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Valeurs de VE/VCO₂ au seuil ventilatoire et de la VO₂ maximale à l'Exploration fonctionnelle (cardio-) respiratoire d'eXercice (EFX) pour le dépistage de l'hypertension pulmonaire associée à la sclérodermie systémique : revue systématique de la littérature et méta-analyses

Julie Better

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**Valeurs de VE/VCO₂ au seuil ventilatoire et de la VO₂ maximale
à l'Exploration Fonctionnelle (cardio-)respiratoire d'exercice
(EFX) pour le dépistage de l'hypertension pulmonaire
associée à la sclérodémie systémique :
revue systématique de la littérature et méta-analyses**

Thèse présentée et soutenue publiquement

Le 4 octobre 2024

A la Faculté de Médecine de Nice

par :

Mme. Julie BETTER

née le 27 mars 1996 à Colmar

Pour obtenir le Diplôme d'Etat de Docteur en Médecine

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PAGE TITRE**Titre en anglais tel que cela apparait dans la soumission****VE/VCO₂ at ventilatory threshold and peak VO₂ in CPET studies of Patients with PAH-associated Systemic Sclerosis: a systematic review and meta-analyses.****Auteurs et collaborateurs****Julie BETTER**

Department of Internal Medicine, University Hospital of Nice, Nice, France; Côte d'Azur University, France

Sylvie LEROY

Department of Pulmonology, University Hospital of Nice, Nice, France; Institut de Pharmacologie Moléculaire et Cellulaire, Non-Coding Genome & Lung Disorders, CNRS UMR7275, Valbonne, France; FHU OncoAge, Côte d'Azur University, Nice, France

Maarten NINABER

Departments of Pulmonology, Leiden University Medical Center, Leiden, the Netherlands

Mattia BELLAN

Department of Translational Medicine, Università del Piemonte Orientale UPO, Novara, Italy

Georgia TRAKADA

Division of Pulmonology, Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, 11528 Athens, Greece

Bilge KESIKBURUN

Ankara Bilkent City Hospital, Physical Medicine and Rehabilitation Hospital, Ankara, Turkey

Stephan ROSENKRANZ

Clinic III for Internal Medicine (Department of Cardiology, Pulmonology and Intensive Care Medicine); Cologne Cardiovascular Research Center (CCRC), Heart Center at the University Hospital Cologne, Cologne, Germany

Daniel DUMITRESCU

Cologne Cardiovascular Research Center (CCRC), University of Cologne, Cologne, Germany

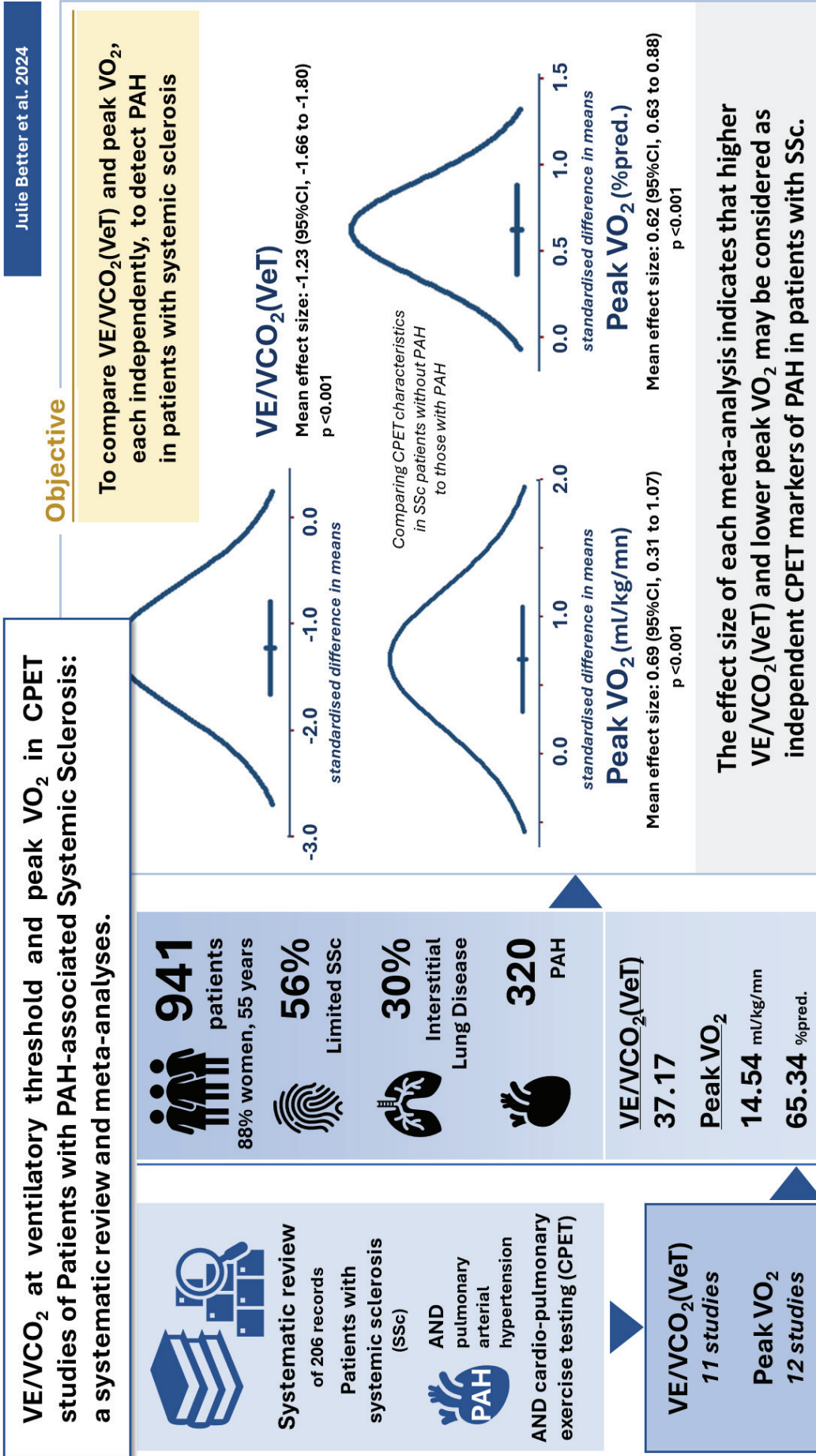
Yanis KOUCHIT

Medical Intensive Care and Resuscitation Department, Cannes General Hospital, Cannes, France; Côte d'Azur University, France

Nihal MARTIS

Department of Internal Medicine, University Hospital of Nice, Nice, France; Côte d'Azur University, France; Institut de Pharmacologie Moléculaire et Cellulaire, Non-Coding Genome & Lung Disorders, CNRS UMR7275, Valbonne, France; Mediterranean Centre for Molecular Medicine, Control of gene expression (COdEX), INSERM U1065, Nice, France

RESUME GRAPHIQUE / GRAPHICAL ABSTRACT



VE/VC₂(VeT), Ventilatory equivalent for carbon dioxide at the ventilatory threshold (VeT)
Peak VO₂, peak volume of oxygen uptake

RESUME (en français)

Contexte :

Les complications cardio-pulmonaires, parmi lesquelles figure l'hypertension artérielle pulmonaire (HTAP), sont les principales causes de morbi-mortalité chez les patients atteints de sclérodémie systémique (ScS). L'Exploration Fonctionnelle (cardio-)respiratoire d'exercice (EFX) a été étudiée pour détecter l'HTAP associée à la ScS.

Objectifs :

Il s'agit d'évaluer la valeur diagnostique de la consommation maximale en oxygène (VO₂max) et de l'équivalent ventilatoire pour le CO₂ au seuil ventilatoire (SV) [VE/VCO₂(SV)], chacun isolément, pour dépister l'HTAP associée à la ScS en comparant des groupes de patients atteints d'HTAP à ceux qui n'en sont pas atteints.

Méthodes :

Une revue systématique de la littérature, sur la période de 1993 à 2024, a été complétée par des méta-analyses conformément aux recommandations PRISMA pour inclure des articles originaux relatifs à l'étude de la ScS et de l'EFX rapportant les valeurs de VE/VCO₂(SV) et de la VO₂max. Un modèle à effets aléatoires a été choisi pour les méta-analyses étudiant, respectivement, le VE/VCO₂(SV) et la VO₂max (indexée sur le poids et en pourcentage de la théorique [%th.]). Une méta-régression n'a été effectuée que pour le VE/VCO₂(SV) avec 3 co-variables : le pourcentage de patients présentant une forme cutanée limitée de ScS, la proportion de patients présentant une pneumopathie interstitielle diffuse et la VO₂max (exprimée en %th.).

