Sclerosis: The Use of Cardiopulmonary Exercise Testing. *Respiration*, *91*(2), 115-123.

Brown, Z., Proudman, S., Morrisroe, K., Stevens, W., Hansen, D., & Nikpour, M. (2021). Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: A systematic review and meta-analysis of long-term outcomes. *Seminars in arthritis and rheumatism*, *51*(3), 495-512.

Bruni, C., Buch, M. H., Djokovic, A., De Luca, G., Dumitru, R. B., Giollo, A., Galetti, I., Steelandt, A., Bratis, K., Suliman, Y. A., Milinkovic, I., Baritussio, A., Hasan, G., Xintarakou, A., Isomura, Y., Markousis-Mavrogenis, G., Mavrogeni, S., Gargani, L., Caforio, A. L., . . . Matucci-Cerinic, M. (2023). Consensus on the assessment of systemic sclerosis-associated primary heart involvement: World Scleroderma Foundation/Heart Failure Association guidance on screening, diagnosis, and follow-up assessment. *Journal of Scleroderma and Related Disorders*, *8*(3), 169-182.

Butt, S. A., Jeppesen, J. L., Torp-Pedersen, C., Sam, F., Gislason, G. H., Jacobsen, S., & Andersson, C. (2019). Cardiovascular Manifestations of Systemic Sclerosis: A Danish Nationwide Cohort Study [Article]. *Journal of the American Heart Association*, *8*(17), 18, Article e013405.

Calderon, L. M., & Pope, J. E. (2021). Scleroderma epidemiology update. *Current opinion in rheumatology*, *33*(2), 122-127.

Cen, X., Feng, S., Wei, S., Yan, L., & Sun, L. (2020). Systemic sclerosis and risk of cardiovascular disease: A PRISMA-compliant systemic review and meta-analysis of cohort studies. *Medicine (Baltimore)*, *99*(47), e23009.

Chaisson, N. F., & Hassoun, P. M. (2013). Systemic Sclerosis-Associated Pulmonary Arterial Hypertension. *Chest*, *144*(4), 1346-1356.

Chin, K. M., Gaine, S. P., Gerges, C., Jing, Z. C., Mathai, S. C., Tamura, Y., McLaughlin, V. V., & Sitbon, O. (2024). Treatment algorithm for pulmonary arterial hypertension. *European Respiratory Journal*, *64*(4).

Coghlan, J. G., Denton, C. P., Grünig, E., Bonderman, D., Distler, O., Khanna, D., Müller-Ladner, U., Pope, J. E., Vonk, M. C., Doelberg, M., Chadha-Boreham, H., Heinzl, H., Rosenberg, D. M., McLaughlin, V. V., & Seibold, J. R. (2014). Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: The DETECT study [Article]. *Annals of the rheumatic diseases*, *73*(7), 1340-1349.

Crincoli, V., Fatone, L., Fanelli, M., Rotolo, R. P., Chialà, A., Favia, G., & Lapadula, G. (2016). Orofacial Manifestations and Temporomandibular Disorders of Systemic Scleroderma: An Observational Study. *International Journal of Molecular Sciences*, *17*(7).

Cuomo, G., Santoriello, C., Polverino, F., Ruocco, L., Valentini, G., & Polverino, M. (2010). Impaired exercise performance in systemic sclerosis and its clinical correlations. *Scandinavian Journal of Rheumatology*, *39*(4), 330-335.

de Angelis, R., Giuggioli, D., Bajocchi, G., Dagna, L., Zanframundo, G., Foti, R., Cacciapaglia, F., Cuomo, G., Ariani, A., Rosato, E., Guiducci, S., Girelli, F., Riccieri, V., Zanatta, E., Bosello, S., Cavazzana, I., Ingegnoli, F., de Santis, M., Murdaca, G., . . . Ferri, C. (2022). Sex-related Differences in Systemic Sclerosis: A Multicenter Cross-sectional Study From the National Registry of the Italian Society for Rheumatology [Article]. *Journal of Rheumatology*, *49*(2), 176-185.

De Groote, P., Gressin, V., Hachulla, E., Carpentier, P., Guillevin, L., Kahan, A., Cabane, J., Francès, C., Lamblin, N., Diot, E., Patat, F., Sibilia, J., Petit, H., Cracowski, J. L., Clerson, P., & Humbert, M. (2008). Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis [Article]. *Annals of the rheumatic diseases*, *67*(1), 31-36.

Denton, C. P., De Lorenzis, E., Roblin, E., Goldman, N., Alcacer-Pitarch, B., Blamont, E., Buch, M. H., Carulli, M., Cotton, C., Del Galdo, F., Derrett-Smith, E., Douglas, K., Farrington, S., Fligelstone, K., Gompels, L., Griffiths, B., Herrick, A., Hughes, M., Pain, C., . . . Ong, V. H. (2024). The 2024 British Society for Rheumatology guideline for management of systemic sclerosis. Rheumatology, 63(11), 2956-2975.

Denton, C. P., Hughes, M., Gak, N., Vila, J., Buch, M. H., Chakravarty, K., Fligelstone, K., Gompels, L. L., Griffiths, B., Herrick, A. L., Pang, J., Parker, L., Redmond, A., van Laar, J., Warburton, L., & Ong, V. H. (2016). BSR and BHPR guideline for the treatment of systemic sclerosis. *Rheumatology (Oxford)*, *55*(10), 1906-1910.

Denton, C. P., & Khanna, D. (2017). Systemic sclerosis. *The Lancet*, *390*(10103), 1685-1699.

Desai, C. S., Lee, D. C., & Shah, S. J. (2011). Systemic sclerosis and the heart: current diagnosis and management. *Current opinion in rheumatology*, *23*(6), 545-554.

Dorniak, K., Gogulska, Z., Viti, A., Glińska, A., Kulawiak-Gałąska, D., Fijałkowska, J., Wojteczek, A., Wojtowicz, D., Sienkiewicz, K., Hellmann, M., & Smoleńska, Ż. (2025). Cardiac Morpho-Functional Changes, Inflammation and Fibrosis in Systemic Sclerosis-A Pilot Study of a Tertiary Center Cohort. *Diagnostics (Basel)*, *15*(3).

Dumitrescu, D., Nagel, C., Kovacs, G., Bollmann, T., Halank, M., Winkler, J., Hellmich, M., Grünig, E., Olschewski, H., Ewert, R., & Rosenkranz, S. (2017). Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. *Heart*, *103*(10), 774-782.

Erdogan, M., Kilickiran Avci, B., Ebren, C., Ersoy, Y., Ongen, Z., Ongen, G., Hamuryudan, V., & Hatemi, G. (2024). Screening for pulmonary arterial hypertension in patients with systemic sclerosis in the era of new pulmonary arterial hypertension definitions. *Clinical and experimental rheumatology*, *42*(8), 1590-1597.

Ewert, R., Ittermann, T., Habedank, D., Held, M., Lange, T. J., Halank, M., Winkler, J., Glaser, S., Olschewski, H., & Kovacs, G. (2019). Prognostic value of cardiopulmonary exercise testing in patients with systemic sclerosis [Article]. *BMC Pulmonary Medicine*, *19*(1), 12, Article 230.

Fairley, J. L., Ross, L., Quinlivan, A., Hansen, D., Paratz, E., Stevens, W., Kistler, P. M., McLellan, A., La Gerche, A., & Nikpour, M. (2023). Sudden cardiac death, arrhythmias and abnormal electrocardiography in systemic sclerosis: A systematic review and meta-analysis. *Seminars in arthritis and rheumatism*, *62*, 152229.

Farrell, C., Balasubramanian, A., Hays, A. G., Hsu, S., Rowe, S., Zimmerman, S. L., Hassoun, P. M., Mathai, S. C., & Mukherjee, M. (2021). A Clinical Approach to Multimodality Imaging in Pulmonary Hypertension. *Front Cardiovasc Med*, *8*, 794706.

Feghali-Bostwick, C., Medsger, T. A., Jr., & Wright, T. M. (2003). Analysis of systemic sclerosis in twins reveals low concordance for disease and high

concordance for the presence of antinuclear antibodies. *Arthritis and rheumatism*, *48*(7), 1956-1963.

Ferlito, A., Campochiaro, C., Tomelleri, A., Dagna, L., & De Luca, G. (2022). Primary heart involvement in systemic sclerosis, from conventional to innovative targeted therapeutic strategies. *Journal of Scleroderma and Related Disorders*, *7*(3), 179-188.

Fernandez-Codina, A., Simeon-Aznar, C. P., Pinal-Fernandez, I., Rodriguez-Palomares, J., Pizzi, M. N., Hidalgo, C. E., Del Castillo, A. G., Prado-Galbarro, F. J., Sarria-Santamera, A., Fonollosa-Pla, V., & Vilardell-Tarres, M. (2017). Cardiac involvement in systemic sclerosis: differences between clinical subsets and influence on survival [Article]. *Rheumatology International*, *37*(1), 75-84.

Ferri, C., Emdin, A., Nielsen, H., & Bruhlmann, P. (2003). Assessment of heart involvement. *Clinical and experimental rheumatology*, *21*(3), S24-S28. <Go to ISI>://WOS:000183888300006

Ferri, C., Giuggioli, D., Sebastiani, M., Colaci, M., & Emdin, M. (2005). Heart involvement and systemic sclerosis. *Lupus*, *14*(9), 702-707.

Fontes Oliveira, M., Rei, A. L., Oliveira, M. I., Almeida, I., & Santos, M. (2022). Prevalence and prognostic significance of heart failure with preserved ejection fraction in systemic sclerosis. *Future Cardiology*, *18*(1), 17-25.

Giubertoni, A., Bellan, M., Cumitini, L., & Patti, G. (2025). Cardiopulmonary Exercise Testing: Deciphering Cardiovascular Complications in Systemic Sclerosis. *Reviews in Cardiovascular Medicine*, *26*(1), 25914.

Glaab, T., & Taube, C. (2022). Practical guide to cardiopulmonary exercise testing in adults. *Respiratory Research*, *23*(1), 9.

Guazzi, M., Wilhelm, M., Halle, M., Van Craenenbroeck, E., Kemps, H., de Boer, R. A., Coats, A. J. S., Lund, L., Mancini, D., Borlaug, B., Filippatos, G., & Pieske, B. (2022). Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy - A clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology. *European Journal of Heart Failure*, *24*(8), 1327-1345.

Hachulla, A. L., Launay, D., Gaxotte, V., de Groote, P., Lamblin, N., Devos, P., Hatron, P. Y., Beregi, J. P., & Hachulla, E. (2009). Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. *Annals of the rheumatic diseases*, *68*(12), 1878-1884.

Hamaguchi, Y. (2010). Autoantibody profiles in systemic sclerosis: predictive value for clinical evaluation and prognosis. *The Journal of Dermatology*, *37*(1), 42-53.

Handa, R., Gupta, K., Malhotra, A., Jain, P., Kamath, P. K., Aggarwal, P., Dwivedi, S. N., & Wali, J. P. (1999). Cardiac involvement in limited systemic sclerosis: non-invasive assessment in asymptomatic patients. *Clinical Rheumatology*, *18*(2), 136-139.

Hao, Y., Thakkar, V., Stevens, W., Morrisroe, K., Prior, D., Rabusa, C., Youssef, P., Gabbay, E., Roddy, J., Walker, J., Zochling, J., Sahhar, J., Nash, P., Lester, S., Rischmueller, M., Proudman, S. M., & Nikpour, M. (2015). A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Research & Therapy*, *17*(1), 7.

Hassoun, P. M. (2015). The right ventricle in scleroderma (2013 Grover Conference Series). *Pulmonary Circulation*, *5*(1), 3-14.

He, H., Lai, J., Zhou, J., Hou, Y., Xu, D., Li, M., & Zeng, X. (2023). The clinical characteristics and outcomes of patients with systemic sclerosis with myocardial involvement. *Orphanet Journal of Rare Diseases*, *18*(1), 83.

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., . . . Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *79*(17), 1757-1780.

Hemelein, R. A., Lajkó, I., Baráth, K., Varga, J., Ágoston, G., Hulló, D., Bocskai, M., Dobi, D., Rózsavölgyi, Z., Milassin, Á., Varga, A., Somfay, A., & Kovács, L. (2021). Evaluation of cardiopulmonary exercise test in the prediction of disease progression in systemic sclerosis. *Clinical and experimental rheumatology*, *39 Suppl 131*(4), 94-102.

Hinze, A. M., Perin, J., Woods, A., Hummers, L. K., Wigley, F. M., Mukherjee, M., & Shah, A. A. (2022). Diastolic Dysfunction in Systemic Sclerosis: Risk Factors and Impact on Mortality. *Arthritis & Rheumatology*, *74*(5), 849-859.

Hsu, V. M., Chung, L., Hummers, L. K., Wigley, F., Simms, R., Bolster, M., Silver, R., Fischer, A., Hinchcliff, M. E., Varga, J., Goldberg, A. Z., Derk, C. T., Schiopu, E., Khanna, D., Shapiro, L. S., Domsic, R. T., Medsger, T., Mayes, M. D., Furst, D., . . . Steen, V. D. (2014). Development of pulmonary hypertension in a high-risk population with systemic sclerosis in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort study. *Seminars in arthritis and rheumatism*, *44*(1), 55-62.

Hudson, M., Pauling, J. D., Rodriguez-Reyna, T. S., Paik, J. J., Shah, A. A., Frech, T. M., Boin, F., Stevens, W., Mouthon, L., Baniña, M. C., & Medsger, T. A., Jr. (2025). Criteria for defining and dating onset of organ system involvement in systemic sclerosis. *Journal of Scleroderma and Related Disorders*, 23971983251374385.

Hudson, M., Thombs, B. D., Steele, R., Panopalis, P., Newton, E., & Baron, M. (2009). Health-related quality of life in systemic sclerosis: a systematic review. *Arthritis and rheumatism*, *61*(8), 1112-1120.

Hughes, M., & Herrick, A. L. (2019). Systemic sclerosis. *British Journal of Hospital Medicine*, *80*(9), 530-536.

Humbert, M., Guignabert, C., Bonnet, S., Dorfmüller, P., Klinger, J. R., Nicolls, M. R., Olschewski, A. J., Pullamsetti, S. S., Schermuly, R. T., Stenmark, K. R., & Rabinovitch, M. (2019). Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *European Respiratory Journal*, *53*(1).

Humbert, M., Kovacs, G., Hoeper, M. M., Badagliacca, R., Berger, R. M. F., Brida, M., Carlsen, J., Coats, A. J. S., Escribano-Subias, P., Ferrari, P., Ferreira, D. S., Ghofrani, H. A., Giannakoulas, G., Kiely, D. G., Mayer, E., Meszaros, G., Nagavci, B., Olsson, K. M., Pepke-Zaba, J., . . . Rosenkranz, S. (2022). 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*, *43*(38), 3618-3731.

Ingegnoli, F., Ughi, N., & Mihai, C. (2018). Update on the epidemiology, risk factors, and disease outcomes of systemic sclerosis. *Best Practice & Research Clinical Rheumatology*, *32*(2), 223-240.

Jerjen, R., Nikpour, M., Krieg, T., Denton, C. P., & Saracino, A. M. (2022). Systemic sclerosis in adults. Part I: Clinical features and pathogenesis. *Journal of the American Academy of Dermatology*, *87*(5), 937-954.

Jha, M., Wang, M., Steele, R., Baron, M., Fritzler, M. J., & Hudson, M. (2022). NT-proBNP, hs-cTnT, and CRP predict the risk of cardiopulmonary outcomes in systemic sclerosis: Findings from the Canadian Scleroderma Research Group. *Journal of Scleroderma and Related Disorders*, *7*(1), 62-70.

Jin, J., Chou, C., Lima, M., Zhou, D., & Zhou, X. (2014). Systemic Sclerosis is a Complex Disease Associated Mainly with Immune Regulatory and Inflammatory Genes. *The Open Rheumatology Journal*, *8*, 29-42.

Jones, X. M., Bottini, N., Boin, F., & Marbán, E. (2025). Cardiac involvement in systemic sclerosis: A critical review of knowledge gaps and opportunities. *Journal of Scleroderma and Related Disorders*, 23971983241313096.

Kahan, A., Coghlan, G., & McLaughlin, V. (2009). Cardiac complications of systemic sclerosis. *Rheumatology (Oxford)*, *48 Suppl 3*, iii45-48.

Knight, D. S., Karia, N., Cole, A. R., Maclean, R. H., Brown, J. T., Masi, A., Patel, R. K., Razvi, Y., Chacko, L., Venneri, L., Kotecha, T., Martinez-Naharro, A., Kellman, P., Scott-Russell, A. M., Schreiber, B. E., Ong, V. H., Denton, C. P., Fontana, M., Coghlan, J. G., & Muthurangu, V. (2023). Distinct cardiovascular phenotypes are associated with prognosis in systemic

sclerosis: a cardiovascular magnetic resonance study. *European Heart Journal - Cardiovascular Imaging*, *24*(4), 463-471.

Komócsi, A., Vorobcsuk, A., Faludi, R., Pintér, T., Lenkey, Z., Költő, G., & Czirják, L. (2012). The impact of cardiopulmonary manifestations on the mortality of SSc: a systematic review and meta-analysis of observational studies. *Rheumatology*, *51*(6), 1027-1036.

Kovacs, G., Herve, P., Barbera, J. A., Chaouat, A., Chemla, D., Condliffe, R., Garcia, G., Grünig, E., Howard, L., & Humbert, M. (2017). An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *European Respiratory Journal*, *50*(5).

Kwakkenbos, L., Jewett, L. R., Baron, M., Bartlett, S. J., Furst, D., Gottesman, K., Khanna, D., Malcarne, V. L., Mayes, M. D., Mouthon, L., Poiraudeau, S., Sauve, M., Nielson, W. R., Poole, J. L., Assassi, S., Boutron, I., Ells, C., van den Ende, C. H., Hudson, M., . . . Thombs, B. D. (2013). The Scleroderma Patient-centered Intervention Network (SPIN) Cohort: protocol for a cohort multiple randomised controlled trial (cmRCT) design to support trials of psychosocial and rehabilitation interventions in a rare disease context. *BMJ Open*, *3*(8).

Lambova, S. (2014). Cardiac manifestations in systemic sclerosis. *World J Cardiol*, *6*(9), 993-1005.

Lechartier, B., & Humbert, M. (2021). Pulmonary arterial hypertension in systemic sclerosis. *La Presse Médicale*, *50*(1), 104062.

Legendre, P., & Mouthon, L. (2014). [Pulmonary arterial hypertension associated with connective tissue diseases]. *La Presse Médicale*, *43*(9), 957-969.

LeRoy, E. C., Black, C., Fleischmajer, R., Jablonska, S., Krieg, T., Medsger, T. A., Jr., Rowell, N., & Wollheim, F. (1988). Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *The Journal of Rheumatology*, *15*(2), 202-205.

LeRoy, E. C., & Medsger, T. A., Jr. (2001). Criteria for the classification of early systemic sclerosis. *The Journal of Rheumatology*, *28*(7), 1573-1576.

Lui, J. K., El-Adili, F., Cozzolino, M., Winburn, M., Trojanowski, M. A., Gopal, D. M., LaValley, M. P., Klings, E. S., & Bujor, A. M. (2025). A multi-biomarker

approach to risk stratification and detection of early cardiac disease in systemic sclerosis. *PLoS One*, *20*(7), e0328734.

Magda Ș, L., Gheorghiu, A. M., Mincu, R. I., Ciobanu, A. O., Constantinescu, T., Popa, E. C., Mihai, C., & Vinereanu, D. (2024). Non-Invasive Cardiac and Vascular Monitoring in Systemic Sclerosis: Impact of Therapy on Subclinical Dysfunction. *Medicina (Kaunas)*, 60(12).

Madigan, S., Proudman, S., Schembri, D., Davies, H., & Adams, R. (2024). Use of exercise tests in screening for pulmonary arterial hypertension in systemic sclerosis: A systematic literature review. *Journal of Scleroderma and Related Disorders*, *9*(1), 50-58.

Manganaro, R., Marchetta, S., Dulgheru, R., Sugimoto, T., Tsugu, T., Ilardi, F., Cicenia, M., Ancion, A., Postolache, A., Martinez, C., Kacharava, G., Athanassopoulos, G. D., Barone, D., Baroni, M., Cardim, N., Hagendorff, A., Hristova, K., Lopez, T., de la Morena, G., . . . Lancellotti, P. (2020). Correlation between non-invasive myocardial work indices and main parameters of systolic and diastolic function: results from the EACVI NORRE study. *European Heart Journal - Cardiovascular Imaging*, 21(5), 533-541.

Marie, I., Gehanno, J.-F., Bubenheim, M., Duval-Modeste, A.-B., Joly, P., Dominique, S., Bravard, P., Noël, D., Cailleux, A.-F., & Weber, J. (2014). Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmunity Reviews*, *13*(2), 151-156.

Marie, I., Gehanno, J. F., Bubenheim, M., Duval-Modeste, A. B., Joly, P., Dominique, S., Bravard, P., Noël, D., Cailleux, A. F., Benichou, J., Levesque, H., & Goullé, J. P. (2017). Systemic sclerosis and exposure to heavy metals: A case control study of 100 patients and 300 controls. *Autoimmunity Reviews*, *16*(3), 223-230.

Marzlin, N., Hays, A. G., Peters, M., Kaminski, A., Roemer, S., O'Leary, P., Kroboth, S., Harland, D. R., Khandheria, B. K., Tajik, A. J., & Jain, R. (2023). Myocardial Work in Echocardiography. *Circulation: Cardiovascular Imaging*, 16(2), e014419.

Mavrogeni, S. I., & Pepe, A. (2024). The emerging role of cardiovascular magnetic resonance in the evaluation of cardiac involvement in systemic sclerosis. *Rheumatol Immunol Res*, *5*(2), 93-98.

Meune, C., Avouac, J., Wahbi, K., Cabanes, L., Wipff, J., Mouthon, L., Guillevin, L., Kahan, A., & Allanore, Y. (2008). Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: A controlled study of 100 consecutive patients. *Arthritis and rheumatism*, *58*(6), 1803-1809.

Mohameden, M., Vashisht, P., & Sharman, T. (2024). Scleroderma and Primary Myocardial Disease. In *StatPearls*. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.

Mohri, T., Goda, A., Takeuchi, K., Kikuchi, H., Inami, T., Kohno, T., Sakata, K., Soejima, K., & Satoh, T. (2022). High prevalence of occult left ventricular diastolic dysfunction detected by exercise stress test in systemic sclerosis. *Scientific Reports*, *12*(1), 2423.

Morrisroe, K., Huq, M., Stevens, W., Rabusa, C., Proudman, S. M., & Nikpour, M. (2016). Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: results from a large multicenter cohort study. *BMC Pulmonary Medicine*, *16*(1), 134.

Moysidou, G. S., Dara, A., Arvanitaki, A., Skalkou, A., Pagkopoulou, E., Daoussis, D., Kitas, G. D., & Dimitroulas, T. (2023). Understanding and managing cardiac involvement in systemic sclerosis. *Expert Review of Clinical Immunology*, *19*(3), 293-304.

Mukherjee, M., Mercurio, V., Hsu, S., Mayer, S. A., Mathai, S. C., Hummers, L. K., Kass, D. A., Hassoun, P. M., Wigley, F. M., Tedford, R. J., & Shah, A. A. (2021). Assessment of right ventricular reserve utilizing exercise provocation in systemic sclerosis. *The International Journal of Cardiovascular Imaging*, *37*(7), 2137-2147.

Mura, G., Bhat, K. M., Pisano, A., Licci, G., & Carta, M. (2012). Psychiatric symptoms and quality of life in systemic sclerosis. *Clinical Practice & Epidemiology in Mental Health*, *8*, 30-35.

Nagel, C., Henn, P., Ehlken, N., D'Andrea, A., Blank, N., Bossone, E., Böttger, A., Fiehn, C., Fischer, C., Lorenz, H. M., Stöckl, F., Grünig, E., & Egenlauf, B. (2015). Stress Doppler echocardiography for early detection of systemic sclerosis-associated pulmonary arterial hypertension. *Arthritis Research & Therapy*, *17*(1), 165.

Ninagawa, K., Kato, M., Ohira, H., Tsuneta, S., Iwano, H., Kono, M., Fujieda, Y., Oku, K., Tsujino, I., & Atsumi, T. (2021). The assessment of left heart disease in patients with systemic sclerosis and pulmonary hypertension. *Clinical and experimental rheumatology*, *39 Suppl 131*(4), 103-110.

Odonwodo, A., Badri, T., & Hariz, A. (2023). Scleroderma. In *StatPearls*. StatPearls PublishingCopyright © 2023, StatPearls Publishing LLC.

Osgueritchian, R., Mombeini, H., Jani, V. P., Hsu, S., Hummers, L. K., Wigley, F. M., Mathai, S. C., Shah, A. A., & Mukherjee, M. (2025). Myocardial Disease in Systemic Sclerosis: Recent Updates and Clinical Implications. *Current Cardiology Reports*, *27*(1), 3.

Overbeek, M. J., Vonk, M. C., Boonstra, A., Voskuyl, A. E., Vonk-Noordegraaf, A., Smit, E. F., Dijkmans, B. A., Postmus, P. E., Mooi, W. J., Heijdra, Y., & Grünberg, K. (2009). Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. *European Respiratory Journal*, *34*(2), 371-379.

Palange, P., Ward, S. A., Carlsen, K. H., Casaburi, R., Gallagher, C. G., Gosselink, R., O'Donnell, D. E., Puente-Maestu, L., Schols, A. M., Singh, S., & Whipp, B. J. (2007). Recommendations on the use of exercise testing in clinical practice. *European Respiratory Journal*, *29*(1), 185-209.

Parks, J. L., Taylor, M. H., Parks, L. P., & Silver, R. M. (2014). Systemic sclerosis and the heart. *Rheumatic Disease Clinics of North America*, *40*(1), 87-102.

Paulus, W. J., & Zile, M. R. (2021). From Systemic Inflammation to Myocardial Fibrosis: The Heart Failure With Preserved Ejection Fraction Paradigm Revisited. *Circulation Research*, *128*(10), 1451-1467.

Peacock, A. J., Murphy, N. F., McMurray, J. J. V., Caballero, L., & Stewart, S. (2007). An epidemiological study of pulmonary arterial hypertension. *European Respiratory Journal*, *30*(1), 104-109.

Pearson, D. R., Werth, V. P., & Pappas-Taffer, L. (2018). Systemic sclerosis: Current concepts of skin and systemic manifestations. *Clinics in Dermatology*, *36*(4), 459-474.

Phung, S., Strange, G., Chung, L. P., Leong, J., Dalton, B., Roddy, J., Deague, J., Playford, D., Musk, M., & Gabbay, E. (2009). Prevalence of pulmonary arterial hypertension in an Australian scleroderma population: screening allows for earlier diagnosis. *Internal Medicine Journal*, *39*(10), 682-691.

Pokeerbux, M. R., Giovannelli, J., Dauchet, L., Mouthon, L., Agard, C., Lega, J. C., Allanore, Y., Jego, P., Bienvenu, B., Berthier, S., Mekinian, A., Hachulla, E., & Launay, D. (2019). Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. *Arthritis Research & Therapy*, *21*(1), 86.

Pope, J. E., Denton, C. P., Johnson, S. R., Fernandez-Codina, A., Hudson, M., & Nevskaya, T. (2023). State-of-the-art evidence in the treatment of systemic sclerosis. *Nature Reviews Rheumatology*, *19*(4), 212-226.

Pritchard, A., Burns, P., Correia, J., Jamieson, P., Moxon, P., Purvis, J., Thomas, M., Tighe, H., & Sylvester, K. P. (2021). ARTP statement on cardiopulmonary exercise testing 2021. *BMJ Open Respiratory Research 8*(1).

Pugnet, G., Marjanovic, Z., Deligny, C., Boussardon, K., Benzidia, I., Puyade, M., Lansiaux, P., Vandecasteele, E., Smith, V., & Farge, D. (2018). Reproducibility and Utility of the 6-minute Walk Test in Systemic Sclerosis. *Journal of Rheumatology*, *45*(9), 1273-1280.

Qiao, W., Bi, W., Wang, X., Li, Y., Ren, W., & Xiao, Y. (2023). Cardiac involvement assessment in systemic sclerosis using speckle tracking echocardiography: a systematic review and meta-analysis. *BMJ Open*, *13*(2), e063364.

Rallidis, L. S., Papangelopoulou, K., Anthi, A., Tsangaris, I., Varounis, C., Makavos, G., Konstantonis, D., Vlachoyiannopoulos, P., Orfanos, S. E., & Iliodromitis, E. K. (2021). The Role of Exercise Doppler Echocardiography to Unmask Pulmonary Arterial Hypertension in Selected Patients with

Systemic Sclerosis and Equivocal Baseline Echocardiographic Values for Pulmonary Hypertension. *Diagnostics (Basel)*, *11*(7).

Rubio-Rivas, M., Royo, C., Simeón, C. P., Corbella, X., & Fonollosa, V. (2014). Mortality and survival in systemic sclerosis: systematic review and meta-analysis. *Seminars in arthritis and rheumatism*, *44*(2), 208-219.

Russell, K., Eriksen, M., Aaberge, L., Wilhelmsen, N., Skulstad, H., Remme, E. W., Haugaa, K. H., Opdahl, A., Fjeld, J. G., Gjesdal, O., Edvardsen, T., & Smiseth, O. A. (2012). A novel clinical method for quantification of regional left ventricular pressure-strain loop area: a non-invasive index of myocardial work. European Heart Journal, 33(6), 724-733.

Sánchez-Aguilera Sánchez-Paulete, P., Lázaro Salvador, M., Berenguel Senén, A., Méndez Perles, C., & Rodríguez Padial, L. (2022). Role of cardiopulmonary exercise test in early diagnosis of pulmonary hypertension in scleroderma patients. *Medicina Clínica (Barc)*.

Santaniello, A., Casella, R., Vicenzi, M., Rota, I., Montanelli, G., De Santis, M., Bellocchi, C., Lombardi, F., & Beretta, L. (2020). Cardiopulmonary exercise testing in a combined screening approach to individuate pulmonary arterial hypertension in systemic sclerosis. *Rheumatology (Oxford)*, *59*(7), 1581-1586.

Sarı, A., Temiz Karadağ, D., Erdoğan, M., Yayla, M. E., Fırlatan Yazgan, B., Dikkanoğlu Demirok, B., Amikishiyev, S., Yalçınkaya, Y., İnanç, M., Karcıoğlu, O., Karakulak, U. N., Önen, Z. P., Akdeniz, B., Okumuş, G., Mutlu, B., Küçükoğlu, S., & Akdoğan, A. (2025). Screening for Pulmonary Hypertension in Connective Tissue Diseases: Literature Review and Multidisciplinary Consensus Statement. *Anatol J Cardiol*. Saygin, D., & Domsic, R. T. (2019). Pulmonary Arterial Hypertension In Systemic Sclerosis: Challenges In Diagnosis, Screening And Treatment. *Open Access Rheumatology: Research and Reviews*, *11*, 323-333.

Schmidt, C., Magalhães, S., Gois Basilio, P., Gouveia, M., Teixeira, M., Santos, C., Tavares, A. I., Ferreira, J. P., Ribeiro, F., & Santos, M. (2023). Home- versus centre-based EXercise InTervention in patients with Heart Failure

(EXIT-HF trial): A pragmatic randomized controlled trial. *Revista Portuguesa de Cardiologia*.

Schwaiblmair, M., Behr, J., & Fruhmann, G. (1996). Cardiorespiratory responses to incremental exercise in patients with systemic sclerosis. *Chest*, *110*(6), 1520-1525.

Simonneau, G., Montani, D., Celermajer, D. S., Denton, C. P., Gatzoulis, M. A., Krowka, M., Williams, P. G., & Souza, R. (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *European Respiratory Journal*, *53*(1).

Sobolewski, P., Maślińska, M., Wieczorek, M., Łagun, Z., Malewska, A., Roszkiewicz, M., Nitskovich, R., Szymańska, E., & Walecka, I. (2019). Systemic sclerosis - multidisciplinary disease: clinical features and treatment. *Reumatologia*, *57*(4), 221-233.

Stochmal, A., Czuwara, J., Trojanowska, M., & Rudnicka, L. (2020). Antinuclear Antibodies in Systemic Sclerosis: an Update. *Clinical Reviews in Allergy & Immunology*, *58*(1), 40-51.

Sun, X. G., Hansen, J. E., Oudiz, R. J., & Wasserman, K. (2001). Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation*, *104*(4), 429-435.

Tennøe, A. H., Murbræch, K., Andreassen, J. C., Fretheim, H., Garen, T., Gude, E., Andreassen, A., Aakhus, S., Molberg, Ø., & Hoffmann-Vold, A. M. (2018). Left Ventricular Diastolic Dysfunction Predicts Mortality in Patients With Systemic Sclerosis. *Journal of the American College of Cardiology*, *72*(15), 1804-1813.

Tennøe, A. H., Murbræch, K., Andreassen, J. C., Fretheim, H., Midtvedt, Ø., Garen, T., Dalen, H., Gude, E., Andreassen, A., Aakhus, S., Molberg, Ø., & Hoffmann-Vold, A. M. (2019). Systolic Dysfunction in Systemic Sclerosis: Prevalence and Prognostic Implications. *ACR Open Rheumatology*, *1*(4), 258-266.

Tonutti, A., Motta, F., De Angelis, R., Cipolletta, E., Ferri, C., Bajocchi, G., Bellando-Randone, S., Bruni, C., Orlandi, M., Zanframundo, G., Foti, R., Cuomo, G., Ariani, A., Rosato, E., Lepri, G., Girelli, F., Zanatta, E., Bosello,

S. L., Cavazzana, I., . . . De Santis, M. (2025). First-line diagnostic tests to intercept primary heart involvement in systemic sclerosis: Clinical associations from the SPRING-SIR registry. *European Journal of Clinical Investigation*, e70094.

Tuhy, T., & Hassoun, P. M. (2023). Clinical features of pulmonary arterial hypertension associated with systemic sclerosis. *Frontiers in Medicine (Lausanne)*, *10*, 1264906.

Tyndall, A. J., Bannert, B., Vonk, M., Airò, P., Cozzi, F., Carreira, P. E., Bancel, D. F., Allanore, Y., Müller-Ladner, U., & Distler, O. (2010). Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Annals of the rheumatic diseases*, *69*(10), 1809-1815.

van den Hoogen, F., Khanna, D., Fransen, J., Johnson, S. R., Baron, M., Tyndall, A., Matucci-Cerinic, M., Naden, R. P., Medsger, T. A., Jr., Carreira, P. E., Riemekasten, G., Clements, P. J., Denton, C. P., Distler, O., Allanore, Y., Furst, D. E., Gabrielli, A., Mayes, M. D., van Laar, J. M., . . . Pope, J. E. (2013). 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Annals of the rheumatic diseases*, *72*(11), 1747-1755.

Vandecasteele, E., Drieghe, B., Melsens, K., Thevissen, K., De Pauw, M., Deschepper, E., Decuman, S., Bonroy, C., Piette, Y., De Keyser, F., Brusselle, G., & Smith, V. (2017). Screening for pulmonary arterial hypertension in an unselected prospective systemic sclerosis cohort. *European Respiratory Journal*, *49*(5).

Varga, J., Denton, C. P., Wigley, F. M., Allanore, Y., & Kuwana, M. (2017). *Scleroderma - From Pathogenesis to Comprehensive Management* (Second Edition ed.). Springer.

Walkey, A. J., Ieong, M., Alikhan, M., & Farber, H. W. (2010). Cardiopulmonary exercise testing with right-heart catheterization in patients with systemic sclerosis. *Journal of Rheumatology*, *37*(9), 1871-1877.

Weatherald, J., Montani, D., Jevnikar, M., Jaïs, X., Savale, L., & Humbert, M. (2019). Screening for pulmonary arterial hypertension in systemic sclerosis.*European Respiratory Review*, *28*(153).

Weber, B. N., Paik, J. J., Aghayev, A., Klein, A. L., Mavrogeni, S. I., Yu, P. B., & Mukherjee, M. (2023). Novel Imaging Approaches to Cardiac Manifestations of Systemic Inflammatory Diseases: JACC Scientific Statement. *Journal of the American College of Cardiology*, *82*(22), 2128-2151.

Young, A., Moles, V. M., Jaafar, S., Visovatti, S., Huang, S., Vummidi, D., Nagaraja, V., McLaughlin, V., & Khanna, D. (2021). Performance of the DETECT Algorithm for Pulmonary Hypertension Screening in a Systemic Sclerosis Cohort. *Arthritis & Rheumatology*, *73*(9), 1731-1737.

Zagouras, A. A., Chatterjee, S., & Tang, W. H. W. (2021). Heart Failure with Preserved Ejection Fraction and Cardiomyopathy: an Under-recognized Complication of Systemic Sclerosis. *Current Treatment Options in Cardiovascular Medicine*, *23*(11), Article 71.

Zeder, K., Avian, A., Bachmaier, G., Douschan, P., Foris, V., Sassmann, T., Moazedi-Fuerst, F. C., Graninger, W. B., Hafner, F., & Brodmann, M. (2021). Exercise pulmonary resistances predict long-term survival in systemic sclerosis. *Chest*, *159*(2), 781-790.

Zhang, F., Yu, C., Zhang, J., Zhang, C., He, D., Hu, X., Li, S., Zhu, T., & Jin, W. (2025). Noninvasive left ventricular myocardial work identifies subclinical myocardial dysfunction in patients with systemic sclerosis. *Clinical Rheumatology*, 44(6), 2343-2354.

CHAPTER II

Research Gaps

Although the growing recognition of the diagnostic and prognostic value of CPET in SSc, the existing evidence remains fragmentary and focused on narrow clinical scenarios. Most published studies have evaluated CPET primarily as a tool to characterize exercise intolerance or to monitor patients with established PAH, rather than as a strategic component of the diagnostic workup in SSc. In particular, data on the ability of CPET to accurately rule out PAH in SSc patients with suspected disease are scarce, with only a few studies systematically addressing its negative predictive value and its potential to reduce the need for right heart catheterization. Dumitrescu *et al*., with the aim of assessing the diagnostic accuracy of key parameters derived from CPET for detecting and ruling out SSc-associated PAH, submitted to CPET and RHC, 173 SSc patients without know PAH. Their results show that a peak VO_2 >18.7 mL/kg/min was reached by 38 patients (22%) and excluded PAH in their cohort (negative predictive value 1.0), reporting also that a nadir VE/VCO_2 ratio > 45.5, presented a positive predictive value of 1.0 (Dumitrescu et al., 2017). Santaniello *et al*., aiming to evaluate whether CPET could enhance the performance of the DETECT algorithm in screening for PAH, demonstrated that incorporating the VE/VCO_2 slope into the algorithm reduced the number of unnecessary RHC while preserving its sensitivity (Santaniello et al., 2020). However, these findings have not yet been independently confirmed or extended to other SSc cohorts. Consequently, the role of CPET as a reliable non-invasive tool to refine the diagnostic workup of SSc patients referred for suspected PAH remains insufficiently defined. Addressing this gap motivated the first aim of this thesis:

STUDY I – *Diagnostic utility of cardiopulmonary exercise testing for pulmonary arterial hypertension in systemic sclerosis*:

a) to investigate the diagnostic performance of cardiopulmonary exercise testing in excluding PAH among SSc patients referred to a pulmonary hypertension unit.

Second, cardiac involvement is recognized as a major determinant of morbidity and mortality in SSc, but most research has predominantly focused on

PAH, leaving primary myocardial disease and secondary heart failure relatively underexplored. The prevalence, distribution across HF stages, and clinical correlates of HF in SSc patients without PAH are not well established, despite evidence that both subclinical and symptomatic cardiac dysfunction are frequent in this population. Furthermore, although functional tests such as the 6MWTD and CPET are commonly used in the evaluation of PAH, their value for characterizing HF stages and stratifying HF risk in SSc has not been systematically evaluated. In particular, it remains unclear how exercise-based parameters (notably the 6MWT distance and CPET-derived indices of ventilatory efficiency) relate to HF severity and to the broader systemic disease profile in SSc patients without PAH. This gap underpins the second aim of the thesis:

STUDY II - *Cardiac Involvement and Heart Failure Staging in Patients with Systemic Sclerosis*

a) to assess the prevalence of HF stages in SSc patients without PAH;
b) to study its clinical and functional correlates.

Third, despite significant advances in echocardiographic imaging, the early detection of myocardial involvement in SSc remains a major challenge, as conventional parameters such as LVEF often fail to identify subtle dysfunction. Global longitudinal strain improves sensitivity but is still influenced by loading conditions and image quality, limiting its reliability as a standalone marker of early cardiac disease (Čelutkienė et al., 2018; Klaeboe & Edvardsen, 2019; Sugimoto et al., 2017). Myocardial work, which integrates strain and afterload to provide a more comprehensive assessment of left ventricular performance, has emerged as a promising parameter for uncovering subclinical myocardial dysfunction (Manganaro et al., 2020; Roemer et al., 2021). However, research on MW in SSc is still scarce, with only two studies—by Magda *et al*. and Zhang *et al*.—reporting reduced MW indices in SSc patients compared to controls, even when conventional echocardiographic parameters were normal. Importantly, these

studies were limited to patients without clinical cardiac involvement and did not explore potential associations between MW and functional capacity markers such as those derived from cardiopulmonary exercise testing (CPET) or the six-minute walk test (6MWT) (Magda Ș et al., 2024; Zhang et al., 2025). Clarifying the incremental value of MW beyond LVEF and GLS, and its association with functional status, could substantially improve the detection of early myocardial dysfunction and inform more tailored management strategies. These considerations led to the third aim of the thesis:

STUDY III - *Myocardial Work as a Tool for Detecting Subclinical Cardiac Dysfunction and Its Association with Functional Capacity in Systemic Sclerosis*

a) to describe the myocardial work in a prospectively assessed cohort of SSc patients and evaluate its ability to detect subclinical cardiac dysfunction in comparison with ejection fraction and global longitudinal strain;
b) to test its association with functional capacity markers.

To address these interrelated gaps, three cross-sectional studies were conducted in SSc patients referred to a pulmonary hypertension unit. Together, these studies were designed to i) define the diagnostic utility of CPET for excluding PAH and potentially reducing unnecessary invasive testing; ii) delineate the burden and determinants of HF stages in SSc without PAH, integrating clinical and functional assessments; and iii) evaluate the role of MW as an early marker of myocardial dysfunction and its link to exercise tolerance.

In the following chapter, the collected data presented and discussed in three original studies: Study I, Study II and Study III.

REFERENCES

Čelutkienė, J., Plymen, C. M., Flachskampf, F. A., de Boer, R. A., Grapsa, J., Manka, R., Anderson, L., Garbi, M., Barberis, V., Filardi, P. P., Gargiulo, P., Zamorano, J. L., Lainscak, M., Seferovic, P., Ruschitzka, F., Rosano, G. M. C., & Nihoyannopoulos, P. (2018). Innovative imaging methods in heart failure: a shifting paradigm in cardiac assessment. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure*, 20(12), 1615-1633.

Dumitrescu, D., Nagel, C., Kovacs, G., Bollmann, T., Halank, M., Winkler, J., Hellmich, M., Grünig, E., Olschewski, H., Ewert, R., & Rosenkranz, S. (2017). Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. *Heart*, *103*(10), 774-782

Klaeboe, L. G., & Edvardsen, T. (2019). Echocardiographic assessment of left ventricular systolic function. *Journal of Echocardiography* , 17(1), 10-16.

Magda Ș, L., Gheorghiu, A. M., Mincu, R. I., Ciobanu, A. O., Constantinescu, T., Popa, E. C., Mihai, C., & Vinereanu, D. (2024). Non-Invasive Cardiac and Vascular Monitoring in Systemic Sclerosis: Impact of Therapy on Subclinical Dysfunction. *Medicina* (Kaunas), 60(12).

Manganaro, R., Marchetta, S., Dulgheru, R., Sugimoto, T., Tsugu, T., Ilardi, F., Cicenia, M., Ancion, A., Postolache, A., Martinez, C., Kacharava, G., Athanassopoulos, G. D., Barone, D., Baroni, M., Cardim, N., Hagendorff, A., Hristova, K., Lopez, T., de la Morena, G., . . . Lancellotti, P. (2020). Correlation between non-invasive myocardial work indices and main parameters of systolic and diastolic function: results from the EACVI NORRE study. *European Heart Journal - Cardiovascular Imaging*, 21(5), 533-541.

Roemer, S., Jaglan, A., Santos, D., Umland, M., Jain, R., Tajik, A. J., & Khandheria, B. K. (2021). The Utility of Myocardial Work in Clinical Practice. *Journal of the American Society of Echocardiography*, 34(8), 807-818.

Santaniello, A., Casella, R., Vicenzi, M., Rota, I., Montanelli, G., De Santis, M., Bellocchi, C., Lombardi, F., & Beretta, L. (2020). Cardiopulmonary exercise testing in a combined screening approach to individuate pulmonary arterial hypertension in systemic sclerosis. *Rheumatology (Oxford)*, *59*(7), 1581-1586.

Sugimoto, T., Dulgheru, R., Bernard, A., Ilardi, F., Contu, L., Addetia, K., Caballero, L., Akhaladze, N., Athanassopoulos, G. D., Barone, D., Baroni, M., Cardim, N., Hagendorff, A., Hristova, K., Lopez, T., de la Morena, G., Popescu, B. A., Moonen, M., Penicka, M., ... Lancellotti, P. (2017). Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. *European Heart Journal - Cardiovascular Imaging*, 18(8), 833-840.

Zhang, F., Yu, C., Zhang, J., Zhang, C., He, D., Hu, X., Li, S., Zhu, T., & Jin, W. (2025). Noninvasive left ventricular myocardial work identifies subclinical myocardial dysfunction in patients with systemic sclerosis. *Clinical Rheumatology*, 44(6), 2343-2354.

CHAPTER III

Original articles

Study I

Diagnostic utility of cardiopulmonary exercise testing for pulmonary arterial hypertension in systemic sclerosis

ABSTRACT

Objectives: Systemic sclerosis (SSc) patients are at increased risk of developing pulmonary arterial hypertension (PAH). Effective screening strategies are needed to improve early PAH detection and management. This study aimed to investigate the diagnostic performance of cardiopulmonary exercise testing (CPET) in excluding PAH among SSc patients referred to a pulmonary hypertension unit.

Methods: This was an observational retrospective cross-sectional study. Consecutive SSc patients referred for suspected PAH to a tertiary PH center underwent right heart catheterization (RHC) and CPET for suspected PAH. Demographic, clinical, and echocardiographic data were collected. Statistical analysis included comparisons between groups and diagnostic accuracy assessment using ROC analysis.

Results: Among 43 included patients, 26% were diagnosed with PAH. CPET variables showed significant differences between PAH and non-PAH groups, with an acceptable discriminative ability (equal or above 0.80). A peak VO_2 of 16 mL/min/Kg, a VE/VCO_2 slope of 33, and peak $PetCO_2$ of 33 mmHg were the estimated thresholds for a specificity of 100%. Notably, these CPET parameters could exclude PAH in up to 40% of patients who underwent RHC.

Conclusion: Our findings support the role of CPET in excluding PAH among SSc patients. Systematic implementation of CPET in clinical practice could aid risk stratification and decision-making, potentially reducing unnecessary invasive procedures.

KEY WORDS: CPET; diagnosis; PAH; Systemic Sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by microvascular dysfunction, immune activation, and progressive fibrosis. Among its cardiopulmonary complications, pulmonary arterial hypertension (PAH) represents one of the most severe, affecting up to 20% of patients (Humbert et al., 2022; Pope et al., 2023) and accounting for nearly one-third of SSc-related mortality (Lechartier & Humbert, 2021; Anthony J Tyndall et al., 2010; Weatherald et al., 2019). PAH screening allows an earlier diagnosis at a stage of less advanced hemodynamic impairment and has been shown to improved survival in this population (Brown et al., 2021; Vandecasteele et al., 2017).

Current clinical guidelines recommend annual screening for PAH using a combination of electrocardiogram, echocardiography, lung testing, and plasma biomarkers (Humbert et al., 2022). However, the specificity and positive predictive value of these screening strategies remain modest. Consequently, a substantial proportion of screened patients undergo right heart catheterization (RHC), which although it stands as the gold-standard tool for PAH diagnosis, is invasive and resource-intensive (Humbert et al., 2022). Using the DETECT algorithm, 60% of screened SSc patients will undergo RHC, but up to 40% are found to have normal hemodynamic findings (Coghlan et al., 2014; Hao et al., 2015; Young et al., 2021). This inefficiency highlights an ongoing need for more accurate, non-invasive tools to refine SSc-PAH screening and reduce unnecessary invasive testing.

Cardiopulmonary exercise testing (CPET) is a safe, reproducible, and non-invasive method that provides an integrated assessment of cardiovascular, pulmonary, and muscular responses to exercise (Humbert et al., 2022; Sun et al., 2001). In the context of suspected PAH, CPET is particular informative because affected patients typically exhibit a characteristic abnormal exercise response, including impaired ventilatory efficiency and an increased right ventricle afterload (Dumitrescu et al., 2017; Weatherald et al., 2019). These pathophysiological features make CPET an attractive tool for refining the diagnostic evaluation of patients with suspected PAH.

Despite its established diagnostic and prognostic value in pulmonary hypertension, the role of CPET in the screening and early diagnostic workup of SSc-associated PAH remains incompletely defined. In one of the largest cohorts studied to date, Dumitrescu *et al*. reported that a VE/VCO_2 nadir of 45.4 was strongly predictive of PAH, whereas a peak oxygen uptake (VO_2) >18.7 mL/min/kg was associated with a high negative predictive value, suggesting a potential role for CPET in ruling out disease (Dumitrescu et al., 2017). More recently, Santaniello and colleagues showed that incorporating CPET parameters, particularly the VE/VCO_2 slope, into the DETECT algorithm could enhance specificity and reduce unnecessary RHC referrals without compromising sensitivity (Santaniello et al., 2020). However, these findings have not been consistently replicated across independent cohorts, and data remain limited regarding CPET performance in broader clinical contexts.

An additional challenge in SSc is the high prevalence of left heart disease, which is increasingly recognized as a common and prognostically relevant

complication (Humbert et al., 2022; Ninagawa et al., 2021). Left heart disease may lead to post-capillary pulmonary hypertension and contribute to false-positive PAH screening results. Whether CPET-derived parameters preferentially reflect pre-capillary pulmonary vascular disease rather than elevated left-sided filling pressures remains an important unresolved question with direct clinical implications.