Résultats :

Sur les 206 publications recensées, 13 études ont été incluses pour la méta-analyse, totalisant 941 patients. La valeur du VE/VCO₂(SV) était statistiquement plus basse chez les patients ne présentant pas d'HTAP (n= 550) avec une taille de l'effet de -1,233 (IC95%, -1,664 à -0,802 ; p<0,001) (I²= 79,58). Avec une taille de l'effet de 0,686 (IC95%, 0,305 à 1,067 ; p<0,001), des valeurs indexées plus élevées de la VO₂max étaient associées à l'absence d'HTAP (I²= 75,51). De la même manière pour la VO₂max en %th., avec une taille de l'effet de 0,620 (IC95%, 0,363 à 0,876 ; p<0,001), des valeurs plus élevées étaient associées à l'absence d'HTAP (I²= 46,14). La méta-régression (7 études) n'identifiait pas de facteurs de risque statistiquement significatifs.

Conclusion :

Des valeurs plus élevées de VE/VCO₂(SV) et des valeurs plus basses de la VO₂max apparaissent comme des marqueurs indépendants d'HTAP chez les patients atteints de ScS. L'EFX est une procédure sûre qui, en association avec les techniques d'imagerie conventionnelle, peut améliorer, de manière non-invasive, l'estimation du risque d'HTAP.

MOTS-CLEFS

Sclérodémie systémique ; sclérodémie ; EFX ; explorations fonctionnelles cardio-respiratoires d'exercice ; pneumopathie interstitielle diffuse ; hypertension artérielle pulmonaire ; dyspnée

RESUME (en anglais) / abstract

Context

Pulmonary arterial hypertension (PAH) is one of the leading causes of mortality in patients with systemic sclerosis (SSc). Cardiopulmonary exercise testing (CPET) has been studied to detect SSc-associated PAH.

Objectives

To evaluate the diagnostic value of the ventilatory equivalent for CO₂ at ventilatory threshold [VE/VCO₂(VeT)] and peak oxygen uptake (peak VO₂) for SSc-associated PAH obtained by CPET.

Methods

The systematic database search from 1993 to 2024 and meta-analysis were performed according to PRISMA guidelines to include original studies relating to SSc and CPET reporting VE/VCO₂(VeT) and peak VO₂. The random-effects model was chosen for the meta-analyses studying VE/VCO₂(VeT), indexed and predicted percentage (%pred.) peak VO₂, respectively. Meta-regression was only performed for VE/VCO₂(VeT) with covariates defined as the percentage of limited cutaneous disease, percentage of interstitial lung disease, and %pred. of peak VO₂.

Results

Out of 206 studies, 941 SSc patients from 13 studies were included. VE/VCO₂(VeT) (11 studies) was statistically lower in patients without PAH (n= 550) with a mean effect size of -1.233 (95%CI, -1.664 to -0.802; p<0.001) (I²= 79.58). The mean effect size was 0.686 (95%CI, 0.305 to 1.067; p<0.001) favouring higher values of weight-indexed peak VO₂ (11 studies) for patients without SSc-associated PAH (I²= 75.51). Similarly, the mean effect size for %pred. peak VO₂ (12 studies) was 0.620 (95%CI, 0.363 to 0.876; p<0.001) reflecting higher values in patients without PAH (I²= 46.14). Meta-regression analysis of data from 7 studies did not yield significant p-values for the covariates.

Conclusions

The effect size of each meta-analysis indicates that higher VE/VCO₂(VeT) and lower peak VO₂ may be considered as independent CPET markers of PAH in patients with SSc. CPET is a non-invasive and safe procedure for exploring dyspnoea in patients with SSc and, in association with conventional imaging techniques, may provide a reliable assessment of the presence of PAH.

KEY-WORDS

[MeSH terms] *Systemic sclerosis; sclerosis; exercise test; cardiopulmonary exercise testing; interstitial lung disease; pulmonary arterial hypertension; exertional dyspnoea.*

Sigles et abréviations

Version française :

| | | | |
|-------------|--|------------------------|---------------------------------------|
| DVG | Dysfonction ventriculaire gauche | VCO₂ | Volume de dioxyde de carbone expiré |
| EFR | Epreuves Fonctionnelles Respiratoires (statiques) | VO₂ | Volume maximal d'absorption d'oxygène |
| EFX | Epreuve Fonctionnelle (cardio-)respiratoire d'exercice | VP | Vasculopathie pulmonaire |
| HTAP | Hypertension artérielle pulmonaire | | |
| LPM | Limitations périphériques musculo-articulaires | | |
| PID | Pneumopathie Interstitielle Diffuse | | |
| ScS | Sclérodémie systémique | | |
| SV | Seuil ventilatoire | | |
| TM6 | Test de marche de 6 minutes | | |
| VE | Ventilation minute | | |

Version anglaise :

| | | | |
|-----------------------------|---|----------------------------|--|
| ACR | American College of Rheumatology | PAH | Pulmonary arterial hypertension |
| ATS/ACCP | American Thoracic Society/American College | peak VO₂ | Peak respiratory oxygen uptake |
| CPET | Cardiopulmonary exercise testing | PetCO₂ | End-tidal partial pressures for CO ₂ |
| CPK | creatinine phosphokinase | PFT | Pulmonary function tests |
| CT-scan | Computed tomography scan | PML | Peripheral muscular limitation |
| D[a-v]O₂ | Arteriovenous oxygen difference | PRISMA | Preferred Reporting Items for Systematic reviews and Meta-Analyses |
| DLCO | Diffusing capacity of lung for carbon monoxide | RHC | Right heart catheterisation |
| d-SSc | Diffuse cutaneous systemic sclerosis | RVSP | Right ventricular systolic pressure |
| ESC/ERS | European Society of Cardiology / European Respiratory Society | SD | Standard deviation |
| EULAR | European League Against Rheumatism | sPAP | Systolic pulmonary pressure |
| ILD | Interstitial lung disease | SSc | Systemic sclerosis |
| I-SSc | Limited cutaneous systemic sclerosis | SV | Stroke volume |
| LVD | Left ventricular dysfunction | USA | United States of America |
| MCTD | Mixed connective tissue disease | VCO₂ | Volume of exhaled carbon dioxide |
| MET | Metabolic Equivalent of the Task | Vd | Volume of (physiological) dead space |
| mPAP | Mean pulmonary arterial pressure | VE | Minute ventilation |
| n | Number | VE/VCO₂ | Ventilatory equivalent for CO ₂ |
| N | Sample size | VeT | Ventilatory threshold |
| NA | Not available | VO₂ | Volume of oxygen uptake |
| O₂-pulse | Ratio of oxygen uptake to heart rate | Vt | Tidal volume |
| P(Ai-a)O₂ | Alveolar-arterial pressure gradient | ΔPetCO₂ | Change in PetCO ₂ from rest to VeT |
| PaCO₂ | Partial arterial pressure of CO ₂ | | |

INTRODUCTION (en français)

La sclérodémie systémique (ScS) est une connectivite rare, d'étiologie indéterminée, caractérisée par des désordres immunologiques, la présence d'auto-anticorps, une dysfonction du tissu conjonctif ainsi que des lésions vasculaires touchant la microcirculation [1,2]. L'ensemble de ces désordres n'affecte pas uniquement la peau mais aboutit à différentes atteintes d'organes tels que les poumons, le cœur, les reins et le système gastro-intestinal [3]. Ces dysfonctions d'organe apparaissent précocement dans l'histoire de la maladie, notamment durant les cinq premières années d'évolution, entraînant un taux élevé de mortalité spécifique à la maladie [4].

L'amélioration des connaissances sur la maladie et de sa prise en charge a entraîné une évolution des étiologies de la mortalité. La crise rénale sclérodémique est exceptionnelle, plaçant maintenant les complications cardio-pulmonaires en tête des causes de morbi-mortalité des patients sclérodémiques [5]. Plus précisément, la pneumopathie interstitielle diffuse (PID) et/ou l'hypertension artérielle pulmonaire (HTAP) sont les manifestations les plus fréquemment associées à la ScS et sont responsables, respectivement, de 33% et 20% des décès liés à la maladie [6].

L'HTAP est une maladie grave qui affecte la vascularisation pulmonaire précapillaire responsable d'une augmentation des résistances vasculaires pulmonaire entraînant une défaillance de la fonction ventriculaire droite grevant le pronostic avec un taux de mortalité élevé. La prévalence de l'HTAP associée à la ScS varie de 5 à 12% [7]. Son identification précoce est cruciale pour permettre une intervention thérapeutique optimale et améliorer le pronostic des patients. Néanmoins, le diagnostic est difficile et souvent retardé car l'HTAP est initialement pauci- ou asymptomatique.

Les premiers symptômes des complications pulmonaires associées à la ScS sont la dyspnée et l'intolérance à l'exercice [8]. Ces symptômes sont non-spécifiques et multifactoriels, pouvant témoigner de la présence d'une PID et/ou d'une HTAP mais aussi d'une dysfonction ventriculaire gauche (DVG) ou pouvant être le reflet de causes secondaires, notamment musculo-articulaires ou encore neuropsychologiques [9,10]. De plus, les complications pulmonaires associées à la ScS présentent, aux stades initiaux, une évolution insidieuse durant laquelle la vasculopathie pulmonaire n'est pas détectée par les explorations de repos, entraînant un retard de diagnostic préjudiciable aux

patients [11]. C'est pourquoi il paraît intéressant de combiner des méthodes complémentaires comme des explorations à l'effort pour la détecter [12].