In the present study, we aimed to evaluate the diagnostic performance of CPET in excluding PAH among patients with SSc referred to a PH unit for suspected disease. Specifically, we sought to assess whether selected CPET variables could reliably discriminate PAH from non-PAH hemodynamic profiles, including cases of PH due to left heart disease, thereby supporting a more refined and pragmatic diagnostic strategy applicable to real-world clinical practice.

METHODS

This retrospective observational cross-sectional study included 70 consecutive adults with SSc referred for suspected PAH to the pulmonary hypertension unit of Centro Hospitalar Universitário de Santo António (CHUdSA), Porto, Portugal, between April 2021 and April 2023. All participants underwent both right heart catheterization and CPET as part of the standardized diagnostic work-up for suspected PAH.

Eligible subjects were older than 18 years and fulfilled the 2013 ACR/EULAR classification criteria for SSc (van den Hoogen et al., 2013). Taking into account the extent of skin involvement, classification into limited cutaneous and diffuse cutaneous systemic sclerosis was made according to the LeRoy

criteria (LeRoy et al., 1988). Individuals without detectable skin involvement, but with hallmark serological and clinical features were classified with SSc *sine* scleroderma; and patients with other connective tissue disease, in addition to SSc were classified as having overlap syndrome (Allanore et al., 2015). Patients with an established diagnosis of PAH before referral, according to the 2022 ESC/ERS Guidelines (Humbert et al., 2022), were excluded, as were patients in whom either CPET or RHC was not completed or was of insufficient technical quality for analysis.

Demographic and clinical data were extracted from electronic medical records and included age, sex, body mass index (BMI), disease subtype and duration, blood analysis, comorbidities, medication, pulmonary function tests, echocardiographic and 6MWD data.

Ethical standards

The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments, and the principles of Good Clinical Practice. Approval was obtained from the CHUdSA Ethics Committee (2020.031(023-DEFI/025-CE), which waived the requirement for informed consent due to the retrospective design and use of anonymized data.

Cardiopulmonary exercise testing

Symptom-limited CPET was performed on an electronically braked treadmill (Medisoft, Medel 870C) using an individualized ramp protocol designed after a brief interview about patient's usual level of physical activity (Glaab & Taube, 2022; Pritchard et al., 2021). Breath-by-breath gas exchange data were

collected and averaged over 30-second intervals and analyzed using Blue Cherry® Software (Geratherm Respiratory GmbH, Bad Kissingen, Germany). Patients were encouraged to exercise to maximal effort, aiming for a peak respiratory exchange ratio (RER) greater than 1.10. The comprehensive protocol for CPET adopted in our laboratory has been described in detail elsewhere (Schmidt et al., 2023). Other CPET parameters were recorded in the database but, a priori, peak VO_2, VE/VCO_2 slope, and peal $PetCO_2$ were prespecified as the primary CPET variables of interest because of their mechanistic link to pulmonary vascular disease and prior evidence of diagnostic utility in SSc-associated PAH (Dumitrescu et al., 2017; Santaniello et al., 2020).

Hemodynamic assessment

Hemodynamic assessment was performed by right heart catheterization using a Swan-Ganz catheter, according to institutional protocol. Measurements were obtained at rest, in the supine position, without sedation and after at least 10 minutes of stabilization via an ultrasound -guided internal jugular or brachial vein approach by experienced operators. Pulmonary artery, right atrial, and pulmonary capillary wedge pressures were recorded and averaged over 3 respiratory cycles. Cardiac output (CO) was calculated from an average of at least three measurements using the thermodilution method following current recommendations (Simonneau et al., 2019).

Pulmonary hypertension (PH) was defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, in line with the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (Humbert et al., 2022).

Pre-capillary PH was defined by mPAP > 20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) >2 Wood Units (WU). Post-capillary PH was defined by PAWP >15 mmHg. The later were further subclassified as combined post- and precapillary PH (Cpc-PH) when PVR >2 WU, or isolated postcapillary PH (Ipc-PH) when PVR ≤2 WU.

Outcomes and blinding

The primary outcome was the presence of SSc-associated PAH as determined by RHC. Secondary outcomes included the characterization of CPET-derived patterns of exercise limitation according to PAH status and the description of resting hemodynamic profiles. CPET data were analyzed by physicians with expertise in exercise physiology who were unaware of the invasive hemodynamic results at the time of CPET interpretation. RHC operators and readers were not provided with CPET measurements during invasive assessment, thereby minimizing classification bias.

Statistical analysis

Continuous variables are expressed as mean (standard deviation) for normally distributed data or median [interquartile range] for nonnormally distributed data. Categorical variables are summarized as the counts and proportion [n (%)]. Comparisons between groups were performed using two-sided unpaired or paired t-tests or Wilcoxon rank sums test for normally and non-normally distributed data, respectively.

The three prespecified CPET variables (i.e. Peak VO_2, VE/VCO_2 slope, and peak $PetCO_2$) were evaluated as predictors of the primary outcome. Logistic regression analysis was conducted on the entire cohort to evaluate the association between these CPET variables and the presence of PAH. Associations between exercise capacity parameters (peak VO_2 and $PetCO_2$) and hemodynamic variables (mPAP and PVR) were assessed using univariate linear regression analysis. The coefficient of determination R^2 was used to evaluate the proportion of variance explained by the model. Diagnostic accuracy of CPET parameters for excluding PAH was further determined using receiver operating characteristic (ROC) curves analysis. For each parameter, the area under the ROC curve (AUC) with 95% confidence intervals was calculated, and thresholds were identified both by maximizing the Youden index and by targeting very high specificity (up to 100%) to explore their potential role as rule-out criteria. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios were derived for selected cut-offs.

Missing data were handled by complete-case analysis; the proportion of missingness for key variables was reported, and no imputation was performed. A two-sided p-value < 0.05 was considered significant. Statistical analyses were done with STATA 12.1 (StataCorp LLC, Texas, USA).

RESULTS

Out of the 70 consecutive patients referred for suspected PAH, a total of 43 SSc patients were included in the study cohort. Of the remaining 27 patients, 8 had already an established diagnosis of PAH, and the other 19 were excluded

due to absence or insufficient technical quality of CPET or RHC for analysis. The demographic, clinical, and echocardiographic data of the studied patients are summarized in Table 1. Supplementary Table S1 provides more clinical characteristics of the studied patients. Of the final cohort, 11 (26%) were diagnosed with SSc-associated PAH (pre-capillary PH due to Group 1 PAH by ESC/ERS criteria), whereas 32 (74%) had normal hemodynamics or post-capillary PH phenotypes. The mean age was 64 years and mostly female (98%). Patients with PAH and non-PAH patients were similar in age, sex, body mass index and disease duration, and NYHA functional class (Table 1).

Table 1 Baseline clinical, pulmonary function, echocardiographic, hemodynamic, and functional characteristics of systemic sclerosis patients with and without PAH

	Total (n=43)	**No PAH (n=32)**	**PAH (n=11)**	**p-value**
Age, years	64 (12)	64 (12.9)	65 (9.5)	0.68
Female sex, n (%)	42 (97.7%)	32 (100%)	10 (90.9)	0.08
BMI, kg/m^2	26.3 (5.4)	26.4 (6)	25.8 (3.2)	0.75
Disease duration, months	87.5 (64.4)	85.6 (67.1)	92.6 (59)	0.76
Pulmonary function testing				
DLCO (% predicted)	66.3 (19)	71.8 (18.3)	50.9 (11.6)	**0.03**
FVC/DLCO ratio	1.8 (0.6)	1.7 (0.6)	2.2 (0.4)	0.07
NT-proBNP, pg/mL	311.9 (359.7)	277.3 (331.2)	412.5 (434.3)	0.29
Echocardiography				
Tricuspid regurgitation, cm/s	2.5 (1.2)	2.4 (1)	2.8 (1.6)	0.34

Estimated PASP, mmHg	45.9 (30.6)	44.7 (29.7)	48.8 (34.2)	0.71
Estimated PASP <35 mmHg, %	17 (39.5%)	14 (43.8%)	3 (27.3%)	0.33
PAAT, ms	104.7 (26.1)	110.3 (25)	88 (22.9)	**0.02**
Right atrial volume, mL/m2	25.3 (9.4)	24.4 (9.4)	27.9 (9.3)	0.31
TAPSE, mm	21 (3.8)	21.3 (3.5)	20 (4.7)	0.33
FAC, %	43.5 (6.3)	44.4 (5.5)	40 (8)	0.08
Pericardial effusion, n	7 (17.5%)	5 (17.2%)	2 (18.2%)	0.94
Hemodynamic measurements				
mPAP, mmHg	24.4 (10.8)	20.4 (6.3)	35.9 (13.1)	**<0.01**
PAWP, mmHg	10.5 (4.1)	10.8 (4.4)	9.6 (2.7)	0.38
RA, mmHg	5.3 (2.6)	4.9 (2.4)	6.3 (2.8)	0.91
CI, L/min/m^2	3.5 (0.9)	3.6 (1)	3.2 (0.4)	0.22
PVR, WU	2.6 (1.9)	1.7 (0.7)	5.0 (2.1)	**<0.01**
6MWD				
Distance, m	373.6 (94.1)	393.9 (79.7)	316.2 (110.9)	**0.02**
Predicted distance, %	78.9 (18.3)	83.7 (15.3)	65.5 (21)	**<0.01**

Data are presented as mean (standard deviation, sd) or n (%), as appropriate. A p value < 0.05 was considered significant. PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; BMI, body mass index; NT-proBNP, N-terminal pro B-natriuretic peptide; DLCO/VA, diffusing capacity for carbon monoxide; FVC, forced vital capacity; PASP, pulmonary arterial systolic pressure; PAAT, pulmonary artery acceleration time; TAPSE, Tricuspid Annular Plane Systolic Excursion; FAC, fractional area change; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; RA, right atrium; CI, cardiac index; PVR, pulmonary vascular resistance; WU, wood units; 6MWD, 6-min walking distance.

Pulmonary function testing revealed significantly lower DLCO (50.9±11.6% vs 71.8±18.3% predicted, p=0.03) and a trend toward higher FVC/DLCO ratio (2.2±0.4 vs 1.7±0.6, p=0.07) in the PAH group. NT-proBNP

levels were numerically higher in PAH patients but not significantly different (412.5±434.3 vs 277.3±331.2 pg/mL, p=0.29). Echocardiographic screening parameters showed no significant differences in estimated PASP or tricuspid regurgitation velocity, but PAAT was markedly reduced in PAH patients (88±22.9 vs 110.3±25 ms, p=0.02). Hemodynamic assessment confirmed elevated mPAP (35.9±13.1 vs 20.4±6.3 mmHg, p<0.001) and PVR (5.0±2.1 vs 1.7±0.7 Wood units, p<0.001) in the PAH group, with no differences in pulmonary artery wedge pressure or cardiac index. Functional capacity assessed by 6MWD was significantly reduced in PAH patients (316.2±110.9 vs 393.9±79.7 m, p=0.02).

Cardiopulmonary exercise testing

Patients achieved comparable maximal effort during CPET, as indicated by similar peak respiratory exchange ratio values (Table 2). However, those with PAH exhibited significantly reduced peak VO_2 (15.3±3.6 vs 21.1±5.2 mL/kg/min, p<0.001), VE/VCO_2 slope (37.5±6.2 vs 29.8±4.1, p<0.001) and peak $PetCO_2$ (29.8±4.2 vs 36.5±5.1 mmHg, p<0.001) compared with the non-PAH group. These differences reflect reduced exercise capacity and ventilatory inefficiency consistent with pulmonary vascular disease. Indeed, CPET variables showed significant associations with resting hemodynamic variables related to pulmonary vascular disease, including mPAP and PVR. Additional CPET variables are presented in Supplementary Table S2.

Table 2 CPET characteristics between groups

	Total (n=43)	No PAH (n=32)	PAH (n=11)	p-value
Peak RER	1.1(0.1)	1.1 (0.1)	1.1 (0.1)	0.46
Peak VO_2, mL/min/Kg	15.3 (4.3)	16.5 (3.9)	11.7 (2.9)	**<0.01**
Peak VO_2, % predicted	73.1 (19.4)	79.7 (16.4)	53.6 (13.5)	**<0.01**
VE/VCO_2 slope	40 (9)	37.4 (7)	47.8 (10.3)	**<0.01**
Peak PET CO_2, mmHg	28.7 (6.1)	30.5 (5.4)	23.4 (4.7)	**<0.01**

Data are presented as mean (standard deviation, sd). A p value < 0.05 was considered significant. RER, respiratory exchange ratio; VO_2, O_2 consumption; VCO_2, carbon dioxide production; PET CO_2, end-tidal carbon dioxide partial pressure;

Negative correlations were observed between peak VO_2 and mPAP (coef. -1.12, p-value 0.003, R^2 0.19), and PVR (coef. -0.22, p-value 0.001, R^2 0.26); $PetCO_2$ at peak exercise and mPAP (coef. -0.70, p-value 0.009, R^2 0.16), and PVR (coef. -0.17, p-value <0.001, R^2 0.32).

Diagnostic performance of CPET variables

The ROC curve analysis demonstrated good discriminative ability for peak VO_2, VE/VCO_2 slope, and peak $PetCO_2$ to exclude PAH, with AUCs ≥0.80 for all three parameters (Figure 1). In our studied population, a peak VO_2 > 16 mL/min/Kg or a VE/VCO_2 slope < 34 or a peak $PetCO_2$ > 33 mmHg appropriately excluded a PAH diagnosis with a specificity of 100% and correctly identified SSc patient without PAH, respectively (Table 3). Computing a score where any of these variables crossed the above-described thresholds would be weighted as 1, a score > 0 excludes with 100% of specificity the presence of PAH; this means that

regardless of the parameter, if any of them is met, it excluded with 100% of specificity the presence of PAH in our cohort. The diagnostic performance of CPET variables to detect the absence of PAH among studied SSc patients is presented in Table 3.

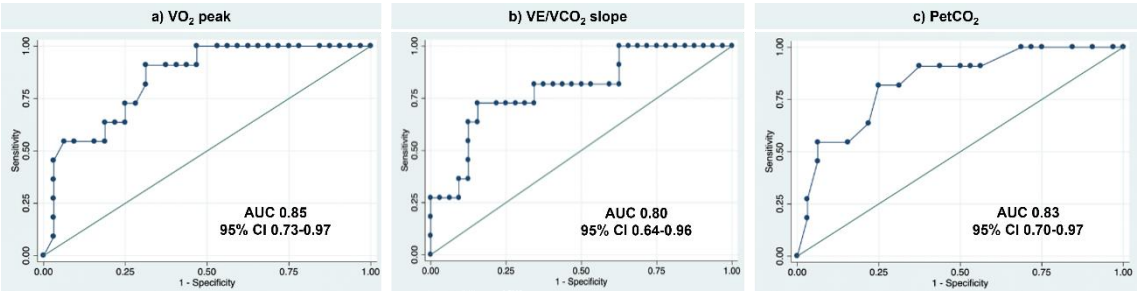

Figure 1 Receiver operating characteristic (ROC) analyses of PAH detected by exercise gas exchange parameters (a) VO2 peak, b) VE/VCO2 slope, and c) PetCO2 peak). AUC – area under the curve. CI, confidence interval.

Table 3 Diagnostic performance of CPET variables to exclude PAH among studied SSc patients.

	Sensitivity	Specificity	Threshold	No PAH correctly identified	AUC (95%CI)
Peak VO_2 (mL/min/Kg)	53%	100%	> 16.1	65%	0.85 (0.73-0.97)
VE/VCO_2 slope	63%	100%	< 33.1	47%	0.80 (0.64-0.96)
Peak $PetCO_2$ (mmHg)	44%	100%	> 34	49%	0.83 (0.70-0.97)

VO_2, O_2 consumption; VCO_2, carbon dioxide production; $PetCO_2$, end-tidal carbon dioxide partial pressure.

DISCUSSION

In this study, we evaluated the diagnostic performance of CPET for excluding PAH in patients with SSc referred to a PH unit for suspected disease. Our study findings support the diagnostic utility of selected parameters of exercise gas exchange (peak VO_2, VE/VCO_2 slope, and peak CO_2) to exclude

the presence of PAH in SSc patients. These parameters are closely linked with the pathophysiological mechanisms that limit exercise in PAH and showed to have an excellent overall discriminative ability to identify those SSc patients without PAH. Using thresholds that minimize false negatives, they were able to correctly identify 47-65% of those patients without PAH. In addition, these 3 parameters seem to be interchangeable as the presence of any of them can exclude PAH. Finally, the diagnostic utility of CPET was preserved in a cohort enriched with patients presenting PH due to left heart disease. Collectively, these findings support a potential role for CPET as a complementary, non-invasive tool to refine the diagnostic workup of SSc patients with suspected PAH.

The diagnostic accuracy of the studied CPET parameters was remarkable (AUC above 0.80) and consistent with previous studies (Dumitrescu et al., 2017; Santaniello et al., 2020). These can be explained by the dramatic pathophysiological implications of PAH to acute cardiorespiratory responses to exercise. The reduced pulmonary vascular reserve limits its normal recruitment and distension when the cardiac output increases and that has an immediate and striking impact on gas exchange (Arena et al., 2010; Guazzi et al., 2022; Sun et al., 2001) due to ventilation/perfusion abnormalities and increased right ventricle afterload. The differences in the determined thresholds and diagnostic performance metrics among studies are mild (Dumitrescu et al., 2017; Santaniello et al., 2020) and likely reflect differences in the characteristics of the study populations, including the prevalence and severity of PAH and the proportion of cases secondary to left heart disease. Together, these data suggest that while

absolute cut-off values may vary, the directionality and physiological meaning of CPET abnormalities in PAH are consistent and reproducible.

The percentage of SSc patients without PAH who were identified by CPET ranged from 47 to 65%, depending on the studied CPET variable. This is very relevant to the clinical problem being addressed. The gold-standard method of diagnosing PAH in SSc is unquestionably the RHC and its early diagnosis has prognostic relevance to these patients. However, the screening strategies result in a high number of false-positive testing and unnecessary RHC that, despite its safety, causes a lot of anxiety to patients who usually undergo to frequent exams to manage the multiorgan involvement (Coghlan et al., 2014; Hao et al., 2015; Young et al., 2021). Our study along with others (Santaniello et al., 2020) suggest that CPET could contribute to a more refined diagnostic strategy by identifying a subset of patients in whom PAH can be confidently excluded, potentially reducing the burden of invasive procedures.

Left heart disease is increasingly recognized as a common and clinically relevant complication of SSc and represents an important confounder in PAH screening strategies. Post-capillary PH may produce symptoms and non-invasive findings that overlap with pre-capillary disease, thereby increasing the risk of false-positive PAH screening results (Humbert et al., 2022; Ninagawa et al., 2021). In our cohort, PH due to left heart disease accounted for 16% of patients in the non-PAH group, reflecting real-world referral patterns to specialized PH centers. Interestingly, CPET-derived parameters did not correlate with pulmonary arterial wedge pressure, the hemodynamic marker of left heart disease, supporting their preferential association with pre-capillary pulmonary vascular

abnormalities. This observation is physiologically plausible, as ventilatory inefficiency and impaired $PETCO_2$ kinetics primarily reflect increased dead space ventilation and abnormal pulmonary perfusion rather than elevated left-sided filling pressures. Although left heart disease may contribute to exercise intolerance through distinct mechanisms, our findings suggest that selected CPET variables may help differentiate pre-capillary from post-capillary phenotypes in SSc, particularly in patients with equivocal non-invasive assessments.

Several limitations should be acknowledged. First, it was conducted at a single center, with a retrospective design, which may limit generalizability beyond tertiary PH referral settings. Second, the sample of 43 participants, despite reflecting the low prevalence of this rare auto-immune disease, limited statistical power and precluded robust multivariable adjustment. Third, CPET was not performed exclusively in patients who screened positive on the DETECT algorithm, which is a recommended and evidence-based screening tool. However, the uptake of DETECT is quite variable worldwide (Coghlan et al., 2014) and, in clinical practice, it is very difficult to separate screening from early diagnosis, as patients with SSc often present with multiorgan involvement and unspecific exertional intolerance. Therefore, our pragmatic study design (SSc patients referred to a PH unit) better reflects real-world clinical practice, where CPET can be more useful. Finally, our results require validation in independent cohorts to reduce the risk of overfitting and increase its generalizability.

Conclusion

CPET-derived parameters demonstrated meaningful diagnostic performance for excluding PAH in patients with SSc referred for suspected disease, even in the presence of left heart disease. These findings support further prospective validation of CPET as a complementary, non-invasive tool to refine the diagnostic evaluation of SSc-associated PAH. Future multicenter studies should aim to define standardized CPET thresholds, assess integration with established screening algorithms, and evaluate the impact of CPET-guided strategies on clinical decision-making and patient outcomes.

REFERENCES

Allanore, Y., Simms, R., Distler, O., Trojanowska, M., Pope, J., Denton, C. P., & Varga, J. (2015). Systemic sclerosis. *Nature Reviews Disease Primers*, *1*, 15002.

Arena, R., Lavie, C. J., Milani, R. V., Myers, J., & Guazzi, M. (2010). Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. *Journal of Heart and Lung Transplantation*, *29*(2), 159-173.

Brown, Z., Proudman, S., Morrisroe, K., Stevens, W., Hansen, D., & Nikpour, M. (2021). Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: A systematic review and meta-analysis of long-term outcomes. *Seminars in arthritis and rheumatism*, *51*(3), 495-512.

Coghlan, J. G., Denton, C. P., Grünig, E., Bonderman, D., Distler, O., Khanna, D., Müller-Ladner, U., Pope, J. E., Vonk, M. C., Doelberg, M., Chadha-Boreham, H., Heinzl, H., Rosenberg, D. M., McLaughlin, V. V., & Seibold, J. R. (2014). Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: The DETECT study [Article]. *Annals of the rheumatic diseases*, *73*(7), 1340-1349.

Dumitrescu, D., Nagel, C., Kovacs, G., Bollmann, T., Halank, M., Winkler, J., Hellmich, M., Grünig, E., Olschewski, H., Ewert, R., & Rosenkranz, S. (2017). Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. *Heart*, *103*(10), 774-782.

Glaab, T., & Taube, C. (2022). Practical guide to cardiopulmonary exercise testing in adults. *Respiratory Research*, *23*(1), 9.

Guazzi, M., Wilhelm, M., Halle, M., Van Craenenbroeck, E., Kemps, H., de Boer, R. A., Coats, A. J. S., Lund, L., Mancini, D., Borlaug, B., Filippatos, G., & Pieske, B. (2022). Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy - A clinical consensus statement of the Heart Failure Association and

European Association of Preventive Cardiology of the European Society of Cardiology. *European Journal of Heart Failure*, *24*(8), 1327-1345.

Hao, Y., Thakkar, V., Stevens, W., Morrisroe, K., Prior, D., Rabusa, C., Youssef, P., Gabbay, E., Roddy, J., Walker, J., Zochling, J., Sahhar, J., Nash, P., Lester, S., Rischmueller, M., Proudman, S. M., & Nikpour, M. (2015). A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Research & Therapy*, *17*(1), 7.

Humbert, M., Kovacs, G., Hoeper, M. M., Badagliacca, R., Berger, R. M. F., Brida, M., Carlsen, J., Coats, A. J. S., Escribano-Subias, P., Ferrari, P., Ferreira, D. S., Ghofrani, H. A., Giannakoulas, G., Kiely, D. G., Mayer, E., Meszaros, G., Nagavci, B., Olsson, K. M., Pepke-Zaba, J., . . . Rosenkranz, S. (2022). 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*, *43*(38), 3618-3731.

Lechartier, B., & Humbert, M. (2021). Pulmonary arterial hypertension in systemic sclerosis. *Presse Médicale*, *50*(1), 104062.

LeRoy, E. C., Black, C., Fleischmajer, R., Jablonska, S., Krieg, T., Medsger, T. A., Jr., Rowell, N., & Wollheim, F. (1988). Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *Journal of Rheumatology*, *15*(2), 202-205.

Ninagawa, K., Kato, M., Ohira, H., Tsuneta, S., Iwano, H., Kono, M., Fujieda, Y., Oku, K., Tsujino, I., & Atsumi, T. (2021). The assessment of left heart disease in patients with systemic sclerosis and pulmonary hypertension. *Clinical and experimental rheumatology*, *39 Suppl 131*(4), 103-110.

Pope, J. E., Denton, C. P., Johnson, S. R., Fernandez-Codina, A., Hudson, M., & Nevskaya, T. (2023). State-of-the-art evidence in the treatment of systemic sclerosis. *Nature Reviews Rheumatology*, *19*(4), 212-226.

Pritchard, A., Burns, P., Correia, J., Jamieson, P., Moxon, P., Purvis, J., Thomas, M., Tighe, H., & Sylvester, K. P. (2021). ARTP statement on cardiopulmonary exercise testing 2021. *BMJ Open Respiratory Research*, *8*(1).

Santaniello, A., Casella, R., Vicenzi, M., Rota, I., Montanelli, G., De Santis, M., Bellocchi, C., Lombardi, F., & Beretta, L. (2020). Cardiopulmonary exercise testing in a combined screening approach to individuate pulmonary arterial hypertension in systemic sclerosis. *Rheumatology (Oxford)*, *59*(7), 1581-1586.

Schmidt, C., Magalhães, S., Gois Basilio, P., Gouveia, M., Teixeira, M., Santos, C., Tavares, A. I., Ferreira, J. P., Ribeiro, F., & Santos, M. (2023). Home- versus centre-based EXercise InTervention in patients with Heart Failure (EXIT-HF trial): A pragmatic randomized controlled trial. *evista Portuguesa de Cardiologia*.

Simonneau, G., Montani, D., Celermajer, D. S., Denton, C. P., Gatzoulis, M. A., Krowka, M., Williams, P. G., & Souza, R. (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *European Respiratory Journal*, *53*(1).

Sun, X. G., Hansen, J. E., Oudiz, R. J., & Wasserman, K. (2001). Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation*, *104*(4), 429-435.

Tyndall, A. J., Bannert, B., Vonk, M., Airò, P., Cozzi, F., Carreira, P. E., Bancel, D. F., Allanore, Y., Müller-Ladner, U., & Distler, O. (2010). Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Annals of the rheumatic diseases*, *69*(10), 1809-1815.

van den Hoogen, F., Khanna, D., Fransen, J., Johnson, S. R., Baron, M., Tyndall, A., Matucci-Cerinic, M., Naden, R. P., Medsger, T. A., Jr., Carreira, P. E., Riemekasten, G., Clements, P. J., Denton, C. P., Distler, O., Allanore, Y., Furst, D. E., Gabrielli, A., Mayes, M. D., van Laar, J. M., . . . Pope, J. E. (2013). 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Annals of the rheumatic diseases*, *72*(11), 1747-1755.

Vandecasteele, E., Drieghe, B., Melsens, K., Thevissen, K., De Pauw, M., Deschepper, E., Decuman, S., Bonroy, C., Piette, Y., De Keyser, F.,

Brusselle, G., & Smith, V. (2017). Screening for pulmonary arterial hypertension in an unselected prospective systemic sclerosis cohort. *European Respiratory Journal*, *49*(5).

Weatherald, J., Montani, D., Jevnikar, M., Jaïs, X., Savale, L., & Humbert, M. (2019). Screening for pulmonary arterial hypertension in systemic sclerosis. *European Respiratory Review*, *28*(153).

Young, A., Moles, V. M., Jaafar, S., Visovatti, S., Huang, S., Vummidi, D., Nagaraja, V., McLaughlin, V., & Khanna, D. (2021). Performance of the DETECT Algorithm for Pulmonary Hypertension Screening in a Systemic Sclerosis Cohort. *Arthritis & Rheumatology*, *73*(9), 1731-1737.

Study II

Cardiac Involvement and Heart Failure Staging in Patients with Systemic Sclerosis
(published at *Journal of Clinical Medicine*)

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ABSTRACT

Background/Objectives: Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by fibrosis and vascular damage, significantly increasing the risk of heart failure (HF). **Methods:** This cross-sectional study included 61 SSc patients (92% female, mean age 63±13 years), excluding those with pulmonary arterial hypertension, referred to a tertiary pulmonary hypertension center. HF stages were classified according to updated guidelines. Clinical, echocardiographic, hemodynamic, and functional capacity data were analyzed in relation to HF stages. **Results:** 48% of patients had pre-symptomatic HF (5% stage A, 43% stage B), while 38% had symptomatic HF (stage C). Advanced HF stages were significantly associated with older age (p=0.02) and multiorgan involvement (p=0.045), but not with SSc subtype or autoantibodies. Structural and functional echocardiographic abnormalities were prevalent (77% and 10%, respectively). Markers of elevated ventricular filling pressure such as left atrial volume (p=0.011) and E/e' ratio (p=0.03) correlated with HF severity. Functional impairment was observed with lower 6-minute walk test (6MWT) distance (p=0.017), reduced VO_2 peak (p=0.015), and increased VE/VCO_2 slope (p=0.002). Resting pulmonary artery wedge pressure did not correlate (p=0.93) with HF stage. VE/VCO_2 slope and 6MWT were independently associated with HF severity. **Conclusions:** Preclinical and symptomatic HF are highly prevalent in SSc patients. HF staging was linked to disease severity, age, and cardiovascular risk factors. Functional capacity tests (6MWT and CPET) serve as valuable tools for HF risk stratification. These findings highlight the critical need for comprehensive cardiovascular assessment and targeted management strategies to mitigate HF progression in SSc patients.

Keywords: heart failure; HF staging; systemic sclerosis

1. Introduction

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease (CTD) characterized by immune dysregulation, vascular damage, and progressive fibrosis of the skin and other internal organs, resulting in significant morbidity and mortality (Pope et al., 2023; Saketkoo et al., 2021). Based on the extent of skin involvement, SSc is classified as either limited or difuse (van den Hoogen et al., 2013). Profiling the expression of specific autoantibodies, including anti-centromere, anti-topoisomerase and anti-RNA polymerase III, provides important prognostic insights into disease course and outcomes (Nihtyanova & Denton, 2010). Pulmonary arterial hypertension (PAH) is one of the most feared cardiovascular complications of SSc and is classically associated with limited SSc and anti-centromere antibodies. However, primary cardiac involvement has been increasingly acknowledged as a common complication of SSc and can be found in both limited and diffuse forms (Giuca et al., 2022). SSc-related primary cardiac dysfunction results from microvascular dysfunction and inflammatory-fibrotic infiltration, affecting the coronary circulation, conduction system, myocardium and pericardium (Giuca et al., 2022; Saketkoo et al., 2021). Consequently, a broad spectrum of cardiac disorders may develop, including ischemia, arrhythmias, pericarditis, myocarditis, and both ventricular systolic and diastolic dysfunction (Butt et al., 2019; Nadel et al., 2024).

Due to this diverse cardiac involvement and the common presence of extracardiac manifestations in SSc, diagnosing primary cardiac disease is challenging and requires a high index of suspicion. Most patients present nonspecific symptoms, such as exertional dyspnea and fatigue (Almeida et al., 2011; Ferri et al., 2005). Diagnosis typically requires a multimodal approach, integrating findings from of several techniques, including cardiac imaging, biomarkers, cardiopulmonary function tests, and invasive hemodynamic assessment (Giuca et al., 2022; Saketkoo et al., 2021). Several studies have shown that SSc patients have a three-fold increased risk of developing heart failure (HF), a disease with a significant impact on their quality of life and survival (Butt et al., 2019; Fontes Oliveira et al., 2022). There is a need for an early

diagnosis of primary cardiac cardiomyopathy associated with SSc and the development of specific treatments to prevent the progression of cardiac fibrosis.

HF is currently viewed as a progressive condition that mainly affects people with cardiovascular risk factors (CRFs) (e.g., elderly, hypertension, obesity, diabetes; HF stage A) that will develop several structural and functional cardiac changes over time (left ventricle hypertrophy, diastolic dysfunction, etc.; HF stage B), with eventual onset of symptoms such as exertional intolerance (HF stage C), and progression to a more severe disease stage with the need for advanced HF therapies (HF stage D). This classification put forward by the American Heart Association encourages the diagnosis of HF at an earlier stage and the implementation of treatments that could change its natural history by preventing or postponing its symptomatic stages (P. A. Heidenreich et al., 2022). Despite a similar prevalence of some common CRFs, SSc patients have a three-fold increased risk of experiencing cardiovascular events (Kurmann et al., 2020). Furthermore, left ven-tricular (LV) diastolic dysfunction is present in one-third of SSc patients and precedes the development of symptomatic HF (Tennøe et al., 2018).

In this study, we aimed to assess the prevalence of HF stages in SSc patients without PAH, and to study its clinical and functional correlates.

2. Materials and Methods

2.1. Study Design and Studied Population

We performed an observational cross-sectional study involving consecutive patients referred to the pulmonary hypertension unit at Centro Hospitalar Universitário de Santo António (CHUdSA) since April 2017, who underwent right heart catheterization (RHC) for suspected PAH based on one of the following criteria: an intermediate to high echocardiographic probability of pulmonary hypertension (PH), as defined by 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (Humbert et al., 2022); a high probability of PAH according to the DETECT score; (Coghlan et al., 2014); or otherwise unexplained exertional dyspnea. Subjects had to be over 18 years of age and to meet the ACR/EULAR 2013 Classification Criteria for diagnosis of

SSc (van den Hoogen et al., 2013). Clinical data such as age, sex, body mass index (BMI), New York Heart Association (NYHA) functional class, comorbidities, medication and pulmonary function tests were extracted from clinical records. Patients with a diagnosis of PAH (Group 1 PH) were excluded from this study. The various stages of HF have been defined based on the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure (P. A. Heidenreich et al., 2022). The scope of this study is centered on patients with SSc who are experiencing HF from Stage A to D. Stage 0 indicates no risk factors and no structural heart disease.

2.2. Echocardiography

Echocardiographic image acquisition was performed by a certified cardiologist using a Vivid E95 ultrasound scanner with a M5Sc-D Transducer (2–5 MHz; GE Healthcare, Horten, Norway). Standard 2D images with the patient in a left lateral decubitus position were saved in cine loop digital format, as well as static images of pulsed-wave Doppler, continuous-wave Doppler, and tissue Doppler. All images were analyzed offline using EchoPAC software (versions 201 and 206, GE Healthcare, Horten, Norway). Diastolic function was assessed as recommended by current ASE/EACVI guidelines (Nagueh et al., 2016), using the following variables: annular e' velocities (septal and lateral), mitral E velocity, mitral E/e' ratio (average e' from septal and lateral walls), left atrial volume index (LAVI), and tricuspid regurgitation peak velocity. For speckle-tracking echocardiography, images (apical four-, two- and long axis 2D) were recorded in a digital raw-data format for posterior analysis using EchoPAC software, which automatically tracked the myocardial tissue with manual adjustments to region of interest and tracking made when necessary. Global longitudinal strain (GLS) was obtained according to the consensus documents of the EACVI/ASE/Industry TaskForce (Badano et al., 2018).

2.3. Invasive Hemodynamic Assessment

The hemodynamic assessment was performed using a Swan-Ganz catheter by right heart catheterization according to our institution protocol: at rest, with no

sedation, through an echo-guided internal jugular vein or brachial vein approach by trained operators. Pulmonary artery, right atrial, and pulmonary arterial wedge pressure (PAWP) were recorded at the end of a quiet respiratory cycle. Cardiac output (CO) was calculated from an average of at least three measurements using the thermodilution method. Pulmonary vascular resistance (PVR) was calculated using the standard formulas (Simonneau et al., 2019).

2.4. Submaximal and Maximal Exercise Testing

The 6-minute walk test (6MWT) was performed in a 30-meter-long corridor under the same environmental conditions. Participants were instructed to walk the maximal distance in 6 minutes. Resting stops were allowed when patients found it necessary. The equation for reference values used is the one proposed by Enright and collegues (Enright & Sherrill, 1998). Blood pressure was measured before and after the test.

All patients able to exercise underwent a maximal cardiopulmonary exercise test (CPET). CPET was performed on a treadmill (Medisoft, Medel 870C) and analyzed through Blue Cherry® Software (Geratherm® Respiratory GmbH, Bad Kissingen, Germany). CPET parameters were registered every 30 seconds. The exercise protocol was chosen after a brief interview to assess the patient's level of physical activity (Glaab & Taube, 2022). The patients were encouraged to make a maximum effort (peak RER of 1.1).

2.5. Statistical Analysis

All data were expressed as mean ± standard deviation (sd) or percentage (%), as appropriate. Histograms were used to assess the normality of data distribution. Patients were divided into groups according to their HF stage. Continuous variables were compared between groups by one-way ANOVA, and categorical variables were compared using the Pearson $\chi 2$ test or Fisher exact test, as appropriate. Statistical analyses were conducted using STATA 16.1 (StataCorp LLC, College Station, TX, USA). A two-sided p-value < 0.05 was considered significant.

3. Results

3.1. Population Characteristics

We studied 61 with SSc whose clinical characteristics are presented in Table 1. They were mostly females (92%), with a mean age of 63±13 years. Limited SSc was the most common SSc subtype (75%). Ninety-four percent of the patients presented more than one organ involvement attributed to SSc at the baseline assessment. The skin was the most affected organ (95%), followed by peripheral vessels (80%), gastrointestinal tract (49%), lungs (43%), joints (10%), and kidney (1%).

Table 1 Clinical characteristics of systemic sclerosis patients according to heart failure stages.

	Total	Stage 0	HF Stage A	HF Stage B	HF Stage C	*p*-Value
N of patients (%)	61 (100)	9 (15)	3 (5)	26 (43)	23 (38)	
Age, years (sd)	62.5 (13.3)	52.9 (17.3)	53.0 (16.8)	62.3 (9.45)	67.7 (12.9)	**0.017**
Female sex, n (%)	56 (92)	9 (100)	3(100)	23 (88)	21 (91)	0.690
Systemic sclerosis (SSc) subtypes, n (%)						
Limited	46 (75)	6 (67)	2 (67)	20 (77)	18 (78)	0.257
Diffuse	12 (20)	2 (22)	0 (0)	6 (23)	4 (17)	0.240
Sine scleroderma	3 (5)	1 (11)	1 (33)	0 (0)	1 (4)	-
Overlap, n (%) *	13 (22)	5 (56)	0 (0)	6 (23)	2 (9)	**0.029**
N of organs involved in SSc $ (sd)	2.8 (1.0)	2.44 (1.0)	1.66 (0.6)	2.73 (0.8)	3.1 (1.1)	**0.045**
Disease duration of SSc, months (sd)	75.9 (56.0)	84.4 (55.1)	67.0 (38.2)	66.7 (49.9)	84.7 (65.6)	0.700
Abnormal capillaroscopy, n (%)	49 (80.3)	6 (67)	2 (67)	22 (85)	19 (83)	0.720
Cardiovascular risk factors §						
Obesity, n (%)	10 (16)	0 (0)	1 (33)	6 (23)	3 (13)	0.330
Hypertension ᵠ, n (%)	19 (31)	0 (0)	1 (33)	5 (19)	13 (57)	**0.005**
Dyslipidemia, n (%)	22 (36)	0 (0)	1 (33)	11 (42)	10 (53)	0.110
Diabetes mellitus ʃ, n (%)	9 (15)	0 (0)	0 (0)	4 (15)	5 (22)	0.400
Arteriosclerotic disease £, n (%)	2 (3)	0 (0)	0 (0)	0 (0)	2 (9)	0.330
Echocardiography						
Structural heart disease ǂ, n (%)	46 (77)	0 (0)	0 (0)	23 (92)	23 (100)	**<0.001**
Reduced LV/RV function	7 (11)	0 (0)	0 (0)	1 (4)	6 (26)	**0.049**
Ventricular hypertrophy	5 (9)	0 (0)	0 (0)	2 (8)	3 (14)	0.640
Chamber enlargement	38 (62)	0 (0)	0 (0)	18 (69)	20 (86)	**<0.001**
Wall motion abnormalities	-	-	-	-	-	-
Valvular heart disease	5 (8)	0 (0)	0 (0)	1 (4)	4 (17)	0.260
Increased filling pressure ¥, n (%)	10 (19)	2 (18)	0 (0)	4 (15)	6 (33)	**0.017**
LAVI > 34 mL/m^2	33 (55)	1 (12)	0 (0)	14 (54)	18 (78)	**0.002**
Average E/e' ≥ 15	5 (9)	0 (0)	0 (0)	1 (4)	4 (22)	0.140
Septal e' < 7 cm/s	18 (33)	0 (0)	0 (0)	8(31)	10 (53)	**0.040**
Lateral e' < 10 cm/s	31 (56)	0 (0)	1 (33)	16 (62)	14 (74)	**0.006**
TR velocity > 2.8 m/s	14 (24)	0 (0)	0 (0)	6 (23)	8 (36)	0.170
NYHA functional class, n (%)						**<0.001**
I	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**<0.001**
II	20 (33)	0 (0)	0 (0)	0 (0)	20 (87)	0.407
III	3 (5)	0 (0)	0 (0)	0 (0)	3 (13)	-
Body mass index, Kg/m^2 (sd)	25.8 (5.4)	23.6 (3.0)	28.1 (3.6)	27.5 (6.2)	24.4 (4.9)	**0.010**
Comorbidities						
Chronic kidney disease, n (%)	9 (15)	1 (11)	0 (0)	2 (8)	6 (26)	0.280

Atrial fibrillation, n (%)	3 (5)	0 (0)	0 (0)	0 (0)	3 (13)	0.160
Venous thromboembolism, n (%)	2 (3)	0 (0)	0 (0)	0 (0)	2 (19)	0.330
Neoplasia, n (%)	5 (8)	0 (0)	0 (0)	1 (4)	4 (17)	0.230
Asthma, n (%)	2 (3)	0 (0)	0 (0)	2 (8)	0 (0)	0.430
COPD, n (%)	2 (3)	0 (0)	0 (0)	0 (0)	2 (9)	0.330
Obstructive sleep apnea, n (%)	1 (2)	1 (6)	0 (0)	1 (4)	0 (0)	0.710
Interstitial lung disease, n (%)	6 (10)	0 (0)	0 (0)	4 (15)	2 (9)	0.520
Laboratory values						
NT-proBNP ≥ 125 pg/mL ¤ n (%)	26 (43)	2 (22)	0 (0)	8 (32)	16 (70)	**0.009**
NT-proBNP, pg/mL (sd)	320 (567)	105.7 (73.6)	62.7 (38.4)	160 (228)	612 (810)	**0.015**
Creatinine, mg/dL (sd)	0.74 (0.23)	0.67 (0.10)	0.58 (0.06)	0.72 (0.16)	0.80 (0.32)	0.270
Anti–Scl-70^{+}, n (%)	11 (18)	1 (11)	0 (0)	6 (23)	4 (18)	0.710
Anti-RNAP3^{+}, n (%)	1 (2)	0 (0)	0 (0)	0 (0)	1 (5)	0.620
Anti-centromere^{+}, n (%)	41 (68)	7 (78)	2 (67)	16 (62)	16 (73)	0.770
Treatment						
Oxygen therapy, n (%)	2 (3)	0 (0)	0 (0)	1 (4)	1 (4)	0.092
Loop diuretics, n (%)	14 (23)	0 (0)	0 (0)	3 (12)	11 (48)	**0.004**
ACE inhibitors, n (%)	6 (10)	0 (0)	0 (0)	3 (12)	3 (13)	0.650
Beta-adrenolytics, n (%)	7 (11)	0 (0)	0 (0)	1 (4)	6 (26)	0.050
MRA, n (%)	13 (21)	0 (0)	0 (0)	6 (23)	7 (30)	0.220
Calcium channel blockers, n (%)	31 (51)	4 (44)	2 (67)	16 (62)	9 (39)	0.410
Vasodilators, n (%)	12 (20)	4 (44)	0 (0)	5 (19)	3 (13)	0.180
Statins, n (%)	26 (43)	0 (0)	1 (33)	12 (46)	13 (57)	**0.033**
Antidiabetics, n (%)	9 (15)	0 (0)	0 (0)	4 (15)	5 (22)	0.400
Anticoagulation, n (%)	8 (13)	1 (11)	0 (0)	1 (4)	6 (26)	0.120
Primrose oil, n (%)	21 (34)	3 (33)	1 (33)	12 (46)	5 (22)	0.360
Corticosteroids, n (%)	9 (15)	2 (22)	0 (0)	3 (12)	4 (17)	0.740
Immunomodulators, n (%)	15 (25)	1 (11)	0 (0)	8 (31)	6 (26)	0.490

Clinical characteristics of studied patients are presented by HF stages; Stage 0 means absence of any criteria present in HF staging according to 2022 AHA/ACC/HFSA guidelines. * Patients with other connective tissue disease in addition to SSc. $ Number of organs involved in SSc, excluding the heart. § Coexistence of dyslipidemia and obesity were included as criteria qualifying for HF stage A, being an adaption of 2022 AHA/ACC/HFSA guideline in HF staging as data were not fully available to diagnose metabolic syndrome. φ Hypertension = systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg or antihypertensive pharmacotherapy. ∫ Diabetes mellitus = insulin or antidiabetic drugs. £ Arteriosclerotic disease included coronary artery disease, stroke, or peripheral artery disease; however, for this population, documented atherosclerotic disease were restricted to coronary disease. ¤ Raised NT-proBNP not otherwise explained (e.g., CKD). The patients included in this cohort also did not have known previous exposure to cardiotoxic agents, genetic cardiomyopathy, or family history of cardiomyopathy. ‡ Structural disease included reduced left (LVEF < 50% or GLS < 16%) or right ventricular systolic function (TAPSE < 17 mm or RVFAC < 35%); hypertrophy of either left ventricle (LVMI > 116 g/m^2 for male and >95 g/m^2 for female) or right ventricle (RV free wall thickness > 5 mm); RWT > 0.42; wall motion abnormalities at rest were not reported for this cohort; valvular heart disease were considered positive in the presence of at least moderate stenosis or regurgitation in any heart valve. ¥ According to the diastolic dysfunction criteria of the current ASE/EACVI guidelines. **Abbreviations:** ACE: angiotensin-converting enzyme; CKD: chronic kidney disease defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2; COPD: chronic obstructive pulmonary disease; e': average peak early myocardial relaxation velocity; E: early mitral valve inflow velocity; RVFAC: Fractional Area Change; GLS: global longitudinal strain; HF: heart failure; LA: left atrium; LAVi: left atrial volume index; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro B-natriuretic peptide; RWT: relative wall thickness; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; SSc: systemic sclerosis. The bold formatting was used to highlight significant values (p < 0.05).

3.2. Heart Failure Staging

Forty-eight percent of the studied patients were classified as pre-symptomatic HF stages (5% for stage A and 43% for stage B), while 38% had symptomatic HF (stage C). In the HF stage B, 32% of patients showed elevated NT-proBNP levels. No patients were classified in advanced HF stage D. HF stages were significantly correlated with plasmatic NT-proBNP levels and age (Table 1, Figure 1).

Comorbidities not included in HF staging criteria were not associated with HF stages (Table 1). The number of organs affected by SSc, excluding the heart, was associated with HF stages severity (Figure 1). No significant association was found between the organ involved, disease duration, cappilaroscopy, SSc antibodies, and HF stages. Regarding treatment at the baseline, neurohormonal blockers, loop diuretics, statins and anticoagulants were more frequent in more advanced HF stages. Targeted therapies for SSc, including vasodilators, immunomodulators, and corticosteroids, were similar across HF stages (Table 1).

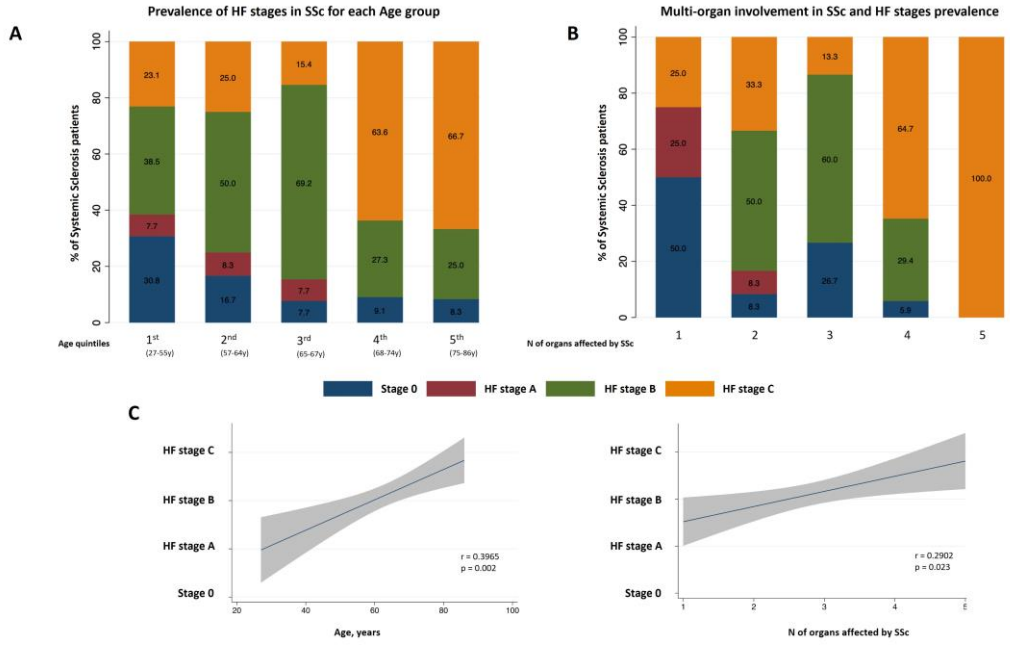

Figure 1 Relationship between heart failure (HF) stages, age and multi-organ involvement in systemic sclerosis (SSc) patients. Panel (A), prevalence of HF stages according to age quintiles. Panel (B), prevalence of HF stages for the number of organs involved in SSc (right-sided plot) with shaded 96% confidence interval. Pearson correlation coefficient (r).

3.3. Cardiac Phenotype and Central Hemodynamics

The index volume of left atrium (LAVi) differed across HF stages. The ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'), a surrogate of LV filling pressure was also different across HF stages, being higher in those with more advanced HF. Three patients had HF with left ventricular ejection fraction (LVEF) below 50% (LVEF ranging from 46 to 48%). Other echocardiographic parameters, including GLS and LVEF, showed no significant variation among HF stages (Table 2).

In right heart catheterization, three patients with HF stage B presented PH, two of them with group 2 PH, and one considered to be multifactorial PH. HF stage C was presented in 5 patients with group 2 PH. Hemodynamic variables assessed invasively, such as mean pulmonary arterial pressure (MPAP) and PAWP, were equivalent across HF stages (Table 2).

Table 2 Echocardiographic, hemodynamic, and pulmonary characteristics in SSc patients.