L'Exploration Fonctionnelle (cardio-)respiratoire d'exercice (EFX) est un outil non-invasif capable d'apporter des informations supplémentaires par rapport aux examens plus conventionnels [13]. Selon les définitions de l'ATS/ACCP, l'EFX fournit une « évaluation globale de la réponse intégrative à l'exercice des systèmes pulmonaire, cardiovasculaire, hématopoïétique, neuro-psychologique et musculaire » [14]. L'EFX est ainsi utile pour le suivi de maladies respiratoires, comme la bronchopneumopathie chronique obstructive, mais aussi pour l'étude des caractéristiques cardio-respiratoires de la ScS, mais sa complexité n'a donné lieu qu'à un nombre limité d'études sur ce sujet [15]. L'EFX s'inscrit parmi les procédures d'investigation dans la ScS, permettant non-seulement de révéler une vasculopathie pulmonaire non-diagnostiquée par les explorations de repos, mais aussi d'identifier et de classer les mécanismes concurrents des limitations cardio-respiratoires souvent intriquées dans cette maladie [16,17]. L'EFX donne également un aperçu du pronostic et éventuellement des effets des thérapeutiques [18–21].

Les altérations de la consommation d'oxygène au pic de l'effort (VO₂max) et de celle de la ventilation minute (VE) rapportée au volume de dioxyde de carbone expiré (VCO₂) au seuil ventilatoire (SV) [ci-après dénommée VE/VCO₂(SV) ou équivalent ventilatoire pour le CO₂] reflètent l'hypoperfusion des acini bien ventilés chez les patients atteints d'hypertension pulmonaire et semblent être des valeurs discriminantes permettant l'identification de l'HTAP associée à la ScS avec une plus grande sensibilité et spécificité [18,20,22,23]. Les mesures des échanges gazeux pendant l'exercice permettent le dépistage précoce des changements caractéristiques identifiées dans l'HTAP des patients sclérodermiques [24,25].

La question se pose, depuis ces deux dernières décennies, de l'application de l'EFX en tant qu'outil de dépistage précoce de l'HTAP associée à la ScS, et ce d'autant plus qu'il a été démontré qu'une intervention thérapeutique à un stade précoce améliorerait la survie [22,26,27]. Les recommandations actuelles sur la prise en charge de l'HTAP selon l'ESC et l'ERS ont reconnu l'utilité de l'EFX dans la ScS [28]. Le dépistage de l'HTAP par des méthodes plus établies telles que l'échocardiographie est connu pour être sous-optimal et des initiatives telles que l'algorithme DETECT,

fondé sur des données d'une étude transversale internationale, ont tenté de remédier à leurs lacunes et de limiter les cathétérismes cardiaques droits réalisés par excès [23,29]. L'enjeu est de permettre un dépistage précoce de la pathologie permettant une optimisation de la prise en charge en vue d'une amélioration de la survie des patients.

Par le biais d'une revue systématique et commentée de la littérature, l'objectif de ce travail a été l'étude quantitative de paramètres de l'EFX en vue d'établir leur valeur diagnostique pour la détection de l'HTAP associée à la ScS. Des méta-analyses se sont intéressées à l'étude de VE/VCO₂(SV) et VO₂max. L'hypothèse de recherche était d'évaluer la valeur diagnostique de ces deux paramètres EFX, indépendamment, en comparant les patients atteints d'HTAP à ceux qui n'en sont pas atteints.

MANUSCRIT (version anglaise)

INTRODUCTION

Systemic sclerosis (SSc) is rare connective tissue disorder (CTD) with pathophysiological features including fibrosis, endothelial dysfunction, and autoimmunity [2]. Cardiopulmonary disease is the leading cause of mortality in patients with SSc [4,6]. Specifically, interstitial lung disease (ILD) and/or pulmonary arterial hypertension (PAH) are the most frequently associated manifestations complicating this CTD, and are responsible for, respectively, up to 33% and 20% of SSc-related deaths [6,30,31].

Cardiopulmonary exercise-testing (CPET) has been used over the last two decades to study cardio-respiratory features of SSc, but its complexity has yielded limited studies on this topic. As stated by the *American Thoracic Society/American College of Chest Physicians (ATS/ACCP)*, CPET gives a “global assessment of the integrative exercise response involving the pulmonary, cardiovascular, hematopoietic, neuropsychologic, and skeletal muscle systems that is not adequately reflected through the measurement of individual organ system function” [14]. This approach helps clinicians to evaluate primary pulmonary disease but also respiratory limitations due to secondary causes (i.e. broncho-aspiration, muscle impairment...) by identifying and ranking competing mechanisms in complex systemic diseases such as SSc [6,14,17].

Morbimortality due to cardiopulmonary complications that often overlap in SSc, make CPET an investigative procedure of choice in patients presenting with dyspnoea [4,6,17]. CPET is able to identify and classify exercise-limiting disorders, and also gives an insight into prognosis and possibly treatment effectiveness [20]. Understandably, it has been studied for early detection of pulmonary vasculopathy in patients with SSc since therapeutic intervention in early PAH has been shown to improve survival [22–25,27,28,32]. The 2022 *European Society of Cardiology (ESC)* and *European Respiratory Society (ERS)* guidelines on the management of PAH have also recognised the usefulness of CPET in populations at risk, such as those with SSc [28]. Screening for PAH through more established methods such as echocardiography is known to be suboptimal and initiatives such as the evidence-based DETECT algorithm have attempted to address their shortcomings and limit unwarranted right heart catheterisation (RHC) [29].

Previous studies have stated that peak oxygen uptake (peak VO₂) could be an appropriate discriminator of pulmonary vasculopathy in SSc although this parameter was found to be systematically reduced even in patients without pulmonary involvement [21,22,33]. However, studies on ventilatory efficiency in SSc have suggested that the ventilatory equivalent for CO₂ – also defined as the ratio of minute ventilation (VE) to the volume of exhaled carbon dioxide (VCO₂) at the ventilatory threshold (VeT) [hereafter referred to as VE/VCO₂(VeT)] – could bring higher sensitivity and specificity to the identification of PAH [18,20,22,23,34].

The research hypothesis was to evaluate the diagnostic value of two commonly reported CPET parameters, VE/VCO₂(VeT) and peak VO₂, each independently, for detecting SSc-associated PAH.

MATERIALS AND METHODS

Systematic literature review and study selection

A review and analyses were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [35] ([supplementary data, Table S1](#)).

The MEDLINE (via PubMed), Cochrane Library, Web of Science, Clinical trials, medRxiv electronic databases were screened over a period that was arbitrarily set from 1993 to the date of the final search that was conducted on March 10th, 2024. Two authors (JB and YK) searched through each database using a combination of keywords ([supplementary data, Table S2](#)). Only original articles written in English were considered for review. Corresponding authors were contacted by email in the case of missing data or if their article was unavailable. Records were subsequently screened for duplicates prior to applying the exclusion criteria that were defined as: i) the absence of either CPET parameter, ii) the absence of pulmonary vasculopathy within the study population, and iii) the inability to recover relevant missing data from the authors. Studies with 15 patients or less were excluded from the quantitative analysis. Discrepancies were resolved by consensus with the help of a third investigator (NM).

Outcome measures and data extraction

Data were independently extracted from each selected study by two investigators (JB and NM) at the end of the screening process. A study-report form was used to compile the following variables: country, study period, number of patients per cohort, age of patients, sex ratio, disease subtype (limited or diffuse cutaneous form), time since disease onset, number of patients with PAH and/or ILD and finally CPET parameters [i.e. VE/CO₂(VeT) and peak VO₂ (indexed per weight and percent of predicted)]. VE/CO₂(VeT) and peak VO₂ between SSc patients with and without PAH were independently compared in the meta-analyses.

In instances where the VE/VCO₂ nadir method was used, we chose to confound it with VE/VCO₂(VeT), as it is considered to be less subject to variability [36]. Studies were also classified according to their design (i.e. single- or multicentre) and type (i.e. prospective, retrospective, registry cohort studies, case-control studies...). In the case of multiple time-points, only data from the time of documented PAH were retained. Due to the non-interventional aspect of the reports included in the systematic review, our study was not registered with an online database. However, data used in this study can be made available on reasonable request.

Quality assessment

The Newcastle-Ottawa scale for cohort and case-control studies was used ([supplementary data, Table S3](#)) [37]. Quality assessment for each individual study included in the meta-analysis was performed independently by 3 investigators (JB, YK and NM). Studies were categorized according to the overall scoring as “poor”, “fair” or “good”.

Statistical analyses

Continuous variables are expressed as averages with their standard deviations (SD). Sample means and SD and effect sizes of study outcomes were estimated from sample size, median, range and/or interquartile range [38,39]. Categorical variables are expressed as percentages. SD were not estimated for pooled percentages or for pooled averages.