	Stage 0	HF Stage A	HF Stage B	HF Stage C	*p*-Value
Echocardiography					
LVEF, % (sd)	58.3 (4.4)	60.7 (1.5)	62.5 (6.3)	61.7 (8.3)	0.540
GLS, % (sd)	−19.6 (2.3)	−18.5 (-)	−18.8 (2.6)	−18.3 (2.3)	0.830
LAVI, mL/m^2 (sd)	26.4 (2.5)	28.0 (0.8)	34.3 (9.9)	50.2 (29.4)	**0.011**
LVEDVi, ml/m^2	43.2 (8.1)	42.6 (10.4)	42.9 (10.2)	45.0 (12.2)	0.940
E/A (sd)	1.41 (0.3)	1.20 (0.58)	1.07 (0.28)	1.06 (0.51)	0.180
E/e' (sd)	6.85 (1.04)	5.71 (1.32)	9.77 (3.8)	11.6 (5.4)	**0.026**
RVFAC, % (sd)	43.7 (5.4)	51.0 (3.0)	42.6 (6.2)	43.4 (6.7)	0.200
TAPSE, mm (sd)	23.7 (3.1)	20.0 (4.4)	21.5 (2.6)	20.2 (4.8)	0.170
RA, mL/m^2 (sd)	23.6 (6.9)	20.0 (4.4)	20.8 (5.8)	27.6 (12.8)	0.085
RVEDA, cm^2/m^2 (sd)	9.87 (0.9)	10.4 (1.4)	10.1 (1.4)	11.3 (2.4)	0.120
TR, m/s (sd)	2.00 (0.91)	1.63 (1.4)	2.0 (1.3)	2.2 (1.2)	0.820
Right heart catheterization					
MPAP, mmHg (sd)	15 (1.41)	18.0 (1.41)	20.6 (5.6)	21.7 (7.7)	0.310
PAWP, mmHg (sd)	9.25 (2.1)	10.5 (3.53)	11.1 (4.9)	11.1 (5.7)	0.930
PAWP > 15 mmHg, n (%)	5 (8.2)	0 (0)	3 (27)	5 (26)	0.560
RAP, mmHg (sd)	4.25 (0.96)	6.5 (3.5)	4.82 (2.6)	5.05 (3.0)	0.820
CI, L/min/m^2 (sd	3.2 (0.6)	4.25 (0.49)	3.64 (1.14)	3.13 (1.0)	0.340
PVR, WU (sd)	1.12 (0.52)	1.65 (1.5)	1.63 (0.78)	2.33 (1.1)	0.095
Pulmonary function tests					
DLCO, % predicted (sd)	79.6 (19.4)	63.5 (-)	70.0 (19.9)	60.8 (14.3)	0.400
FVC, % predicted (sd)	94.1 (8.1)	96.4 (-)	95.4 (24.1)	96.2 (23.4)	1.000
FVC/DLCO, ratio (sd)	1.23 (0.35)	1.51 (-)	1.41 (0.34)	1.65 (0.51)	0.370

Abbreviations: CI: cardiac index; DLCO: diffusing capacity of the lungs for carbon monoxide; E/A: ratio of the early to late diastolic transmitral flow velocity; E/e': average ratio of the early mitral valve inflow velocity (E) to peak early myocardial relaxation velocity (e'); FVC: forced vital capacity; GLS: global longitudinal strain; LAVi: left atrial volume index; LVEF: left ventricular ejection fraction; LVEDVi: left ventricular end-diastolic volume index; MPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance (WU, Woods units); RA: right atria; RAP: right atrial pressure; RVEDA: right ventricular end-diastolic area; RVFAC: Fractional Area Change; SV: stroke volume; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; SSc: systemic sclerosis. The bold formatting was used to highlight significant values ($p < 0.05$).

3.4. Cardiopulmonary Exercise Test and 6-Minute Walking Test

All patients performed the 6MWT and the walking distance correlated with HF stage severity (Table 3). CPET was performed in 48 patients (79%). At peak, VO2, VCO2, and PET CO2 decreased with HF severity. Conversely, the VE/VCO2 slope, a marker of ventilatory inefficiency, increased with HF severity (Table 3).

Table 3 Submaximal and maximal functional capacity across HF stages in SSc patients.

	Stage 0	HF Stage A	HF Stage B	HF Stage C	*p*-Value
Six-minute walk test (6MWT)					
Distance, m (sd)	508 (109)	414 (33)	378 (114)	360 (91)	**0.017**
% predicted distance (sd)	92.9 (9.5)	84.6 (11.7)	76.9 (21.2)	77.6 (18.5)	0.230
Cardiopulmonary Exercise Testing					
Maximal heart rate, % predicted (sd)	92.7 (7.7)	91.3 (10.7)	85.0 (11.7)	79.0 (14.9)	0.057
VO_2 peak, mL/min/kg (sd)	22.1 (4.8)	17.9 (2.0)	17.1 (4.9)	15.7 (4.3)	**0.015**
% VO_2 predicted	88.9 (17.1)	84.0 (13.5)	77.9 (23.5)	74.2 (17.7)	0.370
Pulse O_2 peak (sd)	8.84 (1.5)	7.1 (2.5)	8.94 (2.9)	7.78 (1.5)	0.360
PET CO_2 peak (sd)	33.8 (3.0)	28.0 (3.6)	33.8 (4.1)	27.9 (4.8)	**0.024**
VE/VCO_2 slope (sd)	31.1 (3.0)	38.7 (5.0)	32.4 (5.1)	38.9 (7.5)	**0.002**
RER peak, (sd)	1.08 (0.74)	1.02 (0.04)	1.05 (0.13)	1.05 (0.13)	0.880

Abbreviations: $PETCO_2$: end-tidal carbon dioxide partial pressure; RER: respiratory exchange ratio of carbon dioxide production to oxygen consumption; SSc: systemic sclerosis; VO_2: O_2 consumption; VCO_2: carbon dioxide production; VE: pulmonary ventilation. The bold formatting was used to highlight significant values ($p < 0.05$).

In multivariate regression analysis, 6MWT distance and VE/VCO2 slope were independently correlated with HF stages (Table 4). The results of the regression analysis also showed that while age, dyslipidemia, hypertension and number of organs affected by SSc were initially associated with HF stage

severity, after adjustment, only hypertension remained statistically significant (Table 4).

Table 4 Univariate and multivariate linear regression models for HF stages in SSc patients.

Variable	Univariate		Multivariate	
	Coefficient (sd)	*p*-Value	Coefficient (sd)	*p*-Value
Age	0.030 (0.009)	**0.002**	0.020 (0.011)	0.062
Sex	−0.40 (0.480)	0.403	0.251 (0.504)	0.621
Hypertension	0.870 (0.260)	**0.001**	0.616 (0.302)	**0.047**
Dyslipidemia	0.589 (0.262)	**0.029**	0.179 (0.300)	0.554
Body mass index	0.001 (0.024)	0.979	0.001 (0.023)	0.959
Diabetes	0.613 (0.361)	0.095	0.291 (0.360)	0.420
Chronic kidney disease	0.484 (0.368)	0.194	0.009 (0.374)	0.980
N organs involved by SSc	0.299 (0.128)	**0.023**	0.258 (0.129)	0.051
6MWT distance	−0.004 (0.001)	**0.003**	−0.003 (0.001)	**0.029**
VO_2 peak	−0.094 (0.028)	**0.002**	−0.070 (0.036)	0.060
VCO_2 peak	−0.072 (0.231)	**0.003**	−0.058 (0.030)	0.061
VE/VCO_2 basal	0.031 (0.019)	0.111	0.038 (0.019)	0.050
VE/VCO_2 peak	0.060 (0.021)	**0.006**	0.069 (0.022)	**0.003**
VE/VCO_2 slope	0.060 (0.225)	**0.011**	0.057 (0.023)	**0.018**
PET CO_2 basal	−0.035 (0.041)	0.384	−0.076 (0.047)	0.110
PET CO_2 peak	−0.046 (0.030)	0.135	−0.060 (0.031)	0.059

Multivariate model adjusted for age, sex, hypertension, dyslipidemia, diabetes, body mass index, and chronic kidney disease. **Abbreviations**: 6MWT: 6-minute walk test; $PETCO_2$: end-tidal carbon dioxide partial pressure; SSc: systemic sclerosis; VO_2: O_2 consumption; VCO_2: carbon dioxide production; VE: pulmonary ventilation. The bold formatting was used to highlight significant values ($p < 0.05$).

4. Discussion

The main findings of our study are the following. First, we observed a significant prevalence of symptomatic HF (stage C) in SSc patients referred for suspected, but not confirmed PAH. Second, 43% of asymptomatic patients were found to be at increased risk of developing HF (stage B HF). These symptomatic and presymptomatic HF stages were more frequent in elderly patients, in those with cardiovascular risk factors, and in those with multiorgan involvement by the SSc. Third, there were no significant differences in resting invasive hemodynamics, namely PAWP, however functional parameters such as walked

distance at 6MWT, peak VO2 or VE/VCO2 slope at CPET correlated with HF staging.

Our findings emphasize the importance of recognizing cardiac involvement in SSc. The prevalence of symptomatic HF (stage C) of 38%, alongside 42% of preclinical HF stage (stage B), suggests a substantial burden of cardiac dysfunction within this population. Symptomatic HF is particularly prevalent in SSc patients with PAH (Faludi et al., 2014; Fernandez-Codina et al., 2017). However, evidence on the prevalence of HF in SSc patients without PAH is limited. Jiang et al. found cardiac involvement in 53% of SSc patients, with 4% of them exhibiting symptomatic HF (Jiang et al., 2022). The higher prevalence of symptomatic HF in our study may be explained by the study design (we studied SSc patients referred for PH suspicion), the older age of our cohort, and the use of the most recent criteria for HF definition (P. A. Heidenreich et al., 2022).

Multiorgan involvement in SSc has been linked to early disease onset and greater disease severity (Jaeger et al., 2016; Pokeerbux et al., 2019), although its association with HF is not well-documented. Our findings suggest a positive correlation between the extent of multiorgan involvement and HF severity. Therefore, multiorgan involvement in SSc patients should raise clinical suspicion of cardiovascular complications, including HF.

The close association between uncontrolled CRFs and the onset of HF is well established (Paul A. Heidenreich et al., 2022). The prevalence of CRFs in this SSc cohort was notably high. About one-third of patients had hypertension, and that was linked to HF severity. While we did not specifically assess blood pressure control, it is likely that this high-risk population could benefit from lower blood pressure targets (systolic BP <120 mmHg) to prevent HF, as shown in the SPRINT trial (Group et al., 2015). Diabetes and obesity were also common, affecting 15% and 16% of patients, respectively. These patients may benefit from antidiabetic drugs with favorable effects on weight control and cardiovascular protection, such as GLP-1 receptor agonists and SGLT2 inhibitors (Wilcox et al., 2020).

The inflammatory-fibrotic myocardial milieu in SSc is associated with a 3-fold risk of cardiovascular events compared to the general population (Kurmann

et al., 2020). It has been hypothesized that the vascular dysfunction underlying Raynaud's phenomenon also affects the coronary microvasculature, contributing to ischemic abnormalities detected on cardiac stress imaging despite the absence of epicardial coronary artery disease (Giuca et al., 2022). This condition, currently defined as ischemia with no obstructive coronary artery disease (INOCA), is frequently observed in SSc patients and is associated with an increased risk of cardiovascular events and mortality (Follansbee et al., 1984; Steen et al., 1996). Recent advancements in non-invasive cardiac imaging, including coronary flow reserve assessment via coronary computed tomography angiography (CCTA), cardiac magnetic resonance (CMR), and positron emission tomography (PET), may enhance risk stratification and facilitate more tailored therapeutic approaches in this population (Smilowitz et al., 2023; Trimarchi, Pizzino, et al., 2024).

Most HF patients in stages B and C had preserved LVEF, with a high prevalence of left ventricular diastolic dysfunction (LVDD), which is consistent with prior studies. Reported LVDD prevalence varies widely in the literature (17-67%) depending on the studied population and diagnostic criteria applied (Faludi et al., 2014; Porpáczy et al., 2018; Tennøe et al., 2018). This supports HFpEF as the predominant type of HF in SSc (Fontes Oliveira et al., 2022; Rivera et al., 2021). Therefore, these patients should be treated according to current guideline recommendations, with emphasis on CRF control and the use of SGLT2 inhibitors for prognosis modification (Paul A. Heidenreich et al., 2022; McDonagh et al., 2021). Among chronic inflammatory diseases, SSc, along with systemic lupus erythematosus, carries the highest risk of HF development (Rivera et al., 2021). The prevalence of HFpEF is likely related to chronic low-level systemic inflammation and immune dysregulation, which contribute to myocardial fibrosis and LVDD (Paulus & Zile, 2021). Controlling inflammation may prevent HF progression in SSc, though this remains speculative (Giuca et al., 2022; Verma et al., 2024).

This study also underscores the importance of SSc phenotyping over time, particularly regarding PAH and LVDD development. Pulmonary vasodilators are commonly used to treat patients with PAH associated with SSc (SSc-PAH) and

also patients without PAH but with Raynaud phenomena (Humbert et al., 2022). Therefore, caution should be taken as, in the presence of LVDD, pulmonary vasodilators can be associated with clinical worsening due to development of pulmonary edema (McLaughlin et al., 2019).

The echocardiography and NT-proBNP are important tools to identify patients at risk of HF development among SSc patients. The most common cardiac abnormalities observed were increased left atrial (LA) volume and elevated E/e' ratio, both of which indicate increased left heart filling pressures—a key feature of HF. Echocardiography is essential as the standard diagnostic tool for characterizing and monitoring heart disease (Giuca et al., 2022). Annual comprehensive echocardiographic evaluations are recommended for SSc patients to detect early ventricular dysfunction (Hoffmann-Vold et al., 2019). Echocardiography coupled with GLS technology can be useful in detecting subtle changes in myocardial function in SSc patients. Although we did not find significant differences between clinical and subclinical HF stages, GLS is increasingly recognized as an important tool for identifying early ventricular dysfunction in asymptomatic SSc patients (Stronati et al., 2024). However, a major limitation of LVEF, GLS, and other non-invasive echocardiographic markers is their load-dependence, which is particularly relevant in SSc. This is due not only to vascular dysfunction and the high prevalence of CRFs but also to the frequent use of vasodilatory therapy, which may complicate the identification of subtle functional abnormalities. Despite being underexplored in this population, myocardial work (MW) assessment by echocardiography represents a promising approach for comprehensive, load-independent myocardial evaluation (Trimarchi, Carerj, et al., 2024). Interestingly, MW appears to be significantly reduced in SSc patients despite having a normal echocardiographic assessment on standard evaluation (Magda et al., 2024). Complementing myocardial functional assessment, emerging cardiac magnetic resonance (CMR) mapping techniques have shown potential in detecting subtle fibrosis and other pathological changes in SSc (Mavrogeni et al., 2015). These advances may, in the future, enable earlier identification of SSc-related cardio-myopathy and subclinical HF stages.

NT-proBNP plays a crucial role in diagnosing HF, and elevated levels should raise suspicion of its presence (Paul A. Heidenreich et al., 2022; McDonagh et al., 2021). The DETECT algorithm includes NT-proBNP quantification and is currently recommended for SSc patients (Humbert et al., 2022). While primarily used for PAH screening, NT-proBNP may also aid in detecting both clinical and subclinical SSc-related cardio-myopathy. However, interpreting elevated NT-proBNP levels requires caution, as various conditions beyond HF can contribute to its increase. Therefore, NT-proBNP should be assessed alongside clinical evaluation and other diagnostic tools, following current recommendations for HF diagnosis and staging (P. A. Heidenreich et al., 2022). In our study, 32% of stage B patients had elevated NT-proBNP levels. In addition, NT-proBNP has demonstrated diagnostic and prognostic value in asymptomatic SSc patients, with elevated levels being able to predict 3-year mortality (Allanore et al., 2016).

Our data also reveals an association between HF severity and functional impairment in SSc patients without PAH. Lower 6MWT distances were independently associated with HF severity. Although decreased 6MWT performance is expected in symptomatic HF, this study highlights that even in asymptomatic patients, 6MWT may identify individuals at risk of HF progression. Consistent with the link between multiorgan involvement and HF stages, other studies have shown that reduced 6MWT distance correlates with SSc severity (Pugnet et al., 2018). CPET is often used in this population for evaluating dyspnea and assessing the functional impact of SSc. In line with 6MWT, HF severity was associated with reduced peak VO_2 and ventilatory inefficiency assessed by VE/VCO2 slope during CPET (Ewert et al., 2019). Low VO_2 peak and a low anaerobic threshold on CPET can differentiate functional impairment due to cardiac involvement from respiratory limitations or pulmonary vasculopathy in SSc (Boutou et al., 2016). Notably, resting invasive hemodynamic parameters did not distinguish HF stages, emphasizing the diagnostic value of functional tests like 6MWT and CPET in assessing HFpEF and HF staging (Guazzi et al., 2022). Patients in HF stages B and C had a higher proportion of post-capillary hypertension (PAWP >15 mmHg), however, no

differences were found between these groups. Interestingly, Sarma et al. recently questioned the significance of elevated PAWP in limiting exercise capacity in HFpEF patients, suggesting that mechanisms other than PAWP may contribute to dyspnea and exercise intolerance in SSc patients (Sarma et al., 2023).

Our study has some limitations that should be acknowledged. The limited sample size reduces the statistical power to adjust for potential confounders. However, given the rarity of SSc, our sample size is comparable to similar studies. We recruited patients referred to a PH Unit, limiting our findings' generalizability to a more general population of patients with SSc. However, the main conclusions remain valid in this challenging clinical context. The cross-sectional design of our study does not allow us to make temporal inferences between patients classified in the different HF stages. However, it is plausible that the common understanding informed by longitudinal cohorts of at-risk HF patients can be applied to SSc patients.

5. Conclusions

In conclusion, our study reveals a notable prevalence of symptomatic HF in patients with SSc, with 38% meeting the criteria for symptomatic HF (stage C).The observed prevalence of preclinical HF stages underscores the importance of early detection and intervention to prevent the progression to symptomatic HF. Cardiovascular comorbidities are prevalent, and controlling them may significantly impact this high-risk population. Cardiopulmonary exercise capacity were associated with HF severity, suggesting a decline in functional capacity as HF progresses.

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Informed Consent Statement: Patient consent was waived due to the observational nature of the study, where no identifiable personal data were collected, ensuring full anonymity of the participants and compliance with ethical standards.

Data Availability Statement: On request, the corresponding author must provide access to the database.

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REFERENCES

Allanore, Y., Komocsi, A., Vettori, S., Hachulla, E., Hunzelmann, N., Distler, J., Avouac, J., Gobeaux, C., Launay, D., Czirjak, L., Kahan, A., & Meune, C. (2016). N-terminal pro-brain natriuretic peptide is a strong predictor of mortality in systemic sclerosis. *International journal of cardiology*, *223*, 385-389.

Almeida, I., Faria, R., Vita, P., & Vasconcelos, C. (2011). Systemic sclerosis refractory disease: from the skin to the heart. *Autoimmunity Reviews* , *10*(11), 693-701.

Badano, L. P., Kolias, T. J., Muraru, D., Abraham, T. P., Aurigemma, G., Edvardsen, T., D'Hooge, J., Donal, E., Fraser, A. G., Marwick, T., Mertens, L., Popescu, B. A., Sengupta, P. P., Lancellotti, P., Thomas, J. D., & Voigt, J. U. (2018). Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European Heart Journal - Cardiovascular Imaging*, *19*(6), 591-600.

Boutou, A. K., Pitsiou, G. G., Siakka, P., Dimitroulas, T., Paspala, A., Sourla, E., Chavouzis, N., Garyfallos, A., Argyropoulou, P., & Stanopoulos, I. (2016). Phenotyping Exercise Limitation in Systemic Sclerosis: The Use of Cardiopulmonary Exercise Testing. *Respiration*, *91*(2), 115-123.

Butt, S. A., Jeppesen, J. L., Torp-Pedersen, C., Sam, F., Gislason, G. H., Jacobsen, S., & Andersson, C. (2019). Cardiovascular Manifestations of Systemic Sclerosis: A Danish Nationwide Cohort Study [Article]. *Journal of the American Heart Association*, *8*(17), 18, Article e013405.

Coghlan, J. G., Denton, C. P., Grunig, E., Bonderman, D., Distler, O., Khanna, D., Muller-Ladner, U., Pope, J. E., Vonk, M. C., Doelberg, M., Chadha-Boreham, H., Heinzl, H., Rosenberg, D. M., McLaughlin, V. V., Seibold, J. R., & group, D. s. (2014). Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Annals of the Rheumatic Diseases*, *73*(7), 1340-1349.

Enright, P. L., & Sherrill, D. L. (1998). Reference equations for the six-minute walk in healthy adults. *American Journal of Respiratory and Critical Care Medicine*, *158*(5 Pt 1), 1384-1387.

Ewert, R., Ittermann, T., Habedank, D., Held, M., Lange, T. J., Halank, M., Winkler, J., Glaser, S., Olschewski, H., & Kovacs, G. (2019). Prognostic value of cardiopulmonary exercise testing in patients with systemic sclerosis [Article]. *BMC Pulmonary Medicine*, *19*(1), 12, Article 230.

Faludi, R., Költo, G., Bartos, B., Csima, G., Czirják, L., & Komócsi, A. (2014). Five-year follow-up of left ventricular diastolic function in systemic sclerosis patients: Determinants of mortality and disease progression [Article]. *Seminars in arthritis and rheumatism*, *44*(2), 220-227.

Fernandez-Codina, A., Simeon-Aznar, C. P., Pinal-Fernandez, I., Rodriguez-Palomares, J., Pizzi, M. N., Hidalgo, C. E., Del Castillo, A. G., Prado-Galbarro, F. J., Sarria-Santamera, A., Fonollosa-Pla, V., & Vilardell-Tarres, M. (2017). Cardiac involvement in systemic sclerosis: differences between clinical subsets and influence on survival [Article]. *Rheumatology International*, *37*(1), 75-84.

Ferri, C., Giuggioli, D., Sebastiani, M., Colaci, M., & Emdin, M. (2005). Heart involvement and systemic sclerosis. *Lupus*, *14*(9), 702-707.

Follansbee, W. P., Curtiss, E. I., Medsger, T. A., Jr., Steen, V. D., Uretsky, B. F., Owens, G. R., & Rodnan, G. P. (1984). Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. *New England Journal of Medicine*, *310*(3), 142-148.

Fontes Oliveira, M., Rei, A. L., Oliveira, M. I., Almeida, I., & Santos, M. (2022). Prevalence and prognostic significance of heart failure with preserved ejection fraction in systemic sclerosis. *Future Cardiology*, *18*(1), 17-25.

Giuca, A., Gegenava, T., Mihai, C. M., Jurcut, C., Saftoiu, A., Girnita, D. M., Popescu, B. A., Ajmone Marsan, N., & Jurcut, R. (2022). Sclerodermic Cardiomyopathy-A State-of-the-Art Review. *Diagnostics (Basel)*, *12*(3).

Glaab, T., & Taube, C. (2022). Practical guide to cardiopulmonary exercise testing in adults. *Respiratory Research*, *23*(1), 9.

Group, S. R., Wright, J. T., Jr., Williamson, J. D., Whelton, P. K., Snyder, J. K., Sink, K. M., Rocco, M. V., Reboussin, D. M., Rahman, M., Oparil, S., Lewis, C. E., Kimmel, P. L., Johnson, K. C., Goff, D. C., Jr., Fine, L. J., Cutler, J. A., Cushman, W. C., Cheung, A. K., & Ambrosius, W. T. (2015). A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *New England Journal of Medicine*, *373*(22), 2103-2116.

Guazzi, M., Wilhelm, M., Halle, M., Van Craenenbroeck, E., Kemps, H., de Boer, R. A., Coats, A. J. S., Lund, L., Mancini, D., Borlaug, B., Filippatos, G., & Pieske, B. (2022). Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy – A clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology. *European Journal of Heart Failure*, *24*(8), 1327-1345.

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., . . . Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Journal of the American College of Cardiology*, *79*(17), e263-e421.

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., . . . Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *79*(17), 1757-1780.

Hoffmann-Vold, A. M., Distler, O., Murray, B., Kowal-Bielecka, O., Khanna, D., & Allanore, Y. (2019). Setting the international standard for longitudinal follow-up of patients with systemic sclerosis: a Delphi-based expert consensus on core clinical features. *RMD Open*, *5*(1), e000826.

Humbert, M., Kovacs, G., Hoeper, M. M., Badagliacca, R., Berger, R. M. F., Brida, M., Carlsen, J., Coats, A. J. S., Escribano-Subias, P., Ferrari, P., Ferreira, D. S., Ghofrani, H. A., Giannakoulas, G., Kiely, D. G., Mayer, E., Meszaros, G., Nagavci, B., Olsson, K. M., Pepke-Zaba, J., . . . Rosenkranz, S. (2022). 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*, *43*(38), 3618-3731.

Jaeger, V. K., Wirz, E. G., Allanore, Y., Rossbach, P., Riemekasten, G., Hachulla, E., Distler, O., Airò, P., Carreira, P. E., Balbir Gurman, A., Tikly, M., Vettori, S., Damjanov, N., Müller-Ladner, U., Distler, J. H., Li, M., & Walker, U. A. (2016). Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study. *PLoS One*, *11*(10), e0163894.

Jiang, X., Zhang, F., Li, Y., Ren, J., Xu, D., Cai, R., Yi, Z., Li, C., Liu, T., Zhang, X., Yao, H., Zhu, T., & Mu, R. (2022). Clinical assessment of cardiac impairment favored by two-dimensional speckle tracking echocardiology in patients with systemic sclerosis. *Rheumatology (Oxford)*, *61*(6), 2432-2440.

Kurmann, R. D., Sandhu, A. S., Crowson, C. S., Matteson, E. L., Osborn, T. G., Warrington, K. J., Mankad, R., & Makol, A. (2020). Cardiovascular Risk Factors and Atherosclerotic Cardiovascular Events Among Incident Cases of Systemic Sclerosis: Results From a Population-Based Cohort (1980-2016). *Mayo Clinic Proceedings*, *95*(7), 1369-1378.

Magda, S. L., Gheorghiu, A. M., Mincu, R. I., Ciobanu, A. O., Constantinescu, T., Popa, E. C., Mihai, C., & Vinereanu, D. (2024). Non-Invasive Cardiac and Vascular Monitoring in Systemic Sclerosis: Impact of Therapy on Subclinical Dysfunction. *Medicina (Kaunas)*, *60*(12).

Mavrogeni, S. I., Bratis, K., Karabela, G., Spiliotis, G., Wijk, K., Hautemann, D., Reiber, J. H., Koutsogeorgopoulou, L., Markousis-Mavrogenis, G., Kolovou, G., & Stavropoulos, E. (2015). Cardiovascular Magnetic Resonance Imaging clarifies cardiac pathophysiology in early, asymptomatic diffuse systemic sclerosis. *Inflamm Allergy Drug Targets*, *14*(1), 29-36.

McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Bohm, M., Burri, H., Butler, J., Celutkiene, J., Chioncel, O., Cleland, J. G. F., Coats, A. J. S., Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma, T., Jankowska, E. A., . . . Group, E. S. C. S. D. (2021). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*, *42*(36), 3599-3726.

McLaughlin, V. V., Vachiery, J. L., Oudiz, R. J., Rosenkranz, S., Galie, N., Barbera, J. A., Frost, A. E., Ghofrani, H. A., Peacock, A. J., Simonneau, G., Rubin, L. J., Blair, C., Langley, J., Hoeper, M. M., & Group, A. S. (2019). Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: Results from the AMBITION trial. *Journal of Heart and Lung Transplantation*, *38*(12), 1286-1295.

Nadel, A., Nadel, M., Taborska, N., Stepien, B., Gajdecki, J., Brzezinska, O., Opinc-Rosiak, A., Makowska, J., & Lewandowska-Polak, A. (2024). Heart involvement in patients with systemic sclerosis-what have we learned about it in the last 5 years. *Rheumatology International*, *44*(10), 1823-1836.

Nagueh, S. F., Smiseth, O. A., Appleton, C. P., Byrd, B. F., 3rd, Dokainish, H., Edvardsen, T., Flachskampf, F. A., Gillebert, T. C., Klein, A. L., Lancellotti, P., Marino, P., Oh, J. K., Popescu, B. A., & Waggoner, A. D. (2016). Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*, *29*(4), 277-314.

Nihtyanova, S. I., & Denton, C. P. (2010). Autoantibodies as predictive tools in systemic sclerosis. *Nature Reviews Rheumatology*, *6*(2), 112-116.

Paulus, W. J., & Zile, M. R. (2021). From Systemic Inflammation to Myocardial Fibrosis. *Circulation Research*, *128*(10), 1451-1467.

Pokeerbux, M. R., Giovannelli, J., Dauchet, L., Mouthon, L., Agard, C., Lega, J. C., Allanore, Y., Jego, P., Bienvenu, B., Berthier, S., Mekinian, A., Hachulla, E., & Launay, D. (2019). Survival and prognosis factors in

systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. *Arthritis Research & Therapy*, *21*(1), 86.

Pope, J. E., Denton, C. P., Johnson, S. R., Fernandez-Codina, A., Hudson, M., & Nevskaya, T. (2023). State-of-the-art evidence in the treatment of systemic sclerosis. *Nature Reviews Rheumatology*, *19*(4), 212-226.

Porpáczy, A., Nógrádi, Á., Kehl, D., Strenner, M., Minier, T., Czirják, L., Komócsi, A., & Faludi, R. (2018). Impairment of Left Atrial Mechanics Is an Early Sign of Myocardial Involvement in Systemic Sclerosis. *Journal of Cardiac Failure*, *24*(4), 234-242.

Pugnet, G., Marjanovic, Z., Deligny, C., Boussardon, K., Benzidia, I., Puyade, M., Lansiaux, P., Vandecasteele, E., Smith, V., & Farge, D. (2018). Reproducibility and Utility of the 6-minute Walk Test in Systemic Sclerosis. *Journal of Rheumatology*, *45*(9), 1273-1280.

Rivera, A. S., Sinha, A., Ahmad, F. S., Thorp, E., Wilcox, J. E., Lloyd-Jones, D. M., & Feinstein, M. J. (2021). Long-Term Trajectories of Left Ventricular Ejection Fraction in Patients With Chronic Inflammatory Diseases and Heart Failure: An Analysis of Electronic Health Records. *Circulation. Heart failure*, *14*(8), e008478.

Saketkoo, L. A., Frech, T., Varju, C., Domsic, R., Farrell, J., Gordon, J. K., Mihai, C., Sandorfi, N., Shapiro, L., Poole, J., Volkmann, E. R., Lammi, M., McAnally, K., Alexanderson, H., Pettersson, H., Hant, F., Kuwana, M., Shah, A. A., Smith, V., . . . Steen, V. (2021). A comprehensive framework for navigating patient care in systemic sclerosis: A global response to the need for improving the practice of diagnostic and preventive strategies in SSc. *Best Practice & Research: Clinical Rheumatology*, *35*(3), 101707.

Sarma, S., MacNamara, J. P., Balmain, B. N., Hearon, C. M., Jr., Wakeham, D. J., Tomlinson, A. R., Hynan, L. S., Babb, T. G., & Levine, B. D. (2023). Challenging the Hemodynamic Hypothesis in Heart Failure With Preserved Ejection Fraction: Is Exercise Capacity Limited by Elevated Pulmonary Capillary Wedge Pressure? *Circulation*, *147*(5), 378-387.

Simonneau, G., Montani, D., Celermajer, D. S., Denton, C. P., Gatzoulis, M. A., Krowka, M., Williams, P. G., & Souza, R. (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *European Respiratory Journal*, *53*(1).

Smilowitz, N. R., Prasad, M., Widmer, R. J., Toleva, O., Quesada, O., Sutton, N. R., Lerman, A., Reynolds, H. R., Kesarwani, M., Savage, M. P., Sweeny, J. M., Janaszek, K. B., Barseghian El-Farra, A., Holoshitz, N., Park, K., Albadri, A., Blair, J. A., Jeremias, A., Kearney, K. E., . . . Microvascular, N. (2023). Comprehensive Management of ANOCA, Part 2-Program Development, Treatment, and Research Initiatives: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*, *82*(12), 1264-1279.

Steen, V. D., Follansbee, W. P., Conte, C. G., & Medsger, T. A., Jr. (1996). Thallium perfusion defects predict subsequent cardiac dysfunction in patients with systemic sclerosis. *Arthritis & Rheumatism*, *39*(4), 677-681.

Stronati, G., Guerra, F., Benfaremo, D., Dichiara, C., Paolini, F., Bastianoni, G., Brugiatelli, L., Alfieri, M., Compagnucci, P., Dello Russo, A., & Moroncini, G. (2024). Speckle-tracking global longitudinal strain predicts death and cardiovascular events in patients with systemic sclerosis. *European Heart Journal Open*, *4*(2), oeae023.

Tennøe, A. H., Murbræch, K., Andreassen, J. C., Fretheim, H., Garen, T., Gude, E., Andreassen, A., Aakhus, S., Molberg, Ø., & Hoffmann-Vold, A. M. (2018). Left Ventricular Diastolic Dysfunction Predicts Mortality in Patients With Systemic Sclerosis. *Journal of the American College of Cardiology*, *72*(15), 1804-1813.

Trimarchi, G., Carerj, S., Di Bella, G., Manganaro, R., Pizzino, F., Restelli, D., Pelaggi, G., Lofrumento, F., Licordari, R., Taverna, G., Paradossi, U., de Gregorio, C., Micari, A., Di Giannuario, G., & Zito, C. (2024). Clinical Applications of Myocardial Work in Echocardiography: A Comprehensive Review. *Journal of Cardiovascular Echography*, *34*(3), 99-113.

Trimarchi, G., Pizzino, F., Paradossi, U., Gueli, I. A., Palazzini, M., Gentile, P., Di Spigno, F., Ammirati, E., Garascia, A., Tedeschi, A., & Aschieri, D. (2024).

Charting the Unseen: How Non-Invasive Imaging Could Redefine Cardiovascular Prevention. *Journal of Cardiovascular Development and Disease*, *11*(8).

van den Hoogen, F., Khanna, D., Fransen, J., Johnson, S. R., Baron, M., Tyndall, A., Matucci-Cerinic, M., Naden, R. P., Medsger, T. A., Jr., Carreira, P. E., Riemekasten, G., Clements, P. J., Denton, C. P., Distler, O., Allanore, Y., Furst, D. E., Gabrielli, A., Mayes, M. D., van Laar, J. M., . . . Pope, J. E. (2013). 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Annals of the rheumatic diseases*, *72*(11), 1747-1755.

Verma, S., Petrie, M. C., Borlaug, B. A., Butler, J., Davies, M. J., Kitzman, D. W., Shah, S. J., Ronnback, C., Abildstrom, S. Z., Liisberg, K., Wolf, D., von Lewinski, D., Lelonek, M., Melenovsky, V., Senni, M., Kosiborod, M. N., Committees, S. T.-H. T., & Investigators. (2024). Inflammation in Obesity-Related HFpEF: The STEP-HFpEF Program. *Journal of the American College of Cardiology*, *84*(17), 1646-1662.

Wilcox, T., De Block, C., Schwartzbard, A. Z., & Newman, J. D. (2020). Diabetic Agents, From Metformin to SGLT2 Inhibitors and GLP1 Receptor Agonists: JACC Focus Seminar. *Journal of the American College of Cardiology*, *75*(16), 1956-1974.

Study III

Myocardial Work as a Tool for Detecting Subclinical Cardiac Dysfunction and Its Association with Functional Capacity in Systemic Sclerosis

ABSTRACT

Background/aims: Echocardiography plays a fundamental role as the standard diagnostic tool for characterizing and monitoring heart disease in systemic sclerosis. However, traditional parameters have some limitations. We aim to evaluate the ability of myocardial work to detect subclinical cardiac dysfunction and its association with functional capacity markers in SSc patients.

Methods: We performed an observational, retrospective, cross-sectional, single-center study. Patients with SSc were divided into “without cardiac disease”, “with left cardiac disease” or “with pulmonary arterial hypertension (PAH)” groups. Clinical, echocardiographic, and functional capacity data were analyzed.

Results: Among the 43 SSc patients included, 14% had no cardiac disease, 63% had left-sided cardiac disease, and 23% had PAH. Groups “with left heart disease” and “with PAH” had a higher percentage of patients with abnormal myocardial work values (48.1% and 50%, respectively), despite a much lower percentage of abnormal values of ejection fraction (EF) and global longitudinal strain (GLS). Global work index (GWI) showed a positive correlation with %VO_2 predicted (r=0.38, p=0.026), ventilatory threshold (r=0.43, p=0.04), $PETCO_2$ peak (r=0.45, p=0.006), and a negative correlation with VO/VCO_2 peak (r=-0.40, p=0.016). Global constructive work (GCW) presented a positive correlation with VT (r=0.42, p=0.044), and $PETCO_2$ peak (r=0.46, p=0.006), and a negative correlation with VO/VCO_2 peak (r=-0.44, p=0.007). 6MWD only correlates with EF (r=-0.34, p=0.033).

Conclusions: GWI and GCW stood out as sensitive markers of early myocardial dysfunction in SSc patients with cardiac disease and PAH. Myocardial work indices correlate modestly with exercise performance parameters, highlighting the multifactorial nature of functional limitation in this population.

KEY-WORDS: Systemic sclerosis; myocardial work; EF; GLS; CPET; 6MWD

INTRODUCTION

Cardiac involvement is a common occurrence in systemic sclerosis (SSc), affecting up to 80% of patients (Moysidou et al., 2023). Some of the potential heart-related complications include myocarditis, restrictive cardiomyopathy, myocardial fibrosis, rhythm and conduction disturbances, systolic/diastolic ventricular dysfunction, heart failure (HF), coronary artery disease (CAD), valvular regurgitation, pericardial effusion, and fibrosis (Almeida et al., 2011; Giucă et al., 2022; Meune et al., 2010; Schioppo et al., 2012). Evidence suggests that cardiac complications contribute to 26-29% of SSc mortality cases, serving as independent predictors of fatal outcomes (Fernandez-Codina et al., 2017; Lin et al., 2023; A. J. Tyndall et al., 2010). The diagnosis of myocardial involvement in SSc can be challenging, as it may be intertwined with other potential causes, especially when concurrent cardiovascular risk factors are present.

Echocardiography plays a fundamental role as it is the standard diagnostic tool for characterizing and monitoring heart disease in individuals with SSc (Giucă et al., 2022). The ejection fraction (EF) has traditionally been the most widely used and accepted echocardiographic parameter for assessing left ventricular (LV) systolic function (Klaeboe & Edvardsen, 2019; Thomas & Popović, 2006). It has been used as a selection criterion for almost all the major therapeutic trials of HF and is well integrated into clinical guidelines (Heidenreich et al., 2022; Klaeboe & Edvardsen, 2019). Nonetheless, left ventricular ejection fraction (LVEF) has limitations. Ejection fraction is sensitive to both preload and afterload, consequently, it can be either overestimated or underestimated based on varying loading conditions. Moreover, it is operator-dependent and reliant on image quality, particularly the ability to visualize the endocardial border. (Čelutkienė et al., 2018; Karlsen et al., 2019; Klaeboe & Edvardsen, 2019; Thomas & Popović, 2006).

Global longitudinal strain (GLS) by speckle-tracking echocardiography (STE) is a more sensitive indicator of LV dysfunction compared to LVEF. It has superior prognostic value in various heart diseases with a wide range of myocardial dysfunction (Čelutkienė et al., 2018; Klaeboe & Edvardsen, 2019; Sugimoto et al., 2017). For instance, impaired GLS is a risk marker for cardiac

death and mortality in HF with preserved EF (HFpEF), independent of LVEF, clinical predictors, and diastolic function (Klaeboe & Edvardsen, 2019). GLS is known for its superior intra- and inter-observer reproducibility when compared to LVEF, which makes it less reliant on operator skill and enhances its consistency in clinical assessments (Karlsen et al., 2019; Stanton et al., 2009). However, GLS still has some weaknesses. It is dependent on good imaging quality, vulnerable to heart rate variability and breathing translation, and susceptible to the right placement of the region of interest in the myocardium (Klaeboe & Edvardsen, 2019).

Myocardial work (MW) is a recently validated non-invasive tool that considers myocardial deformation and afterload (through blood pressure) to study LV performance (Manganaro et al., 2020; Marzlin et al., 2023; Russell et al., 2012). MW analysis includes LV pressure, therefore offering additional information beyond what is provided by LVEF and strain measurements (Boe et al., 2019). This is particularly valuable because LVEF and strain assessments are sensitive to loading conditions, and the inclusion of LV pressure data helps to account for these influences, offering a more comprehensive evaluation of myocardial function (Boe et al., 2019). Although it also has its limitations, such as good image quality and blood pressure availability, MW could offer further information for the evaluation of cardiac performance in conditions of subclinical LV dysfunction as well as in HFpEF, emerging as a promising new tool (Manganaro et al., 2020; Roemer et al., 2021). In SSc, MW is in its early stages, and to our knowledge, only two recent studies have described it in these patients. Magda *et al.*, and Zhang *et al*., describe the values of myocardial work in SSc cohorts (versus matched controls), and compared to LVEF and GLS, which are the most traditional/accepted parameters to assess LV function. They both conclude that MW was deteriorated in SSc patients, even when standard echocardiography parameters were normal, reflecting subclinical myocardial dysfunction and suggesting that MW could serve as a screening marker for identifying patients at higher risk of cardiac complications (Magda Ș et al., 2024; Zhang et al., 2025).

The present study aims to investigate left ventricular myocardial work indices in patients with SSc without PAH and to explore their relationship with conventional echocardiographic parameters and functional exercise capacity assessed by CPET and the 6MWT. We hypothesized that myocardial work indices would detect subclinical myocardial dysfunction not captured by LVEF and would show closer associations with exercise capacity than conventional echocardiographic measures, thereby providing novel insights into the mechanisms of exercise intolerance in systemic sclerosis.

METHODS

We performed an exploratory, observational retrospective cross-sectional, single-center study involving 96 consecutive SSc patients evaluated in a PH reference center from April 2017 to April 2023.

Patient population

Subjects were over 18 years of age and fulfilled the ACR/EULAR 2013 Classification Criteria for diagnosis of SSc (van den Hoogen et al., 2013). Taking into account the extent of skin involvement, classification into limited cutaneous and diffuse cutaneous systemic sclerosis, was made according to the LeRoy criteria (LeRoy et al., 1988). Individuals without detectable skin involvement, but with hallmark serological and clinical features were classified with SSc *sine* scleroderma and patients with other connective tissue disease, in addition to SSc, were classified with overlap syndrome (Allanore et al., 2015). Exclusion criteria included more than moderate left valvular stenosis or regurgitation, prosthetic heart valves, or fixed LV outflow tract obstruction. Patients without good-quality images and blood pressure measurements were also excluded.

Pulmonary hypertension (PH) was defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, according to the most recent hemodynamic definition from the 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH (Humbert et al., 2022). Precapillary PH if mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) >2 WU. If patients had mPAP ≤ 20

mmHg, they were considered as not having PH (no PH) (Humbert et al., 2022). Patients were classified with pulmonary arterial hypertension (PAH) if characterized hemodynamically by pre-capillary PH and in the absence of other causes of pre-capillary PH, such as CTEPH and PH associated with lung disease (Humbert et al., 2022).

Clinical data such as age, sex, body mass index (BMI), New York Heart Association (NYHA) functional class, comorbidities, and medication were extracted from medical records. We divided our cohort of SSc patients into 3 groups: the first one “without cardiac disease”, for patients without clinical symptoms and signs of heart failure; the second one “with left heart disease”, for patients with clinical symptoms and/or signs of heart failure, based on stages HF criteria (Heidenreich et al., 2022); and the third one “with pulmonary arterial hypertension”, for patients who presented invasive hemodynamic diagnosis of PAH, as described above.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Unidade Local de Saúde de Santo António (2020.031; 023-DEFI/025-CE; approval date 10 February 2020).

Blood sample collection and Six-minute walking test

All subjects, immediately before the doctor's appointment, underwent venous blood sampling drawn from an antecubital vein. Samples were processed immediately, and N-terminal brain natriuretic peptide (NT-proBNP) and others, were measured on the day of blood sampling using the standard protocol of our hospital laboratory (Roche NT-proBNP assay).

The 6-minute walking distance test (6MWD) was performed in a 30-meter-long corridor under the same environmental conditions. Participants were instructed to walk the maximal distance in 6 minutes. Resting stops were allowed when patients found it necessary. The equation for reference values used is the one proposed by Enright and colleagues (Enright & Sherrill, 1998). Blood pressure was measured before and after the test.

Echocardiography

Echocardiographic image acquisition was performed by a certified cardiologist using a Vivid E95 ultrasound scanner with an M5Sc-D Transducer (2–5 MHz; GE Healthcare, Horten, Norway). Standard 2D images with the patient in a left lateral decubitus position were saved in cine loop digital format, as well as static images of pulsed-wave Doppler, continuous-wave Doppler, and tissue Doppler. All images were analyzed offline by an experienced clinical physiologist and a medical cardiologist, according to current guidelines (Lang et al., 2015; Mitchell et al., 2019; Zoghbi et al., 2017), using EchoPAC Version 201.

Speckle-Tracking Echocardiography and Myocardial Work

Echocardiographic images (apical four-, two- and long axis 2D) were recorded, at a minimum frame rate of 40 frames/s, in a digital raw-data format for posterior analyzes using software (EchoPAC Version 206, GE Healthcare, Horten, Norway) which automatically tracked the myocardial tissue with manual adjustments to region of interest and tracking made when necessary. Global longitudinal strain (GLS) was obtained. Measurements were performed according to the consensus documents of the EACVI/ASE/Industry TaskForce (Badano et al., 2018; Voigt et al., 2015). Myocardial Work (MW) indices were calculated using a combination of 2D speckle-tracking LV strain and non-invasively estimated pressure (by measuring blood pressure at rest), through pressure-strain loops (Manganaro et al., 2019; Roemer et al., 2021). Work was evaluated from the moment the mitral valve closed to the moment it opened again. Global work index (GWI) was obtained as the amount of myocardial work performed by LV during systole. Additionally, additional indices of MW were calculated as follows: global constructive work (GCW, work during shortening in systole plus work during lengthening in isovolumetric ventricular contraction); global wasted work (GWW, work during lengthening is systole plus work during shortening in isovolumetric ventricular contraction); and global work efficiency (GWE, percentage of constructive work over total work). We use the cutoff values for abnormal work indices, reported by Olsen *et al*.: 1576 mmHg% for GMI, 1708 mmHg% for GCW, 159 mmHg% for GWW, and 93% for GWE (Olsen et al., 2022).

Cardiopulmonary exercise test

All patients with clinical indications and no physical limitations underwent a cardiopulmonary exercise test (CPET). CPET was performed on a treadmill (Medisoft, Model 870C) and analyzed through Blue Cherry Software (Geratherm Respiratory GmbH, Bad Kissingen, Germany). CPET parameters were registered every 30 seconds. Exercise protocol was chosen after a brief interview to accurately assess the patient's level of physical activity (Glaab & Taube, 2022; Pritchard et al., 2021). The patients were encouraged to make maximum effort, and test end criteria were respected, as in the case of interruption due to the patient's symptoms. The determination of the 1st ventilatory threshold was made later, at the end of the test.

Hemodynamic assessment

Hemodynamic assessment was performed using a Swan-Ganz catheter by right heart catheterization according to our institution protocol: at rest, with no sedation, through an echo-guided internal jugular vein or brachial vein approach by trained operators. Pulmonary artery, right atrial, and pulmonary capillary wedge pressures (PAWP) were recorded at the end of a quiet respiratory cycle. Cardiac output (CO) was calculated from an average of at least three measurements using the thermodilution method. Pulmonary vascular resistance (PVR) was calculated using the standard formulas (Simonneau et al., 2019).

Statistics

Statistical analyses were conducted using IBM® SPSS® Statistics (IBM, New York, United States), version 28. The Shapiro–Wilk normality test, as well as histograms, were performed to check the Gaussian distribution of the data. Continuous variables are expressed as mean ± standard deviation for normally distributed data or median [range] for nonnormally distributed data. Categorical variables were expressed as number of subjects and proportion [n (%)]. Continuous variables were compared between groups by one-way ANOVA, and

categorical variables were compared using the Pearson 2 test or Fisher exact test, as appropriate. A two-sided p-value < 0.05 was considered significant.

RESULTS

Population characteristics

Out of the 96 patients with SSc that our center monitored, 43 patients made up the cohort that was studied. The remaining 53 patients fulfill at least one exclusion criteria for this study. The patients' characteristics are presented in Table 1. With a median age of 66 (56 – 69) years, this cohort was primarily made up of females (95.3%). The majority of these patients presented clinical symptoms and/or signs of HF (62.79%) and were allocated to the "with left heart disease" group. PAH criteria were met by 23.3% of patients, and the remaining 13.95% did not meet any criteria for either left heart disease or PAH.

Eighty-four percent of patients had limited SSc, the most prevalent subtype of SSc, followed by diffuse SSc (14%) and sine sclerosis (2%); 21% of patients had SSc overlap with another connective tissue disease.

Table 1 Patients' characteristics by groups

	Overall Systemic Sclerosis (*n*=43)	**Without Cardiac Disease** (*n*=6)	**With Left Heart Disease** (*n*=27)	**With Pulmonary Arterial Hypertension** (*n*=10)	***p-value***
Demographic characteristics					
Age (years), median (IQR)	66 (56-69)	57 (29-67)	66 (58-70)	66 (58-74)	0.365
Female, *n* (%)	41 (95)	6 (100)	25 (93)	10 (100)	0.537
Body mass index, Kg/m^2 (sd)	25.3 (5.6)	24.1 (4)	25.8 (6.3)	24.3 (4.4)	0.682
Systemic sclerosis (SSc) subtypes, n (%)					
Limited	36 (84)	4 (67)	22 (82)	10 (100)	0.169
Diffuse	6 (14)	1 (17)	5 (19)	0 (0)	0.436

Sine Scleroderma	1 (2)	1 (17)	0 (0)	0 (0)	0.140
Overlap	9 (21)	1 (17)	8 (30)	0 (0)	0.216
Disease duration of SSc, months (sd)	89.2 (60.1)	79.7 (46.8)	77.1 (59.2)	126.4 (59)	0.077
Comorbidities					
Hypertension [φ], n (%)	10 (23)	0 (0)	7 (6)	3 (2)	0.445
Dyslipidemia, n (%)	16 (37)	1 (17)	11 (41)	4 (40)	0.594
Diabetes mellitus [ǂ], n (%)	4 (9)	0 (0)	3 (11)	1 (10)	1.000
Interstitial lung disease, n (%)	5 (12)	0 (0)	5 (19)	0 (0)	0.291
Venous thromboembolism, n (%)	2 (5)	0 (0)	1 (4)	1 (10)	0.611
Atrial Fibrillation, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Neoplasia, n (%)	3 (7)	0 (0)	2 (7)	1 (10)	1.000
Obstructive sleep apnea, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Asthma, n (%)	1 (2)	0 (0)	1 (4)	0 (0)	1.000
COPD, n (%)	1 (2)	0 (0)	1 (4)	0 (0)	1.000
Laboratory values					
NT-proBNP ≥ 125 pg/mL . n (%)	27 (63)	2 (33)	18 (67)	7 (70)	0.294
NT-proBNP, pg/mL (sd)	372 (558)	90 (79)	313 (385)	692 (909)	0.075
Creatinine, mg/dL (sd)	0.8 (0.3)	0.6 (0.1)	0.8 (0.3)	0.8 (0.3)	0.393
Anti–Scl-70+, n (%)	5 (12)	0 (0)	5 (19)	0 (0)	0.381
Anti-RNAP3+, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Anti-centromere+, n (%)	9 (21)	3 (50)	5 (19)	1 (10)	0.251

[φ] Hypertension = systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg or antihypertensive pharmacotherapy. [ǂ] Diabetes mellitus = insulin or antidiabetic drugs. **Abbreviations**: COPD, chronic obstructive pulmonary disease; NT-proBNP, N-terminal pro B-natriuretic peptide.