The random-effects model was chosen for the analysis. Standard differences in means are expressed with a 95% confidence interval (95%CI). Statistical testing was two-tailed with an alpha level of 0.05. The Q-test was used to assess heterogeneity, and the I-squared (I²) statistic calculated for each analysis.

Meta-regression was performed for VE/CO₂(VeT) to assess the influence of the following 3 variables: proportion of I-SSc, proportion of ILD, and mean percent of predicted (%pred.) of peak VO₂. Only studies with all the latter 3 covariates were to be included in the meta-regression analysis.

A sensitivity analysis by subgroup according to the quality assessment category was conducted. Similarly, a “remove-one” analysis was also performed for the 3 CPET parameters in order to gauge each study's impact on the combined effect. Publication bias was assessed for analyses of 10 studies or more with the help of a funnel plot. *Comprehensive Meta-Analysis* software (version 4.0, 2022) was employed for the analyses.

RESULTS

Study selection and characteristics

Fifteen studies from the initial 206 references were selected for the qualitative study (**Figure 1**). Study characteristics are featured in **Table 1**. Ten studies had a prospective design and all but two were carried out in Europe. Quality assessment according to the Newcastle-Ottawa scale is illustrated with **Figure 2**. Ultimately, 13 reports were eligible for the quantitative analysis (**Figure 1**) identifying 941 patients overall. Further data were provided by the authors in 6 cases (**Table 1**) [17,18,22,27,40,41].

A descriptive summary of CPET-related studies on SSc-associated PAH is presented in table form (**Table 2**). In these studies, patients were mostly women with a pooled percentage of 88% and had an average age of 55 years. Overall, 433/768 patients (56%) had a limited cutaneous form of the disease, 223 patients (30%) had ILD and another 320 had PAH. When right-heart catheterisation (RHC) was performed, the latter was hemodynamically defined according to 2015 ESC/ERS guidelines [42]. In 5 reports, PAH was suspected on clinical and/or echocardiographic parameters [18,24,25,40,41].

Pooled average values of CPET parameters, in the quantitative analysis, were: 37.17, 14.54 mL/kg/mn

and 65.34 %pred., respectively, for VE/VCO₂(VeT) (11 studies), peak indexed VO₂ expressed (12 studies), peak VO₂ (12 studies).

VE/VCO₂(VeT)

There were 11 studies reporting this parameter in 887 patients (**Figure 3-A**). VE/VCO₂(VeT) was found to be systematically and statistically lower in patients without PAH (n= 550) with a mean effect size of -1.233 (95%CI, -1.664 to -0.802; p<0.001). Pooled average VE/VCO₂(VeT) for patients with PAH was 40.5 (n=300), whereas the pooled average for patients without PAH was 33.84 (n=550). The Q-value was 48.97 with a p-value <0.001 and an I² statistic of 79.58 (supplementary data, Table S4-A).

The meta-regression analysis of the association between the 3 prechosen covariates and the variation of standard differences in mean VE/VCO₂(VeT) throughout 7 studies did not yield significant p-values (**Table 3**).

Though the sensitivity analysis by Newcastle-Ottawa subgroups found that the 2 studies of “poor” quality did not have a statistically significant mean effect size, the overall analysis was not impacted (supplementary data, Table S5-A). “Remove-one” analysis confirmed the reliability of the mean effect size in the meta-analysis (p<0.001) (supplementary data, Figure S1-A). Publication bias was minimal but favoured studies with more patients and greater precision (supplementary data, Figure S2-A).

Indexed peak VO₂

Of the 13 studies reporting peak VO₂, only 11 had VO₂ weight-indexed values. Among these 11 studies, information on VE/VCO₂(VeT) was provided in 10 cases. Eight hundred and eighty-four patients with SSc were included in the analysis (**Figure 3-B**). The mean effect size was 0.686 (95%CI, 0.305 to 1.067; p<0.001) favouring higher values of peak VO₂ for patients without SSc-associated PAH. Pooled average peak VO₂ for patients with PAH was 13.06 mL/kg/mn (n=291), whereas it was 16.02 mL/kg/mn for those without PAH (n=557).

The null hypothesis for common effect size was rejected due to a Q-value of 50.83 with 10 degrees of freedom and a p-value <0.001 (supplementary data, Table S4-B). The I² statistic was 75.51.

The sensitivity subgroup analysis did underscore the “weight” of better-quality studies on the overall

analysis; though this cross-validation did not find dependence on any one study ([supplementary data, Figure S1-B](#)). Visual assessment found an asymmetry in the distribution of studies on the funnel plot suggesting moderate publication bias ([supplementary data, Figure S2-B](#)).

Predicted percentage of peak VO₂

Predicted percentage of peak VO₂ was reported in 12 studies, accounting for a total of 887 patients, among whom 303 were identified as having PAH. The mean effect size was 0.620 (95%CI, 0.363 to 0.876; p<0.001) favouring higher values of peak VO₂ in populations without PAH (i.e. pooled average of 71.55 vs. 61.10 %pred.) (**Figure 3-C**). The Q-value was 20.42, with a p-value of 0.04 and the I² statistic of 46.14 ([supplementary data, Table S4-C](#)).

Sensitivity analyses found minimal impact of articles from the “low-quality” subgroup on the overall results of the meta-analysis. The mean effect size was not impacted by one individual study ([supplementary data, Figure S1-C](#)). Publication bias was minimal ([supplementary data, Figure S2-C](#)).

DISCUSSION

Key messages

The effect size of each meta-analysis indicates that higher VE/VCO₂(VeT) and lower peak VO₂ may be considered as independent CPET markers of PAH in patients with SSc. In other words, these findings not only emphasize the significance of having two relatively reliable physiological markers of scleroderma-associated PAH but also place CPET as an interesting investigative procedure prior to RHC, in situations where more conventional non-invasive approaches tend to be inconclusive. To the best of our knowledge, this is the first systematic review and meta-analysis on the topic.

Screening for PAH in SSc

The 2022 ESC/ERS guidelines recommend that patients with SSc with unexplained breathlessness should benefit from RHC after non-invasive assessments among which CPET features in the diagnostic algorithm for PAH [28]. Risk of PAH could be stratified based on CPET as also suggested by previous recommendations [43]. Patients with VE/VCO₂(VeT) <36 and peak VO₂ ≥15 mL/kg/mn (or >65 %pred.)

were classified as being at low risk (< 5% risk of death at one year) for PAH in the “tree-strata model” [28] ([supplementary data, Table S6](#)).

Whereas cut-off values for peak VO₂ may vary according to study populations, pathological VE/VCO₂(VeT) are conventionally defined by values greater than 36 with “normal” values of less than 30 reflecting a non-existent risk of pulmonary vasculopathy [14]. We chose not only to assess indexed peak VO₂ but also to evaluate VO₂ expressed in %pred. since the latter accounts for differences in age and gender [42,43]. Normal peak VO₂ seems to exclude the risk of SSc-associated PAH [22]. In practice, identifying reliable threshold values for each physiological parameter for predicting PAH is still unresolved, notably because of confounding factors. Furthermore, the predictive values of these thresholds need to be analysed concomitantly, which to date has never been done.

There had been uncertainty as to the clinical and prognostic values of what has been known as “borderline” PAH for values of mean pulmonary arterial pressure (mPAP) between 21 and 24 mmHg. More recent classifications have reappraised the definition of precapillary pulmonary hypertension to include pulmonary vascular resistances ≥ 3 Wood Units and a mPAP >20 mmHg [28,44]. This approach is now also recognised in SSc-related PAH in the light of findings suggesting that previously “borderline” PAH was associated with worse outcome [45–47]. A few authors have stated that CPET can identify scleroderma patients with mPAP of 21 to 24 mmHg and Santaniello et al. have even combined CPET findings with the DETECT score to further refine criteria for RHC referral [17,23].

Rationale for the choice of CPET parameters and their limitations

A bit of pathophysiology

Loss of lung perfusion due to pulmonary vasculopathy translates into a reduction in exhaled CO₂ or VCO₂. In order to eliminate excess metabolic CO₂, there must be an increase in VE. The latter is defined from a physiological perspective by the following equation: $VE = 863 * VCO_2 / PaCO_2 * (1 - Vd/Vt)^{-1}$, where PaCO₂ is the partial arterial pressure of CO₂ and Vd/Vt, the physiologic dead space to tidal volume ratio [48]. Therefore, an elevation in VE/VCO₂ also reflects increased Vd/Vt, and/or hypoxemia and ultimately ventilation to perfusion mismatching (and even possibly hyperstimulation of lung receptors) [14]. There is also, to a lesser extent than in PAH, a mismatch in ventilation-perfusion of the

lung in ILD or during left ventricular dysfunction (LVD) leading to increase of VE/VCO₂(VeT). Previous authors have associated the study of end-tidal partial pressures for CO₂ (PetCO₂) [24,25]. However, the latter is underestimated in hyperventilating patients [49].

VO₂ equates to the rate of oxygen transport and is estimated with the Fick equation: $VO_2 = (\text{heart rate}) * SV * D[a-v]O_2$; where SV is the stroke volume and D[a-v]O₂ the arteriovenous oxygen difference [14]. Peak VO₂ is a general marker of maximal exercise capacity and is influenced by numerous factors including the accuracy of its estimation. “Normal” or expected peak VO₂ is therefore a good discriminator for the exclusion of PAH but does not alleviate the need to assess all available CPET parameters [50].

Pitfalls associated with CPET interpretation

As illustrated by this review, patients with SSc have limited exercise capacity (**Table 2**). Most, if not all, of the studies presented in this review describe a reduced maximal exercise oxygen consumption. At peak exercise, this equates roughly to an average 4.2 MET or metabolic equivalent of the task. Patients with SSc have a significantly reduced peak VO₂ compared to healthy subjects, regardless of the extent of skin involvement and SSc phenotype [21,33,40,51]. In other words, these patients are unable to sustain vigorous activities and this would seemingly translate into limitations of daily physical activity especially in scleroderma patients with lung involvement and/or PAH [52,53]. These data also suggest that, even without pulmonary involvement, patients have reduced aerobic capacity [33]. This only highlights why – by integrating metabolic, ventilatory, cardiovascular parameters, and even gas exchange analysis, a multimodal approach to CPET is preferred to a more conventional dichotomous decision-making approach [17,50] (supplementary data, Figure S3). Therefore, one might reasonably argue that VE/VCO₂(VeT) indiscriminately reflects pulmonary vasculopathy regardless of its origin (i.e. primitive PAH or ILD or even overlapping left heart failure) if aspects such as underlying ILD or echocardiographic assessment are not established [14,17].

Differential diagnoses to consider

ILD is a common confounder for dyspnoea and may overlap with PAH in patients with SSc [54]. The peak oxygen alveolar–arterial pressure gradient or P(Ai-a)O₂ may constitute an essential and even an early marker for SSc-associated ILD, but needs to be interpreted in relation to Vd/Vt (supplementary

data, Figure S3) and, with an understanding of the clinical context and, of course, CT-scan findings [17]. Arterial blood gasses at peak exercise to estimate P(Ai-a)O₂ were performed in only 4 studies [16,17,55,56].

Circulatory impairment has, for some time, been described in scleroderma patients – and also translates into exercise impairment [57]. More recent findings show the extent of peripheral muscle limitation in SSc as suspected by impaired oxygen extraction or utilisation [17]. Some patients with SSc are known to present with myositis or elevated creatinine phosphokinase (CPK) levels [58,59]. However, such patients are uncommon in CPET studies (such as those herein reviewed). It is hypothesized that peripheral muscle limitation, though partly explained by a state of physical deconditioning (as in patients with chronic diseases), may also reflect subclinical vasculopathy and/or fibrosis [60,61]. Vascular involvement is more common in scleroderma-related muscle disease than in idiopathic inflammatory myositis [61]. Histopathological analyses of muscle biopsies are thus needed to address this issue. The early identification of muscle involvement, especially in patients presenting with weakness and normal CPK levels, could lead to changes in patient management since fibrosing myopathy seems to be associated with worse prognosis and cardiac death [62].

CPET-assisted decision-making for RHC referral

Expert consensus for performing right-heart catheterisation has been: signs of right heart failure and/or worsening dyspnoea in scleroderma patients, estimated echocardiographic systolic pulmonary arterial pressure (sPAP) ≥ 45 mmHg, and diffusing capacity of lung for carbon monoxide (DLCO) < 50 %pred. in patients without pulmonary fibrosis or other explanation [63].

There are still lacking data to promote associating CPET findings with echocardiography and DLCO measurements. Echocardiography with peak velocity of tricuspid regurgitation measurements ≥ 3.0 m/s in patients presenting with dyspnoea has shown to provide adequate sensitivity for identifying moderate PAH [64]. Of interest, however, 50% of diagnoses of PAH at rest were missed in the DETECT study according to Coghlan et al. [29,47]. At the same time, early detection of PAH should avoid the caveat of excessive referral to RHC as it was also the case in the DETECT study with a 65% rate of unnecessary RHC (albeit with 2015 ESC/ERS criteria) [29]. Markers such as elevated N-terminal

pro-brain natriuretic peptide and low DLCO do not discriminate between PAH, extensive lung disease and/or associated LVD.

Associating the VE/VCO₂(VeT) to the DETECT algorithm has been found to improve specificity for the diagnosis of PAH to a median of 0.778 (interquartile range [IQR], 0.714; 0.846) with positive and negative predictive median values, respectively, of 0.636 (IQR, 0.556; 0.750) and 1.0 (IQR, 1.0;1.0) [23]. In daily practice, CPET interpretation is not restricted to a single ventilatory parameter and integrates features such as a decreasing Δ PetCO₂ (or changes in PetCO₂ from rest to VeT), subnormal oxygen-pulse and elevated P(Ai-a)O₂ in defining pulmonary vascular disease.

CPET needs not be performed when DETECT criteria are positive after step 2, with volume of tricuspid regurgitation \geq 3.0 m/s (or sPAP >45 mmHg) and an absence of interstitial lung involvement, since RHC is systematically recommended in such circumstances [63]. It is when such criteria are incomplete, that CPET may sift between competing mechanisms of dyspnoea or simply an increase in ventilation [17,25,56].

Limits of the meta-analysis

A major limit is the extent of discrepancies, between studies, in defining scleroderma-associated PAH. For instance, in 5 studies, PAH was not diagnosed by RHC but defined through clinical context and echocardiographic assessment [18,24,25,40,41]. It is also important to highlight that most of the patients were symptomatic and that treatment groups were not always specified. Furthermore, overlap of pulmonary vasculopathy in the case of ILD was difficult to assess and meta-regression analysis could not be performed using ILD as a covariate due to the limited number of studies with a complete dataset of the variables of interest. Moreover, most studies included in the meta-analyses did not have sufficient data to evaluate potential associations with parameters such as left heart failure, time from disease onset, and/or SSc-defining autoantibodies. Heterogeneity was significant throughout the analyses – but is expected when there are such variations in sample sizes and disparate patient populations and methodology between studies. However, despite these drawbacks, sensitivity analysis and cross-validation seemed to confirm the robustness of our findings.

CONCLUSION

This systematic review and meta-analysis on VE/VCO₂(VeT) and peak VO₂ during CPET in patients with SSc provided a comprehensive overview of parameters that can be used for detecting PAH in clinical practice. CPET is a non-invasive and safe procedure for exploring dyspnoea in scleroderma patients and, in association with conventional imaging techniques, can provide a reliable assessment of the risk of PAH.

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Competing interest

The authors have no competing interests to declare.

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TABLEAUX ET FIGURES / TABLES AND FIGURES**Table 1. Study and patient characteristics**

| Study | Country | Quality | Study period | Study type | N | %fem. | Time since onset, y ±SD | Age, y ±SD | I-SSc, n | PAH, n | ILD, n | Study outcome |
|---------------------------------------|-------------|---------|--------------|---------------|-----------------|-------|-------------------------|------------|----------|--------|--------|---------------|
| Bellan et al. 2021 [27] | Italy | +++* | 2016 to 2019 | retrospective | 90 | 90 | 6.0 ±6.8 | 60.2 ±12.6 | 64 | 6 | 84 | PAH |
| Bournia et al. 2021 [18] | Greece | +* | 2006 to 2010 | prospective | 69 [†] | 90 | 6.67 ±5.83 | 53.3 ±11.2 | 24 | 2 | NA | Survival |
| Boutou et al. 2016 [24] | Greece | ++ | 2008 to 2013 | retrospective | 78 | 89.7 | NA | 53.7 ±13.7 | 40 | 25 | 8 | Overall |
| Dumitrescu et al. 2010 [25] | Germany | ++ | NA | prospective | 28 | 82.1 | NA | 48.9 ±10.5 | 21 | 11 | 13 | PAH |
| Dumitrescu et al. 2017 [22] | Germany | +++* | NA | prospective | 173 | 86 | 7.04 ±7.4 | 61 ±11 | NA | 48 | NA | PAH |
| Ewert et al. 2019 [20] | Germany | ++ | 2006 to 2016 | retrospective | 210 | 80.9 | 4.67 ±5.97 | 61.2 ±3.7 | 112 | 38 | 74 | Survival |
| Kesikburun et al. 2019 [40] | Turkey | +* | NA | prospective | 25 | 92 | 4.87 ±4.69 | 43.7 ±13.2 | 17 | 6 | 6 | Overall |
| Kovacs et al. 2009 [45] | Austria | + | NA | prospective | 29 | 89.6 | 6.0 ±6.0 | 57 ±11 | 7 | 14 | 0 | PAH |
| Kovacs et al. 2017 [#] [32] | Austria | + | NA | prospective | 58 | 89.7 | 3.5 ±1.3 | 51.3 ±3.1 | 44 | 2 | 0 | PAH |
| Martis et al. 2018 [17] | France | ++* | 2009 to 2015 | retrospective | 27 | 88.9 | NA | 58.7 ±11.4 | 22 | 15 | 16 | Overall |
| Morelli et al. 2000 [65] | Italy | ++ | NA | prospective | 18 | 100 | 11.8 ±8.4 | 48.6 ±12.5 | 9 | 7 | 0 | PAH |
| Ninaber et al. 2014 [41] | Netherlands | +++* | NA | prospective | 121 | 79.3 | NA | 56.0 ±14.4 | 63 | 23 | NA | PAH |
| Santaniello et al. 2019 [23] | Italy | +++ | 2017 to 2019 | prospective | 54 | 96 | 14.1 ±7.1 | 63.4 ±12.1 | 44 | 17 | 7 | PAH |
| Sudduth et al. 1993 [#] [57] | USA | + | NA | prospective | 15 | 100 | 3.7 ±0.8 | 42.3 ±3.1 | 4 | 4 | 8 | Overall |
| Walkey et al. 2010 [56] | USA | + | 2003 to 2008 | retrospective | 19 | 73.7 | NA | 51.3 ±13.5 | 10 | 3 | 15 | PAH |