Echocardiographic Parameters

Table 2 provides echocardiographic data for this cohort of SSc patients. The mean values of all myocardial indices are within the normal range, with no significant difference across groups in GCI, GCW, GWW, and GWE. However, the group with left heart disease and the group with PAH had a higher percentage of patients with abnormal myocardial work values (48,1% vs. 50%, respectively

– Figure 1). The group without cardiac disease had no abnormal GCW, GWW, and GWE values, but 33.3% had GWI below 1576 mmHg%. Two patients, belonging to the group with left heart disease, presented a mildly reduced EF (47% and 48%). Ejection fraction was the only variable significantly different across groups. Abnormal values of GLS were also found in two patients, but without significant differences between groups. Groups "without cardiac disease" and "with pulmonary arterial hypertension" did not have any patients with abnormal values of LVEF or GLS (Figure 2).

Table 2 Myocardial work indices, left ventricular (LV) global longitudinal strain, and LV ejection fraction of the studied population by groups

	Overall Systemic Sclerosis (*n*=43)	**Without Cardiac Disease** (*n*=6)	**With Left Heart Disease** (*n*=27)	**With PAH** (*n*=10)	***p-value***
Myocardial work					
GWI, mmHg%, median (IQR)	1831 (1633-2147)	1756 (1558.5-2232.2)	1972 (1639-2206)	1734.5 (1407.7-1833.5	0.200
Abnormal GWI, *n* (%)	8 (18.6)	2 (33.3)	3 (11.1)	3 (30.0)	0.218
GCW, mmHg%, median (IQR)	2223 (2000-2596)	2186.5 (1876.7-2611)	2313 (2053-2629)	2064 (1734.7-2306.7)	0.385
Abnormal GCW, *n* (%)	2 (4.7)	0	1 (3.7)	1 (10.0)	0.611
GWW, mmHg%, median (IQR)	131 (91-218)	104.5 (73.2-127)	153 (103-226)	118 (82-185.7)	0.109
Abnormal GWW, *n* (%)	15 (34.9)	0	12 (44.4)	3 (30.0)	0.095
GWE, %, median (IQR)	94 (91-95)	95 (94-95.5)	93 (91-96)	94.5 (91-95.2)	0.345
Abnormal GWE, *n* (%)	14 (32.6)	0	11 (40.7)	3 (30.0)	0.188
Any abnormal myocardial work, *n* (%)	20 (46.5)	2 (33.3)	13 (48.1)	5 (50.0)	0.821
Myocardial work score, median (IQR)*	0 (0-2)	0 (0-1)	0 (0-2)	0.5 (0-2)	0.468
Myocardial work score ≥ 2, *n* (%)	15 (34.9)	0	11 (40.7)	4 (40.0)	0.161
LV GLS and LVEF					

LV GLS (%), median (IQR)	-18.9 (-20,-17.4)	-19.2 (-20.8,-18)	-18.9 (-19.7,-17.4)	-18.8 (-20.8,-16.5)	0.793
Abnormal LV GLS (>-16%), *n* (%)	2 (4.7)	0	2 (7.4)	0	1.000
LVEF (%), median (IQR)	63 (58-66)	58.5 (52.7-62)	64 (60-66)	61 (56.5-65.5)	**0.044**
Reduced LVEF (<50%), *n* (%)	2 (4.7)	0	2 (7.4)	0	1.000

*The myocardial work score is determined by the sum of abnormal myocardial work indices. **Abbreviations:** GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; GLS, global longitudinal strain; LV, left ventricle; LVEF, left ventricle ejection fraction; PAH, pulmonary arterial hypertension.

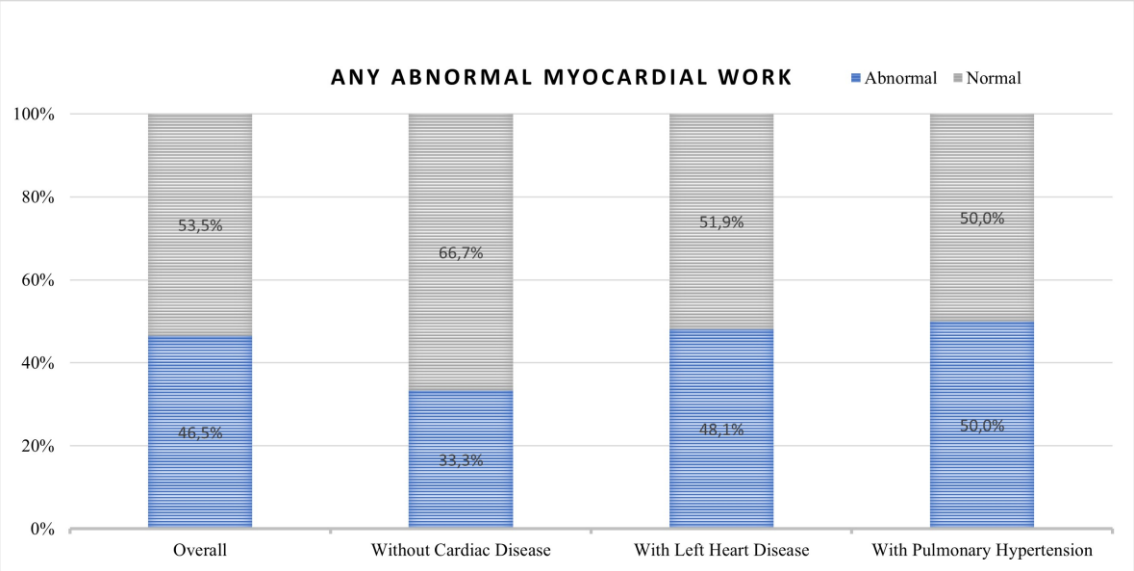

Figure 1 Abnormal Myocardial Work by groups.

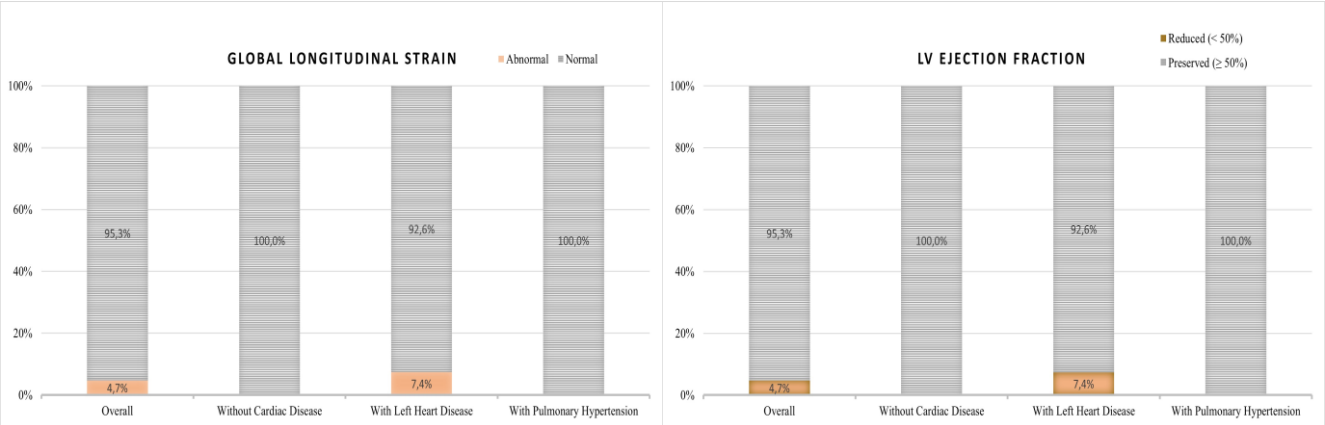

Figure 2 Left ventricular global longitudinal strain (left) and ejection fraction (right), by groups.

Association Between Myocardial Work with Cardiopulmonary Exercise Testing and Six-Minute Walk Distance

Correlations between myocardial work indices and CPET parameters are presented in Table 3. Among indices of MW, the GWI presented a positive correlation with the percentage of VO_2 peak predicted (%VO_2 predicted; r=0.38; p=0.026), with ventilatory threshold (VT; r=0.43; p=0.040), with $PETCO_2$ peak (r=0.45; p=0.006), and was inversely correlated with VE/VCO_2 peak (r=-0.40; p=0.016). GCW did not present any correlation with the %VO_2 predicted but presented a positive correlation with VT (r=0.42; p=0.044), $PETCO_2$ peak (r=0.46; p=0.006), and a negative correlation with VE/VCO_2 peak (r=-0.44; p=0.007). GWW and GWE did not correlate with any CPET variable. GLS and LVEF also did not present correlations with CPET.

Table 3 Correlation CPET parameters with Myocardial Work Indices

	Linear correlation				
	B	**constant**	***p-value***	**r**	**r^2**
%VO_2 peak predicted					
Global work index (GWI)	**0.021**	32.7	**0.026**	**0.38**	0.14
Global constructive work (GCW)	0.017	34.6	0.055	-	-
Global wasted work (GWW)	0.003	72.0	0.941	-	-
Global work efficiency (GWE)	0.557	20.6	0.633	-	-
LV GLS	-1.04	53.0	0.497	-	-
LVEF	-0.144	81.4	0.813	-	-
VT					

Global work index (GWI)	**0.019**	10.2	**0.040**	**0.43**	0.19
Global constructive work (GCW)	**0.018**	6.9	**0.044**	**0.42**	0.18
Global wasted work (GWW)	0.026	43.3	0.530	-	-
Global work efficiency (GWE)	-0.353	80.1	0.753	-	-
LV GLS	1.15	68.8	0.439	-	-
LVEF	-0.407	72.2	0.495	-	-
VE/VCO_2 peak					
Global work index (GWI)	**-0.011**	62.7	**0.016**	**-0.40**	0.16
Global constructive work (GCW)	**-0.011**	67.2	**0.007**	**-0.44**	0.20
Global wasted work (GWW)	-0.017	44.7	0.424	-	-
Global work efficiency (GWE)	0.017	40.5	0.976	-	-
LV GLS	1.18	64.3	0.105	-	-
LVEF	0.041	39.6	0.890	-	-
$PETCO_2$ peak					
Global work index (GWI)	**0.007**	15.4	**0.006**	**0.45**	0.21
Global constructive work (GCW)	**0.007**	14.0	**0.006**	**0.46**	0.21
Global wasted work (GWW)	0.007	28.1	0.567	-	-
Global work efficiency (GWE)	0.071	22.6	0.834	-	-
LV GLS	-0.822	13.7	0.056	-	-
LVEF	0.057	25.7	0.744	-	-

Abbreviations: GLS, global longitudinal strain; LV, left ventricle; LVEF, left ventricle ejection fraction; PET CO_2, end-tidal carbon dioxide partial pressure; VCO_2, carbon dioxide production; VO_2, O_2 consumption; VT, ventilatory threshold.

The distance of the 6MWT had a negative correlation with LVEF (r=-0.34; p=0.033), telling us that for every one-unit decrease in LVEF, the 6MWD is expected to decrease by 6.74 meters. There are no correlations to myocardial work indices or GLS (Table 4).

Table 4 Correlation of 6MWD with Myocardial Work Indices

6MWD	Linear correlation				
	B	**constant**	***p-value***	**r**	**r^2**
Global work index (GWI)	0.014	349.5	0.789	-	-
Global constructive work (GCW)	-0.004	385.4	0.926	-	-
Global wasted work (GWW)	-0.381	432.8	0.111	-	-
Global work efficiency (GWE)	9.22	-484.8	0.140	-	-
LV GLS	6.47	496.7	0.460	-	-
LVEF	**-6.74**	791.3	**0.033**	**-0.34**	0.11

Abbreviations: 6MWD, 6-minute walking distance; GLS, global longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction.

DISCUSSION

The present study investigated left ventricular myocardial work indices in patients with SSc, with a focus on their ability to detect subclinical myocardial dysfunction not captured by conventional echocardiographic parameters and to explore their relationship with functional exercise capacity assessed by CPET and 6MWT. Our findings indicate that myocardial work indices, particularly GWI and GCW, identify a substantial burden of myocardial dysfunction despite preserved LVEF and largely preserved global longitudinal strain. In addition, myocardial work showed modest but significant associations with selected CPET-derived markers of exercise performance and ventilatory efficiency, whereas no such relationships were observed with the 6MWT. Together, these results partially support our hypothesis and suggest that myocardial work provides complementary insights into early myocardial impairment and its contribution to exercise intolerance in SSc.

The lack of significant differences in GWI, GCW, GWW, and GWE across patient groups in this cohort underscores the inherent limitations of using these global myocardial work indices alone to identify subclinical myocardial dysfunction within these subgroups. However, our results also show that in our cohort, there are more patients with abnormal values of GWW and GWE,

compared to abnormal values of LVEF and GLS, especially in the groups with left heart disease and PAH. These findings suggest that GWW and GWE may be more sensitive indicators of cardiac dysfunction in these specific patient populations. The hypothesis that myocardial work might represents a more sensitive marker than LVEF or GLS is further supported by Wang et al., who showed in a cohort of HFrEF patients (n=508) that GWI offers incremental prognostic value beyond conventional echocardiographic parameters (Wang et al., 2021). Similarly, Zhang et al. reported higher GWW and lower GWE (alongside lower GWI and GCW) in SSc patients, even when LVEF and GLS remained unaltered, corroborating our findings (Zhang et al., 2025). Consistent with these observations, Magda and colleagues also found reduced GCW in SSc patients compared to matched controls, even in the absence of abnormalities in standard 2D echocardiographic parameters (Magda Ș et al., 2024). Collectively, these results reinforce the concept that myocardial work alterations reflect subclinical myocardial dysfunction and may serve as an early screening tool for identifying high-risk patients.

The discordance between conventional measures (LVEF and GLS) and the heightened irregularities in myocardial work underscores the limitations of relying solely on traditional echocardiographic parameters in assessing myocardial function, in this particular context of SSc, and potentially in other conditions as well. Our findings also demonstrate that, in this cohort of SSc patients, those presenting left heart disease and PAH, conditions that have been proven to cause increased pressure in the heart and lungs, have more abnormal values of myocardial work, compared to those without any cardiac condition (Heidenreich et al., 2022; Humbert et al., 2022). This added stress may explain why SSc patients, coupled with these conditions, demonstrate more pronounced abnormalities in myocardial work compared to those lacking these comorbidities.

An important finding of this study is the association between myocardial work indices and CPET-derived parameters. Global work index showed positive correlations with predicted peak VO_2, ventilatory threshold, and peak $PETCO_2$, and a negative correlation with VE/VCO_2 at peak exercise. Global constructive work correlated positively with ventilatory threshold and peak $PETCO_2$, and

negatively with VE/VCO_2 at peak exercise. Only a few studies report this kind of correlation between MW and CPET parameters, but none on SSc patients. Of those that are known to us, Tokodi *et al*., using a cohort of elite swimmer athletes, reported a stronger correlation between GWI and VO_2 peak (r=0.527), and also a moderate correlation between GCW and VO_2 peak (r=0.584) (Tokodi et al., 2022); Hedwig and colleagues, in a HFrEF cohort, reported a weak correlation between GWI and GCW with VO_2 peak of r=0.38 and r=0.36, respectively (Hedwig et al., 2021). Notably, these associations were observed with CPET variables but not with 6MWD, reinforcing the superior sensitivity of CPET in detecting early abnormalities in cardiopulmonary reserve. In contrast to CPET, the 6MWD correlated only with LVEF and not with GLS or myocardial work indices. A weak correlation was also shown by Pugnet *et al*., with a correlation coefficient of 0.085 ($p<0.0001$) between 6MWD and LVEF, in a cohort of SSc patients (Pugnet et al., 2018). A stronger correlation was found by Berisha and colleagues, using a cohort of HFrEF patients (r=0.5, p<0,001) (Berisha et al., 2009). Wolsk *et al*., and Adel *et al*., did not find any association between 6MWD and LVEF (Adel et al., 2015; Wolsk et al., 2018). These modest associations between MW indices with cardiopulmonary exercise parameters in SSc patients, suggest that although these measures may capture some aspects of cardiac performance, their relationship with functional capacity is limited and probably influenced by multiple non-cardiac factors.

Our results suggest that myocardial work indices may provide incremental value over conventional echocardiographic parameters for the early detection of cardiac involvement in SSc. By identifying myocardial dysfunction in patients with preserved LVEF and GLS, myocardial work may improve risk stratification and support a more comprehensive cardiovascular assessment. Furthermore, the association between myocardial work and CPET parameters highlights the potential role of myocardial work in elucidating the cardiac contribution to exercise intolerance in SSc, a frequent and clinically challenging symptom. However, whether myocardial work abnormalities translate into adverse outcomes or predict progression to overt HF remains to be determined.

Several limitations should be acknowledged. This was a single-center, retrospective, cross-sectional study, which limits causal inference and generalizability. The first one is the modest sample size. Only 46% of the total sample size has been available for MW analysis (limitation also reported by Manganaro *et al*., where only 31% of the patients meet the requirements for MW analysis (Manganaro et al., 2020)). On top of this, the patients' subgroups, shaped according to the existing conditions, were not balanced in terms of the number of patients, with an "n" relatively small. Second, our study assumes a cross-sectional design, limiting our ability to establish causation, restricting our interpretation of the observed intriguing correlations between myocardial work indices and functional capacity markers. As the third and final point, we acknowledge the absence of a healthy control group for comparative analysis, as well as the subdivision by clinically distinct groups, differentiates our work from studies such as those by Zhang *et al*. and Magda *et al*. (Magda Ș et al., 2024; Zhang et al., 2025). Future studies should aim to conduct larger, multicenter investigations to confirm and expand the present findings in more diverse systemic sclerosis populations. Longitudinal designs with repeated assessments over time, and including a control group, should also be a priority, since they would help to gain a more in-depth understanding of how systemic sclerosis affects myocardial work, and possibly also establish some causal relations with functional capacity correlates.

CONCLUSION

In conclusion, myocardial work indices identify subclinical LV dysfunction in patients with SSc that is not detected by LVEF and is only incompletely captured by conventional deformation measures. The observed associations between myocardial work and CPET-derived parameters highlight the potential value of myocardial work as a complementary tool for understanding the cardiac contribution to exercise intolerance in this complex, multisystem disease. While these findings provide mechanistic insights and support the use of myocardial work in comprehensive cardiovascular assessment, the modest strength of associations underscores the multifactorial nature of functional limitation in

systemic sclerosis. Prospective studies are required to determine the prognostic relevance of myocardial work abnormalities and to clarify their role in clinical decision-making.

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REFERENCES

Adel, W., Shabana, A., Fakhry, H., & Amin, Y. (2015). Predictors of functional capacity in chronic heart failure: echocardiography versus six-minute walk test. *ournal of Cardiology & Current Research*, *2*(4), 00071.

Allanore, Y., Simms, R., Distler, O., Trojanowska, M., Pope, J., Denton, C. P., & Varga, J. (2015). Systemic sclerosis. *Nature Reviews Disease Primers*, *1*, 15002.

Almeida, I., Faria, R., Vita, P., & Vasconcelos, C. (2011). Systemic sclerosis refractory disease: from the skin to the heart. *Autoimmunity Reviews*, *10*(11), 693-701.

Badano, L. P., Kolias, T. J., Muraru, D., Abraham, T. P., Aurigemma, G., Edvardsen, T., D'Hooge, J., Donal, E., Fraser, A. G., Marwick, T., Mertens, L., Popescu, B. A., Sengupta, P. P., Lancellotti, P., Thomas, J. D., & Voigt, J. U. (2018). Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European Heart Journal - Cardiovascular Imaging*, *19*(6), 591-600.

Berisha, V., Bajraktari, G., Dobra, D., Haliti, E., Bajrami, R., & Elezi, S. (2009). Echocardiography and 6-minute walk test in left ventricular systolic dysfunction. *Arquivos Brasileiros de Cardiologia*, *92*(2), 121-134.

Boe, E., Skulstad, H., & Smiseth, O. A. (2019). Myocardial work by echocardiography: a novel method ready for clinical testing. *European Heart Journal - Cardiovascular Imaging*, *20*(1), 18-20.

Čelutkienė, J., Plymen, C. M., Flachskampf, F. A., de Boer, R. A., Grapsa, J., Manka, R., Anderson, L., Garbi, M., Barberis, V., Filardi, P. P., Gargiulo, P., Zamorano, J. L., Lainscak, M., Seferovic, P., Ruschitzka, F., Rosano, G. M. C., & Nihoyannopoulos, P. (2018). Innovative imaging methods in heart failure: a shifting paradigm in cardiac assessment. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure*, *20*(12), 1615-1633.

Enright, P. L., & Sherrill, D. L. (1998). Reference equations for the six-minute walk in healthy adults. *American Journal of Respiratory and Critical Care Medicine*, *158*(5 Pt 1), 1384-1387.

Fernandez-Codina, A., Simeon-Aznar, C. P., Pinal-Fernandez, I., Rodriguez-Palomares, J., Pizzi, M. N., Hidalgo, C. E., Del Castillo, A. G., Prado-Galbarro, F. J., Sarria-Santamera, A., Fonollosa-Pla, V., & Vilardell-Tarres, M. (2017). Cardiac involvement in systemic sclerosis: differences between clinical subsets and influence on survival [Article]. *Rheumatology International*, *37*(1), 75-84.

Giucă, A., Gegenava, T., Mihai, C. M., Jurcuţ, C., Săftoiu, A., Gîrniţă, D. M., Popescu, B. A., Ajmone Marsan, N., & Jurcuț, R. (2022). Sclerodermic Cardiomyopathy-A State-of-the-Art Review. *Diagnostics (Basel)*, *12*(3).

Glaab, T., & Taube, C. (2022). Practical guide to cardiopulmonary exercise testing in adults. *Respiratory Research*, *23*(1), 9.

Hedwig, F., Nemchyna, O., Stein, J., Knosalla, C., Merke, N., Knebel, F., Hagendorff, A., Schoenrath, F., Falk, V., & Knierim, J. (2021). Myocardial Work Assessment for the Prediction of Prognosis in Advanced Heart Failure. *Front Cardiovasc Med*, *8*, 691611.

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., . . . Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *79*(17), 1757-1780.

Humbert, M., Kovacs, G., Hoeper, M. M., Badagliacca, R., Berger, R. M. F., Brida, M., Carlsen, J., Coats, A. J. S., Escribano-Subias, P., Ferrari, P., Ferreira, D. S., Ghofrani, H. A., Giannakoulas, G., Kiely, D. G., Mayer, E., Meszaros, G., Nagavci, B., Olsson, K. M., Pepke-Zaba, J., . . . Rosenkranz, S. (2022). 2022 ESC/ERS Guidelines for the diagnosis and

treatment of pulmonary hypertension. *European Heart Journal*, *43*(38), 3618-3731.

Karlsen, S., Dahlslett, T., Grenne, B., Sjøli, B., Smiseth, O., Edvardsen, T., & Brunvand, H. (2019). Global longitudinal strain is a more reproducible measure of left ventricular function than ejection fraction regardless of echocardiographic training. *Cardiovascular Ultrasound*, *17*(1), 18.

Klaeboe, L. G., & Edvardsen, T. (2019). Echocardiographic assessment of left ventricular systolic function. *Journal of Echocardiography*, *17*(1), 10-16.

Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F. A., Foster, E., Goldstein, S. A., & Kuznetsova, T. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal-Cardiovascular Imaging*, *16*(3), 233-271.

LeRoy, E. C., Black, C., Fleischmajer, R., Jablonska, S., Krieg, T., Medsger, T. A., Jr., Rowell, N., & Wollheim, F. (1988). Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *Journal of Rheumatology*, *15*(2), 202-205.

Lin, C. Y., Chen, H. A., Chang, T. W., Hsu, T. C., & Su, Y. J. (2023). Association of Systemic Sclerosis With Incident Clinically Evident Heart Failure. *Arthritis Care & Research (Hoboken)*, *75*(7), 1452-1461.