Abbreviations: I-SSc, limited cutaneous systemic sclerosis; N, sample size; NA, not available; PAH, pulmonary arterial hypertension; SD, standard deviation; "Time since onset", refers to mean time since onset of the disease; USA, United States of America; y, years; %fem., percentage of female patients; *raw data provided by the authors of the study; [†], additional patients provided; [#], studies not included in the meta-analysis. +/++/+++ rating of methodological quality from less (+) to best (++++) quality.

Table 2. Synopsis of CPET-related studies on SSc-associated PAH.

| Study, reference | Trial design | N | SSc, n | Key messages | Comments | CPET parameters to consider |
|-----------------------------|--------------------------------|---------|------------------------|---|--|--|
| Bellan et al. 2021 [27] | Retrospective, Single-center | 90 | NA | The use of composite CPET measures in association with the DETECT algorithm may improve diagnostic performance for PAH, and therefore reduce unnecessary RHC. | 6 patients with contraindications for RHC, were diagnosed PAH with echocardiography. CPET is more generally able to detect cardiopulmonary involvement. | Thresholds indicating PAH: VO ₂ [peak] ≤ 14.1 mL/kg/mn VE/VCO ₂ [VeT] > 33.96 Basal PetCO ₂ ≤ 27.2 mmHg |
| Bournia et al. 2021 [18] | Prospective, Single-center | 58 | I-SSc: 24 d-SSc: 34 | Lower baseline VO ₂ max in SSc patients without PAH (at baseline) is a prognostic factor to predict pulmonary function deterioration and death. | Median follow-up time was 9.79 (± 2.78) years. The 10-year survival rate was 88%. Male gender and older age at baseline were also associated with worse prognosis. | VO ₂ [peak] ≤ 14.3 mL/kg/mn predicts mortality. Peak VO ₂ ≤ 13 mL/kg/mn predicts ILD progression. |
| Boutou et al. 2016 [24] | Retrospective, Single-centre | 78 | I-SSc: 40 d-SSc: 38 | The combined evaluation of CPET patterns with baseline measurements could discriminate the causes of exercise limitation among SSc patients, especially for PV and LVD. | RHC was not performed | VE/VCO ₂ [VeT] with decreasing ΔPetCO ₂ was suggestive of PV. |
| Dumitrescu et al. 2010 [25] | Prospective Single-centre | 28 (30) | I-SSc: 21 d-SSc: 7 | LVD and/or PV were common CPET findings in SSc patients. CPET may enable early detection of LVD and/or PV, as well as differentiating between these disorders. | Normal exercise capacity or not limited by heart or lungs assimilated. RHC not performed. Vd/Vt[peak] not measured. 13 patients with ILD on CT-scan. | Peak O ₂ -pulse lower in LVD and PAH. VE/VCO ₂ [VeT] with low PetCO ₂ [VeT] were suggestive of PV (ventilation perfusion mismatch). PetCO ₂ tended to decrease in PV and increase in LVD during CPET. |
| Dumitrescu et al. 2017 [22] | Prospective, Multicentre (n=6) | 173 | NA | CPET is feasible in SSc and has a high diagnostic accuracy. CPET – when associated with other diagnostic tools – may be an effective screening tool for PAH, and thus beneficial in reducing unwarranted RHC. | RHC performed simultaneously with CPET. Patients with known left systolic heart failure were excluded from the study. CT-scans were not part of the study therefore the implication of ILD was not discussed (but there no evidence of restrictive lung disease on LFT). | VO ₂ [peak] and VE/VCO ₂ [VeT] best identified PV. VO ₂ [peak] >18.7 mL/kg/mn reliably excluded PAH. VE/VCO ₂ [VeT] >45.4 was strongly predictive of PAH. |

| Study, reference | Trial design | N | SSc, n | Key messages | Comments | CPET parameters to consider |
|-----------------------------|----------------------------|---------|-------------------------------------|--|---|--|
| Ewert et al. 2019 [20] | Retrospective, Multicentre | 210 | I-SSc: 122 d-SSc: 88 | VO ₂ [peak] <15.6 mL/kg/mn or <64.5 %pred. and VE/VCO ₂ -slope >35 are associated with worse prognosis in SSc patients. 5-year survival was 93.8% and 10-year survival was 86.9%. | Median follow-up of 7.7 years. No prognostic differences in CPET parameters in subgroup analyses of ILD/non-ILD and RHC/non-RHC. | VO ₂ [peak] <15.6 mL/kg/mn. VO ₂ [peak] <64.5 %pred. VE/VCO ₂ -slope >35. |
| Kesikburun et al. 2019 [40] | Prospective, Single-centre | 27 | I-SSc: 19 d-SSc: 8 | Patients with SSc have a lower aerobic capacity compared to healthy individuals. CPET is useful to detect exercise intolerance and provide information on the mechanism of exercise limitation in SSc. | CPET parameters were compared to those of matched healthy subjects (n=23). | Lower VE[peak]. Lower O ₂ -pulse. Higher Vd/Vt[rest] and Vd/Vt[peak]. |
| Kovacs et al. 2009 [45] | Prospective, Single-centre | 29 | I-SSc: 7 d-SSc: 15 overlap: 7 | Decreased exercise capacity is associated with borderline elevation of mPAP at rest and during exercise. Decreased exercise capacity may indicate early PV in SSc. | RHC performed simultaneously with CPET. Inclusion criteria: increased sPAP > 40 mmHg during exercise and/or VO ₂ [peak] < 75 %pred. on CPET. Exclusion of patients with significant heart disease or ILD. | VO ₂ [rest] lower in patients with mPAP > 17 mmHg. |
| Kovacs et al. 2017 [32] | Prospective, Single-centre | 58 (99) | I-SSc: 44 d-SSc: 9 MCTD: 5 | Patients without PAH develop a mild but significant deterioration of pulmonary exercise haemodynamics and exercise capacity over a 4-year period. | RHC performed simultaneously with CPET. Longitudinal cohort study with a mean time interval between 2 CPET of 3.9 ±0.9 years, identifying 3/58 patients with RHC-confirmed PAH. Other causes of decrease in VO ₂ [peak] not considered. Patients had median DLCO values > 77 %pred. 16 patients received bosentan. | Decrease of VO ₂ [peak] over time. |

| Study, reference | Trial design | N | SSc, n | Key messages | Comments | CPET parameters to consider |
|------------------------------|----------------------------------|----------|------------------------|--|---|---|
| Martis et al. 2018 [17] | Retrospective, Multicentre (n=2) | 27 | I-SSc: 22 d-SSc: 5 | CPET is useful for the characterisation of multifactorial exercise limitation in patients with SSc and in identifying SSc-related complications such as ILD and PV. PML is probably underestimated in patients with SSc. Long-term follow-up with serial CPET might identify early pulmonary or vascular impairment. | Authors acknowledge the overlapping of CPET diagnoses. CPET identified 90% of patients with resting mPAP \geq 21 mmHg measured by RHC. | P(Ai-a)O ₂ identifies subjects with ILD. Vd/Vt increases faster in PAH than in ILD. Lower VeT and VO ₂ [peak] suggestive of circulatory impairment. VE/CO ₂ [VeT] and Δ PetCO ₂ not sufficiently accurate in overlapping ILD, PAH and LVD. |
| Morelli et al. 2000 [65] | Prospective, Single-centre | 18 | I-SSc: 9 d-SSc: 9 | Patients with SSc are affected by exercise intolerance. Impairment of exercise performance is associated with PAH. VO ₂ [peak], VO ₂ [VeT] and O ₂ -pulse are reduced in patients "with PAH". | Patients with ILD or restrictive lung disease were excluded from the study. RHC was not performed to diagnose PAH. Physical deconditioning is not considered. | Decreased VO ₂ [peak], and VO ₂ [VeT]. |
| Ninaber et al. 2014 [41] | Prospective, Single-centre | 121 | I-SSc: 63 d-SSc: 58 | O ₂ -pulse breakpoint analysis is capable of detecting abnormal cardiopulmonary vascular responses to exercise. Such patients are at risk of developing PAH. | Comparison of O ₂ -pulse slope to that of a historical cohort [45]. | |
| Santaniello et al. 2019 [23] | Prospective, Multicentre | 54 (314) | I-SSc: 44 d-SSc: 10 | The VE/VO ₂ slope had the best performance to predict PAH. Sequential performance of CPET after a positive DETECT score, reduces the number of referrals to RHC. | Screening with the DETECT algorithm and referral to RHC if positive score. Patients with DLCO <60 %pred. and >3 years since first non-Raynaud sign onset | VE/VO ₂ slope \geq 39 (threshold indicating PAH). |
| Sudduth et al. 1993 [57] | Prospective, Single-centre | 15 | I-SSc: 4 d-SSc: 11 | Circulatory impairment to exercise is common in SSc patients with exercise intolerance. Restrictive lung disease does not limit exercise tolerance in patients capable of maximal effort. | Ventilatory threshold (VeT) correlated with DLCO. VO ₂ [VeT]/VO ₂ [peak predicted] < 40%. | Low peak VO ₂ /HR (O ₂ -pulse). Low VO ₂ [VeT]. |

| Study, reference | Trial design | N | SSc, n | Key messages | Comments | CPET parameters to consider |
|-------------------------|------------------------------|----|-------------------------------------|--|--|--|
| Walkey et al. 2010 [56] | Retrospective, Single-centre | 19 | I-SSc: 10 d-SSc: 5 overlap: 1 | CPET/RHC in SSc is useful in discriminating between the multifactorial aetiologies of unexplained dyspnoea on exertion. A high prevalence of PV and LVD (diastolic) identified in previously undetected cases explored by resting echocardiography. | RHC performed simultaneously with CPET. Major therapeutic changes occurred in 11/19 cases. The authors discuss the limited utility of pre-constructed diagnostic algorithms. | Elevated VE/CO ₂ [VeT] may suggest altered chemosensitivity in SSc. P(Ai-a)O ₂ was able to discriminate between PV and LVD. |

Abbreviations: %pred., percentage of predicted value; CPET, cardiopulmonary exercise testing; DLCO, diffusing capacity of lung for carbon monoxide; d-SSc, diffuse cutaneous systemic sclerosis; ILD, interstitial lung disease; LVD, left ventricular dysfunction; MCTD, mixed connective tissue disease; mPAP, mean pulmonary arterial pressure; n, number; N, sample size; NA, not available; O₂-pulse, ratio of oxygen uptake to heart rate; P(Ai-a)O₂, alveolar-arterial gradient; PAH, pulmonary arterial hypertension; PetCO₂, end-tidal partial pressures for CO₂; PFT, pulmonary function test; PML, peripheral muscular limitation; PPV, predictive positive value; RHC, right heart catheterisation; VCO₂, volume of exhaled carbon dioxide; Vd/Vt, the ratio of physiological dead space to tidal volume; VE, minute ventilation; VE/VCO₂-slope, slope of the relation between ventilation and carbon dioxide output; VeT, ventilatory threshold; VO₂, volume of oxygen uptake; ΔPetCO₂, change in PetCO₂ from rest to VeT; I-SSc, limited cutaneous systemic sclerosis.

Table 3. Meta-regression analysis of the association of the variation of standard differences in mean VE/VCO₂(VeT) and prechosen covariates.

| Covariate | Coefficient | Standard error (95%CI) | p-value |
|--|-------------|---------------------------|---------|
| Proportion of patients with a limited cutaneous form of systemic sclerosis | 0.770 | 4.619 (-13.930 to 15.470) | 0.878 |
| Proportion of patients with interstitial lung disease | -0.391 | 2.104 (-7.085 to 6.304) | 0.865 |
| Mean peak VO ₂ (%pred.) | -0.045 | 0.0645 (-0.250 to 0.160) | 0.536 |

Abbreviations: %pred., percentage of predicted value; 95%CI, 95% confidence interval.

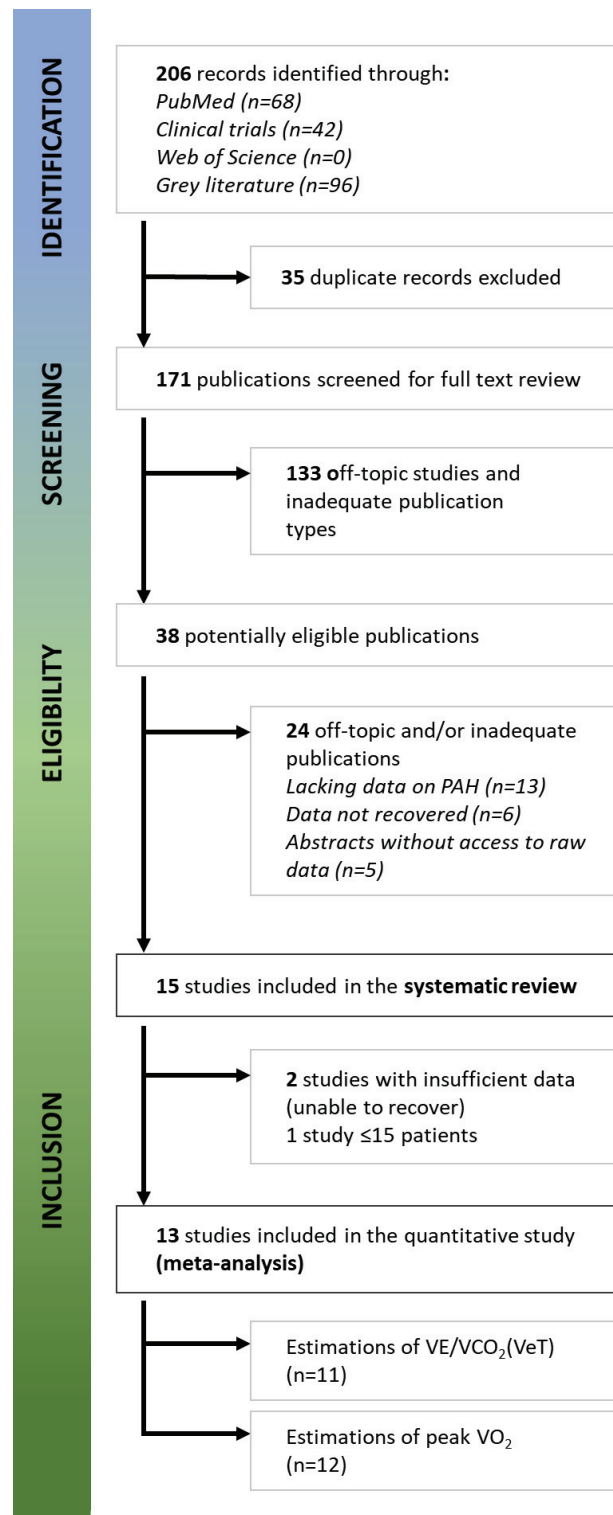


Figure 1. PRISMA flow-chart illustrating the study selection process.

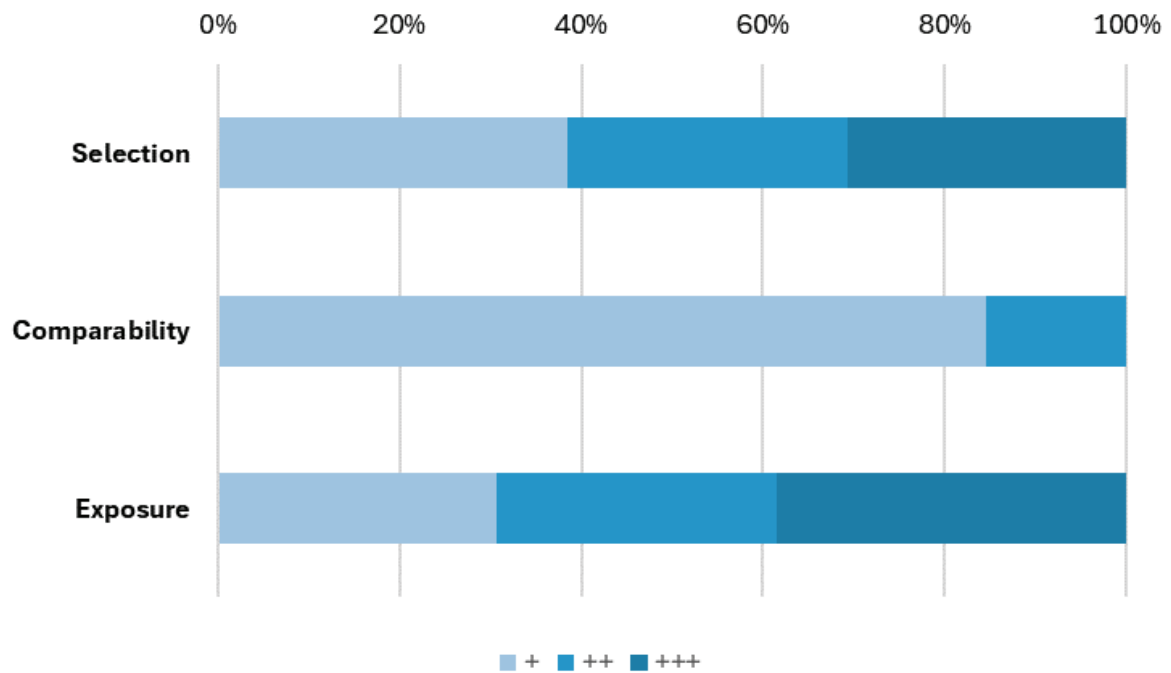


Figure 2. Methodologic assessment of all the studies included in the meta-analysis according to the Newcastle-Ottawa Quality Assessment Scale (supplementary material).