Magda Ș, L., Gheorghiu, A. M., Mincu, R. I., Ciobanu, A. O., Constantinescu, T., Popa, E. C., Mihai, C., & Vinereanu, D. (2024). Non-Invasive Cardiac and Vascular Monitoring in Systemic Sclerosis: Impact of Therapy on Subclinical Dysfunction. *Medicina (Kaunas)*, *60*(12).

Manganaro, R., Marchetta, S., Dulgheru, R., Ilardi, F., Sugimoto, T., Robinet, S., Cimino, S., Go, Y. Y., Bernard, A., Kacharava, G., Athanassopoulos, G. D., Barone, D., Baroni, M., Cardim, N., Hagendorff, A., Hristova, K., López-Fernández, T., de la Morena, G., Popescu, B. A., . . . Lancellotti, P. (2019). Echocardiographic reference ranges for normal non-invasive myocardial

work indices: results from the EACVI NORRE study. *European Heart Journal - Cardiovascular Imaging*, *20*(5), 582-590.

Manganaro, R., Marchetta, S., Dulgheru, R., Sugimoto, T., Tsugu, T., Ilardi, F., Cicenia, M., Ancion, A., Postolache, A., Martinez, C., Kacharava, G., Athanassopoulos, G. D., Barone, D., Baroni, M., Cardim, N., Hagendorff, A., Hristova, K., Lopez, T., de la Morena, G., . . . Lancellotti, P. (2020). Correlation between non-invasive myocardial work indices and main parameters of systolic and diastolic function: results from the EACVI NORRE study. *European Heart Journal - Cardiovascular Imaging*, *21*(5), 533-541.

Marzlin, N., Hays, A. G., Peters, M., Kaminski, A., Roemer, S., O'Leary, P., Kroboth, S., Harland, D. R., Khandheria, B. K., Tajik, A. J., & Jain, R. (2023). Myocardial Work in Echocardiography. *Circ Cardiovasc Imaging*, *16*(2), e014419.

Meune, C., Vignaux, O., Kahan, A., & Allanore, Y. (2010). Heart involvement in systemic sclerosis: evolving concept and diagnostic methodologies. *Archives of Cardiovascular Diseases*, *103*(1), 46-52.

Mitchell, C., Rahko, P. S., Blauwet, L. A., Canaday, B., Finstuen, J. A., Foster, M. C., Horton, K., Ogunyankin, K. O., Palma, R. A., & Velazquez, E. J. (2019). Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *Journal of the American Society of Echocardiography*, *32*(1), 1-64.

Moysidou, G. S., Dara, A., Arvanitaki, A., Skalkou, A., Pagkopoulou, E., Daoussis, D., Kitas, G. D., & Dimitroulas, T. (2023). Understanding and managing cardiac involvement in systemic sclerosis. *Expert Review of Clinical Immunology*, *19*(3), 293-304.

Olsen, F. J., Skaarup, K. G., Lassen, M. C. H., Johansen, N. D., Sengeløv, M., Jensen, G. B., Schnohr, P., Marott, J. L., Søgaard, P., Gislason, G., Svendsen, J. H., Møgelvang, R., Aalen, J. M., Remme, E. W., Smiseth, O. A., & Biering-Sørensen, T. (2022). Normal Values for Myocardial Work

Indices Derived From Pressure-Strain Loop Analyses: From the CCHS. *Circulation: Cardiovascular Imaging*, *15*(5), e013712.

Pritchard, A., Burns, P., Correia, J., Jamieson, P., Moxon, P., Purvis, J., Thomas, M., Tighe, H., & Sylvester, K. P. (2021). ARTP statement on cardiopulmonary exercise testing 2021. *BMJ Open Respiratory Research*, *8*(1).

Pugnet, G., Marjanovic, Z., Deligny, C., Boussardon, K., Benzidia, I., Puyade, M., Lansiaux, P., Vandecasteele, E., Smith, V., & Farge, D. (2018). Reproducibility and Utility of the 6-minute Walk Test in Systemic Sclerosis. *Journal of Rheumatology*, *45*(9), 1273-1280.

Roemer, S., Jaglan, A., Santos, D., Umland, M., Jain, R., Tajik, A. J., & Khandheria, B. K. (2021). The Utility of Myocardial Work in Clinical Practice. *J Am Soc Echocardiogr*, *34*(8), 807-818.

Russell, K., Eriksen, M., Aaberge, L., Wilhelmsen, N., Skulstad, H., Remme, E. W., Haugaa, K. H., Opdahl, A., Fjeld, J. G., Gjesdal, O., Edvardsen, T., & Smiseth, O. A. (2012). A novel clinical method for quantification of regional left ventricular pressure-strain loop area: a non-invasive index of myocardial work. *European Heart Journal*, *33*(6), 724-733.

Schioppo, T., Artusi, C., Ciavarella, T., Ingegnoli, F., Murgo, A., Zeni, S., Chighizola, C., & Meroni, P. L. (2012). N-TproBNP as biomarker in systemic sclerosis. *Clin Rev Allergy Immunol*, *43*(3), 292-301.

Schober, P., Boer, C., & Schwarte, L. A. (2018). Correlation Coefficients: Appropriate Use and Interpretation. *Anesthesia & Analgesia*, *126*(5), 1763-1768.

Simonneau, G., Montani, D., Celermajer, D. S., Denton, C. P., Gatzoulis, M. A., Krowka, M., Williams, P. G., & Souza, R. (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *European Respiratory Journal*, *53*(1).

Stanton, T., Leano, R., & Marwick, T. H. (2009). Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circulation: Cardiovascular Imaging*, *2*(5), 356-364.

Sugimoto, T., Dulgheru, R., Bernard, A., Ilardi, F., Contu, L., Addetia, K., Caballero, L., Akhaladze, N., Athanassopoulos, G. D., Barone, D., Baroni, M., Cardim, N., Hagendorff, A., Hristova, K., Lopez, T., de la Morena, G., Popescu, B. A., Moonen, M., Penicka, M., . . . Lancellotti, P. (2017). Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. *European Heart Journal - Cardiovascular Imaging*, *18*(8), 833-840.

Thomas, J. D., & Popović, Z. B. (2006). Assessment of left ventricular function by cardiac ultrasound. *Journal of the American College of Cardiology*, *48*(10), 2012-2025.

Tokodi, M., Oláh, A., Fábián, A., Lakatos, B. K., Hizoh, I., Ruppert, M., Sayour, A. A., Barta, B. A., Kiss, O., Sydó, N., Csulak, E., Ladányi, Z., Merkely, B., Kovács, A., & Radovits, T. (2022). Novel insights into the athlete's heart: is myocardial work the new champion of systolic function? *European Heart Journal - Cardiovascular Imaging*, *23*(2), 188-197.

Tyndall, A. J., Bannert, B., Vonk, M., Airò, P., Cozzi, F., Carreira, P. E., Bancel, D. F., Allanore, Y., Müller-Ladner, U., Distler, O., Iannone, F., Pellerito, R., Pileckyte, M., Miniati, I., Ananieva, L., Gurman, A. B., Damjanov, N., Mueller, A., Valentini, G., . . . Walker, U. A. (2010). Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Annals of the rheumatic diseases*, *69*(10), 1809-1815.

van den Hoogen, F., Khanna, D., Fransen, J., Johnson, S. R., Baron, M., Tyndall, A., Matucci-Cerinic, M., Naden, R. P., Medsger, T. A., Jr., Carreira, P. E., Riemekasten, G., Clements, P. J., Denton, C. P., Distler, O., Allanore, Y., Furst, D. E., Gabrielli, A., Mayes, M. D., van Laar, J. M., . . . Pope, J. E. (2013). 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Annals of the rheumatic diseases*, *72*(11), 1747-1755.

Voigt, J. U., Pedrizzetti, G., Lysyansky, P., Marwick, T. H., Houle, H., Baumann, R., Pedri, S., Ito, Y., Abe, Y., Metz, S., Song, J. H., Hamilton, J., Sengupta,

P. P., Kolias, T. J., d'Hooge, J., Aurigemma, G. P., Thomas, J. D., & Badano, L. P. (2015). Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European Heart Journal - Cardiovascular Imaging*, *16*(1), 1-11.

Wang, C. L., Chan, Y. H., Wu, V. C., Lee, H. F., Hsiao, F. C., & Chu, P. H. (2021). Incremental prognostic value of global myocardial work over ejection fraction and global longitudinal strain in patients with heart failure and reduced ejection fraction. *European Heart Journal - Cardiovascular Imaging*, *22*(3), 348-356.

Wolsk, E., Kaye, D., Borlaug, B. A., Burkhoff, D., Kitzman, D. W., Komtebedde, J., Lam, C. S. P., Ponikowski, P., Shah, S. J., & Gustafsson, F. (2018). Resting and exercise haemodynamics in relation to six-minute walk test in patients with heart failure and preserved ejection fraction. *European Journal of Heart Failure*, *20*(4), 715-722.

Zhang, F., Yu, C., Zhang, J., Zhang, C., He, D., Hu, X., Li, S., Zhu, T., & Jin, W. (2025). Noninvasive left ventricular myocardial work identifies subclinical myocardial dysfunction in patients with systemic sclerosis. *Clin Rheumatol*, *44*(6), 2343-2354.

Zoghbi, W. A., Adams, D., Bonow, R. O., Enriquez-Sarano, M., Foster, E., Grayburn, P. A., Hahn, R. T., Han, Y., Hung, J., Lang, R. M., Little, S. H., Shah, D. J., Shernan, S., Thavendiranathan, P., Thomas, J. D., & Weissman, N. J. (2017). Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *Journal of the American Society of Echocardiography*, *30*(4), 303-371.

CHAPTER IV

General Discussion

The present thesis resulted in three major findings that together provide a comprehensive characterization of cardiopulmonary involvement in SSc. First, data from **Study I** support the diagnostic utility of selected CPET gas exchange parameters for excluding PAH in SSc patients referred for suspected disease. Second, **Study II** demonstrates a high prevalence of both preclinical and symptomatic HF in SSc patients without PAH, with HF stages closely associated with disease severity, advanced age, and cardiovascular risk factor burden. This study also highlights the value of CPET and the 6MWD for functional risk stratification across HF stages. Third, **Study III** shows that myocardial work indices detect a substantial burden of subclinical myocardial dysfunction and display modest associations with exercise capacity, providing complementary insights into the mechanisms of functional limitation in SSc.

Diagnostic utility of selected parameters of CPET to exclude the presence of PAH in SSc patients

Data specifically addressing the diagnostic accuracy of CPET for the early detection or exclusion of PAH in SSc patients remain limited. Only two published studies (Dumitrescu et al., 2017; Santaniello et al., 2020), as far as we are aware, discuss whether CPET can be a trustworthy non-invasive method for improving the diagnostic workup of SSc patients who have been referred for suspected PAH. Our study adds knowledge to this topic, by demonstrating that peak VO_2, peak VCO_2, and VE/VCO_2 slope, have excellent diagnostic accuracy to exclude PAH in SSc patients. In fact, the diagnostic accuracy of the CPET parameters studied was remarkable (AUC above 0.80) and consistent with previous studies. The profound pathophysiological effects of PAH on acute cardiorespiratory response to exercise may be responsible for this. During exertion, the reduced pulmonary vascular reserve limits normal vascular recruitment and distension in response to increased cardiac output, leading to immediate and marked abnormalities in gas exchange due to ventilation–perfusion mismatch and increased right ventricular afterload (Sun et al., 2001). Together, these results support the use of CPET as a valuable non-invasive tool to refine diagnostic

decision-making and potentially reduce unnecessary invasive testing in selected SSc patients.

Prevalence of HF stages in SSc patients without PAH

To the best of our knowledge, this is the first published study to endorse the prevalence of HF stages in a SSc population. Our data revealed a substantial burden of HF, with 38% presenting symptomatic HF (stage C) and 43% showing preclinical disease (stage B). These findings underscore the high prevalence of occult cardiac involvement in SSc and highlight the limitations of symptom-based assessment alone.

Cardiovascular risk factors, including hypertension, diabetes, and obesity, as well as multiorgan involvement and advanced age, were more prevalent among patients with both symptomatic and presymptomatic HF stages. In addition, our results suggest a positive relationship between the extent of multiorgan involvement and HF severity, supporting the concept that systemic disease burden contributes to cardiac dysfunction. These observations are consistent with contemporary HF frameworks emphasizing the interplay between inflammation, comorbidities, and myocardial remodeling (Heidenreich et al., 2022; Paulus & Zile, 2021). Therefore, multiorgan involvement in SSc patients should raise clinical suspicion of cardiovascular complications, including HF.

Echocardiography and NT-proBNP were identified as key diagnostic tools for detecting early cardiac involvement, with abnormal LA volume, E/e′ ratio, and elevated NT-proBNP serving as markers of increased left heart filling pressures. The findings emphasize the importance of regular cardiovascular monitoring, and aggressive management of modifiable risk factors in this population.

Clinical and functional correlates of HF stages in systemic sclerosis

In SSc patients without PAH, HF severity was associated with functional impairment. Lower 6MWT distance, reduced peak VO_2, and higher VE/VCO_2 slope on CPET correlated with HF stages, even in asymptomatic patients,

highlighting their diagnostic value. Unlike functional tests, resting invasive hemodynamics did not differentiate HF stages, underscoring the importance of exercise-based assessments such as 6MWT and CPET in evaluating HFpEF and staging HF in SSc.

These findings underscore the multifactorial cardiovascular involvement in SSc, where both pulmonary vascular disease and primary myocardial dysfunction coexist and contribute to morbidity and mortality. Despite advances in screening and treatment, early recognition of cardiopulmonary complications remains challenging due to the subclinical onset and overlapping manifestations of PAH and left heart disease. The incorporation of functional and hemodynamic assessments, particularly exercise-based tests such as the 6MWD and CPET, has proven essential for a more comprehensive evaluation of disease severity and progression. These modalities not only provide valuable prognostic information but also help refine therapeutic decision-making and monitor response to targeted therapies.

Myocardial work and its ability to detect subclinical cardiac dysfunction in SSc patients

In Study III, global myocardial work indices (GWI, GCW, GWW, and GWE) did not differ significantly between patient groups. Nonetheless, a greater proportion of abnormal GWW and GWE values was observed, particularly among those with left heart disease and PAH. These findings suggest that GWW and GWE may be more sensitive markers of myocardial dysfunction in these subgroups. Our results are consistent with previous studies showing that MW alterations can reveal subclinical myocardial impairment even when traditional echocardiographic parameters such as LVEF and GLS remain normal, as shown by Wang and colleagues (Wang et al., 2021). Zhang et al. reported higher GWW and lower GWE (alongside lower GWI and GCW) in SSc patients, even when LVEF and GLS remained unaltered, corroborating our findings (Zhang et al., 2025), Magda and colleagues also found reduced GCW in SSc patients

compared to matched controls, even in the absence of abnormalities in standard 2D echocardiographic parameters (Magda Ș et al., 2024). This discordance underscores the limitations of relying solely on conventional echocardiographic measures to detect early cardiac involvement in SSc. Nonetheless, we acknowledge the absence of a healthy control group for comparative analysis in our cohort, as well as the subdivision by clinically distinct groups, which differentiates our work from the reported studies and makes a precise comparison of results difficult.

Myocardial work and its association with function capacity markers

Myocardial work indices demonstrated modest associations with functional capacity parameters. Specifically, GWI and GCW correlated moderately with peak $PETCO_2$, ventilatory threshold, and VE/VCO_2 at peak exercise, and only weakly with predicted peak VO_2 . To the best of our knowledge, only a few studies report this kind of correlation, between MW and CPET parameters, and none are in SSc patients. Hedwig and colleagues reported a weak correlation between GWI and GCW with VO_2 peak (r=0.38 and r=0.36, respectively) in a cohort of HFrEF, and a stronger correlation was reported between GWI and GCW with VO_2 peak (r=0.527 and r=584, respectively) in a cohort of elite swimmer athletes (Hedwig et al., 2021; Tokodi et al., 2022). Regarding the 6MWD, our results are corroborated by Pugnet *et al*., who reported a correlation coefficient of 0.085 ($p<0.0001$) between 6MWD and LVEF, in a cohort of SSc patients (Pugnet et al., 2018). With respect to myocardial work indices, our results showed no correlation with the 6MWD test.

Overall, our results show that myocardial work indices, particularly GWI and GCW, show only modest associations with cardiopulmonary exercise parameters in SSc patients, suggesting that although these measures may capture some aspects of cardiac performance, their relationship with functional capacity is limited and probably influenced by multiple non-cardiac factors

REFERENCES

Dumitrescu, D., Nagel, C., Kovacs, G., Bollmann, T., Halank, M., Winkler, J., Hellmich, M., Grünig, E., Olschewski, H., Ewert, R., & Rosenkranz, S. (2017). Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. *Heart*, *103*(10), 774-782.

Hedwig, F., Nemchyna, O., Stein, J., Knosalla, C., Merke, N., Knebel, F., Hagendorff, A., Schoenrath, F., Falk, V., & Knierim, J. (2021). Myocardial Work Assessment for the Prediction of Prognosis in Advanced Heart Failure*. Front Cardiovasc Med*, 8, 691611.

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., . . . Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *79*(17), 1757-1780.

Magda Ș, L., Gheorghiu, A. M., Mincu, R. I., Ciobanu, A. O., Constantinescu, T., Popa, E. C., Mihai, C., & Vinereanu, D. (2024). Non-Invasive Cardiac and Vascular Monitoring in Systemic Sclerosis: Impact of Therapy on Subclinical Dysfunction. *Medicina (Kaunas)*, 60(12).

Paulus, W. J., & Zile, M. R. (2021). From Systemic Inflammation to Myocardial Fibrosis: The Heart Failure With Preserved Ejection Fraction Paradigm Revisited. *Circulation Research*, *128*(10), 1451-1467.

Pugnet, G., Marjanovic, Z., Deligny, C., Boussardon, K., Benzidia, I., Puyade, M., Lansiaux, P., Vandecasteele, E., Smith, V., & Farge, D. (2018). Reproducibility and Utility of the 6-minute Walk Test in Systemic Sclerosis. *Journal of Rheumatology*, 45(9), 1273-1280.

Santaniello, A., Casella, R., Vicenzi, M., Rota, I., Montanelli, G., De Santis, M., Bellocchi, C., Lombardi, F., & Beretta, L. (2020). Cardiopulmonary

exercise testing in a combined screening approach to individuate pulmonary arterial hypertension in systemic sclerosis. *Rheumatology (Oxford)*, *59*(7), 1581-1586.

Schober, P., Boer, C., & Schwarte, L. A. (2018). Correlation Coefficients: Appropriate Use and Interpretation. Anesth Analg, 126(5), 1763-1768

Sun, X. G., Hansen, J. E., Oudiz, R. J., & Wasserman, K. (2001). Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation*, *104*(4), 429-435.

Tokodi, M., Oláh, A., Fábián, A., Lakatos, B. K., Hizoh, I., Ruppert, M., Sayour, A. A., Barta, B. A., Kiss, O., Sydó, N., Csulak, E., Ladányi, Z., Merkely, B., Kovács, A., & Radovits, T. (2022). Novel insights into the athlete's heart: is myocardial work the new champion of systolic function? *European Heart Journal - Cardiovascular Imaging*, 23(2), 188-197.

Zhang, F., Yu, C., Zhang, J., Zhang, C., He, D., Hu, X., Li, S., Zhu, T., & Jin, W. (2025). Noninvasive left ventricular myocardial work identifies subclinical myocardial dysfunction in patients with systemic sclerosis. Clin Rheumatol, 44(6), 2343-2354.

CHAPTER V

Conclusion and Future Directions

CONCLUSIONS

The following key findings can be summarized based on the overall findings of each study that was included in this thesis:

1. CPET offers robust, non-invasive markers for ruling out PAH in patients with SSc. Parameters including Peak VO_2, VE/VCO_2 slope, and peak $PETCO_2$ demonstrate strong discriminative ability, refining early diagnostic pathways and reducing reliance on invasive procedures.
2. SSc patients exhibit a high prevalence of both preclinical and symptomatic heart failure, even in the absence of PAH. Functional assessments, including 6MWD and CPET-derived measures, reveal clinically significant impairment not apparent from resting hemodynamics, emphasizing the limitations of single-modality evaluation.
3. Advanced echocardiographic measures of myocardial work, such as GWW and GWE, detect early myocardial dysfunction beyond conventional echocardiography. These indices correlate modestly with exercise performance, highlighting that functional limitation in SSc arises from multifactorial cardiopulmonary and myocardial contributions.

Overall, these findings underscore the limitations of resting and single-modality assessments. Combining exercise-based functional testing with advanced echocardiographic techniques provides a more nuanced understanding of cardiovascular involvement, linking subclinical pathophysiology with clinically relevant exercise intolerance in SSc.

FUTURE DIRECTIONS

Future research should focus on validating and extending the utility of exercise-based functional assessments in SSc for both PAH screening and HF staging. Larger, multicenter, and longitudinal studies are needed to confirm these observations, establish disease-specific thresholds, and evaluate the prognostic implications of exercise-derived indices over time. Additionally, future studies should investigate how integrating functional testing with imaging modalities, such as echocardiography or exercise RHC, and biomarkers, such as NT-proBNP, could improve early detection, risk stratification, and management of both primary myocardial involvement and secondary cardiac complications in SSc.

APPENDICES

Supplementary Table S1 Clinical characteristics of studied patients

	Total (n=43)	No PAH (n=32)	PAH (n=11)	p-value (No PAH vs. PAH)
SSc subtypes, n				
Limited	37 (88.1%)	27 (84.4%)	11 (100%)	
Diffuse	4 (9.5%)	4 (12.5%)	0 (0%)	
Sine scleroderma	1 (2.4%)	1 (3.1%)	0 (0%)	
Overlap	9 (20.9%)	7 (21.9%)	2 (18.2%)	
Antibodies, n				
ACA	38 (88.4%)	27 (84.4%)	11 (100%)	0.16
Scl-70	2 (4.8%)	2 (6.2%)	0 (0%)	0.42
RNAP3	1 (2.4%)	1 (3.1%)	0 (0%)	0.57
Comorbidities, n				
AHT	17 (39.5%)	11 (34.4%)	6 (54.5%)	0.24
Hypercholesterolemia	21 (48.8%)	13 (40.6%)	8 (72.7%)	0.07
Diabetes	9 (20.9%)	7 (21.9%)	2 (18.2%)	0.80
Interstitial lung disease	1 (2.3%)	1 (3.1%)	0 (0%)	0.55
Therapeutics, n				
Oxygen therapy	1 (2.3%)	0 (0%)	1 (9.1%)	0.08
Primrose oil	12 (27.9%)	10 (31.2%)	2 (18.2%)	0.40
Immunomodulators	9 (20.9%)	8 (25%)	1 (9.1%)	0.26
Calcium channel blockers	24 (55.8)	19 (59.4%)	5 (45.5%)	0.42
Corticosteroids	7 (16.3%)	6 (18.8%)	1 (9.1%)	0.45

Data are presented as mean (standard deviation, sd) or n (%), as appropriate. A p value < 0.05 was considered significant. PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; ACA, anti-centromere antibodies; Scl-70, Autoantibodies against topoisomerase I; RNAP3, RNA polymerase III; AHT, arterial hypertension;

Supplementary Table S2 CPET characteristics between groups

	Total (n=43)	**No PAH (n=32)**	**PAH (n=11)**	**p-value (No PAH vs. PAH)**
Maximal HR, % predicted	84.3 (11.67)	84.81 (13.14)	82.82 (5.78)	0.63
Running time, s	423.72 (190.81)	438.78 (202.7)	379.91 (150.69)	0.38
HRR	4.83 (4.8)	5.48 (4.62)	3 (5.04)	0.14
VO_2 peak, mL/min/Kg	15.28 (4.25)	16.52 (3.93)	11.67 (2.92)	**0.00**
VO_2 max, % predicted	73.05 (19.36)	79.72 (16.41)	53.64 (13.48)	**<0.00**
VCO_2 basal, mL/min/Kg	3.32 (0.78)	3.47 (0.82)	2.9 (0.51)	**0.04**
VCO_2 peak, mL/min/Kg	16.34 (4.88)	17.52 (4.73)	13 (3.74)	**0.01**
O_2 pulse basal, ml/beat	3.14 (0.68)	3.23 (0.73)	2.89 (0.47)	0.16
VE peak, l/min	48.55 (11.68)	48.26 (10.63)	49.36 (14.81)	0.79
VE peak, % predicted	84.98 (24.74)	86.48 (25.35)	80.73 (23.55)	0.51
BF basal, l/min	18.93 (4.46)	18.84 (4.87)	19.18 (3.19)	0.83
BF peak, l/min	37.5 (7.29)	37.58 (7.6)	37.23 (6.65)	0.91
VE/VO_2 basal	33.84 (8.38)	33.76 (9.02)	34.06 (6.62)	0.92
VE/VO_2 peak	46.35 (11.96)	42.8 (9.83)	56.36 (12.13)	**0.00**
PET CO_2 basal, mmHg	27.62 (3.75)	28.35 (3.67)	25.55 (3.27)	**0.03**
SaO_2 peak, %	91.25 (5.88)	92.24 (5.39)	84.33 (5.03)	**0.03**

Data are presented as mean (standard deviation, sd). A p value < 0.05 was considered significant. HR, heart rate; RER, respiratory exchange ratio; HRR, heart rate recovery; VO_2, O_2 consumption; VCO_2, carbon dioxide production; VE, expired ventilation; BF, breathing frequency; PET CO_2, end-tidal carbon dioxide partial pressure; SaO_2, arterial oxygen saturation.