Distribution of scoring (+, ++ or +++) of the studies within each category (i.e. selection, comparability, exposure) are expressed in percentages.

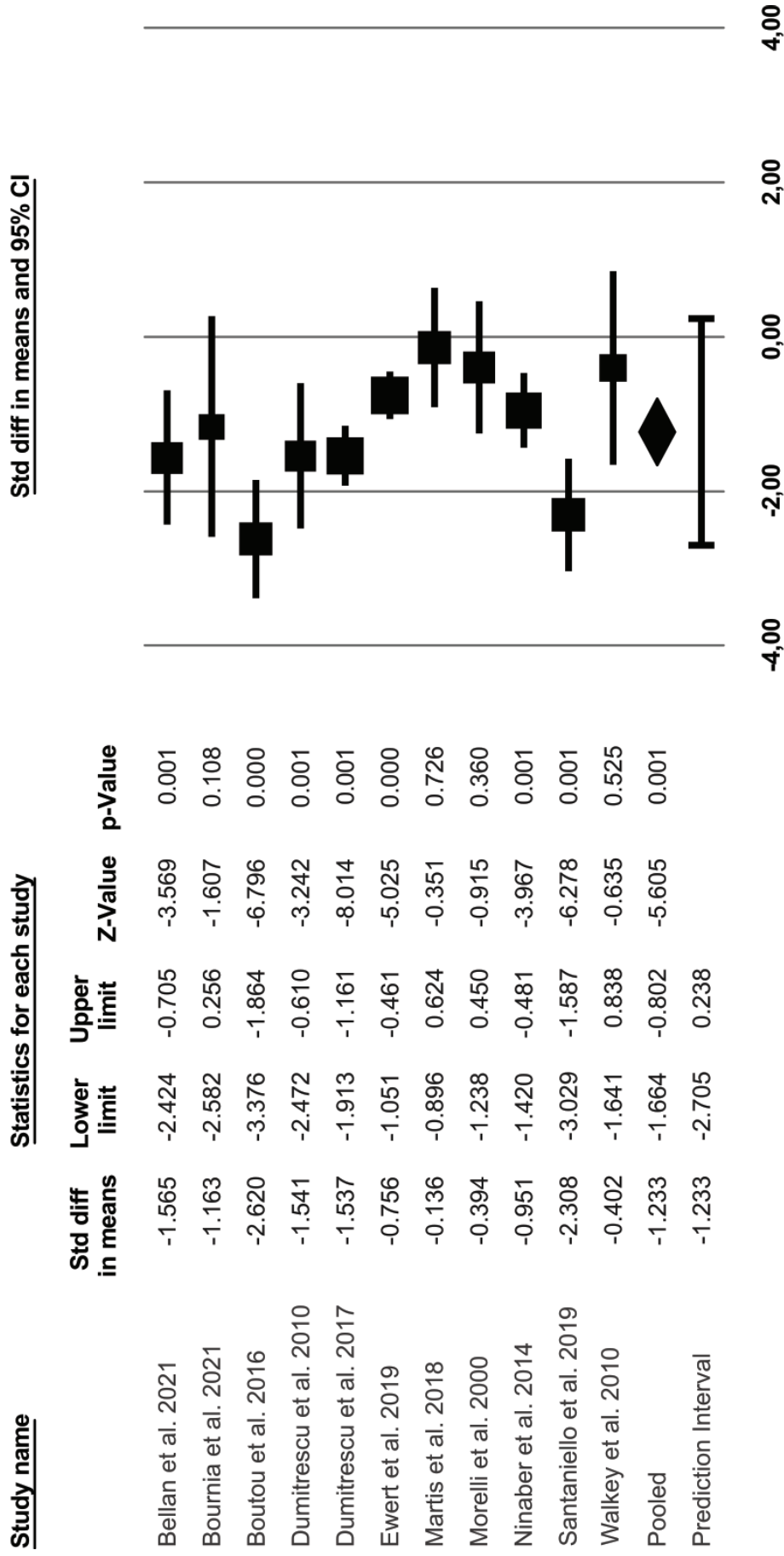


Figure 3-A. Forest plot of studies comparing VE/VCO₂(VeT) in systemic sclerosis patients between those with and without pulmonary hypertension.

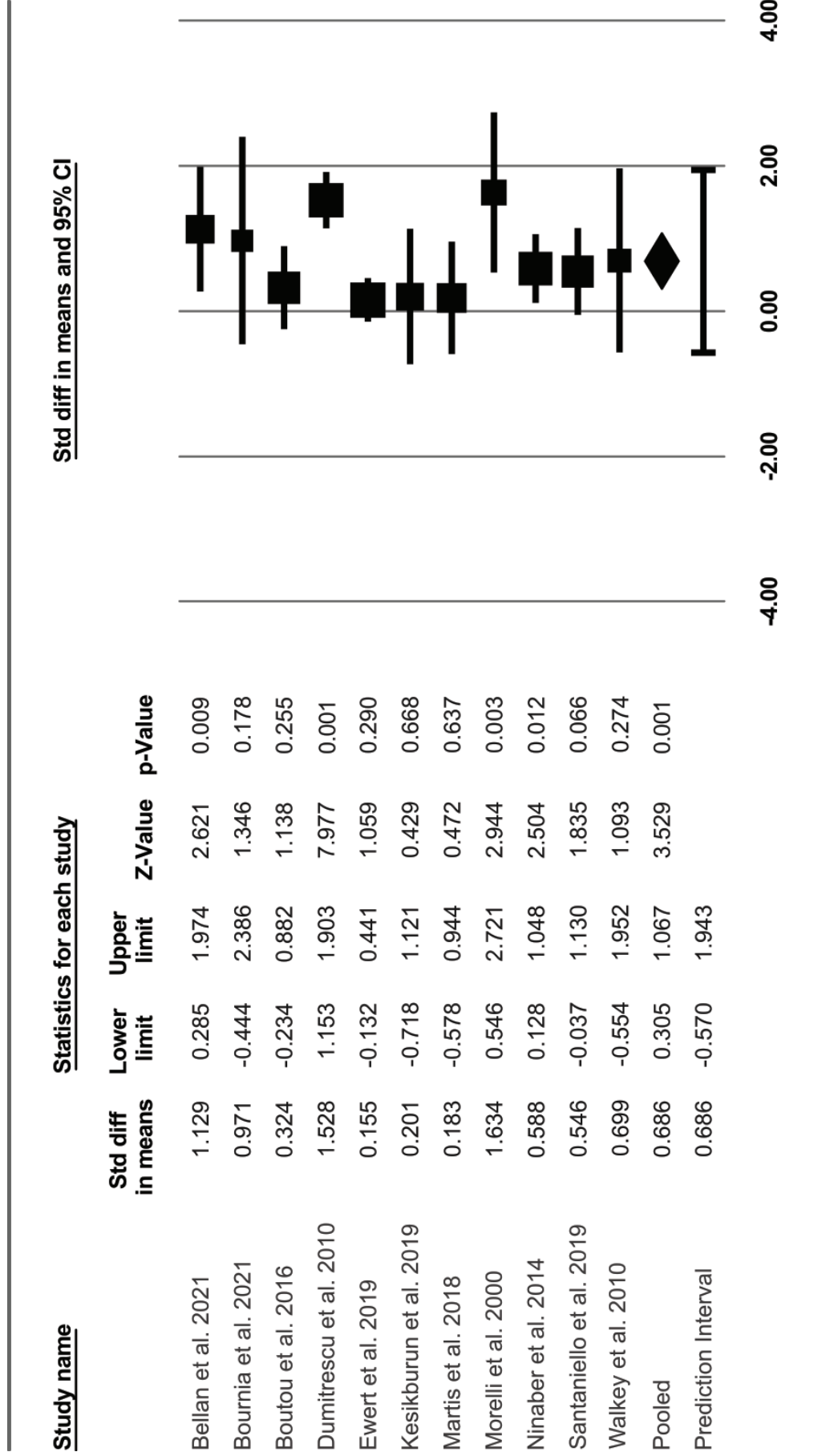


Figure 3-B. Forest plot of studies comparing peak indexed VO₂ (mL/kg/min) in systemic sclerosis patients between those with and without pulmonary hypertension.

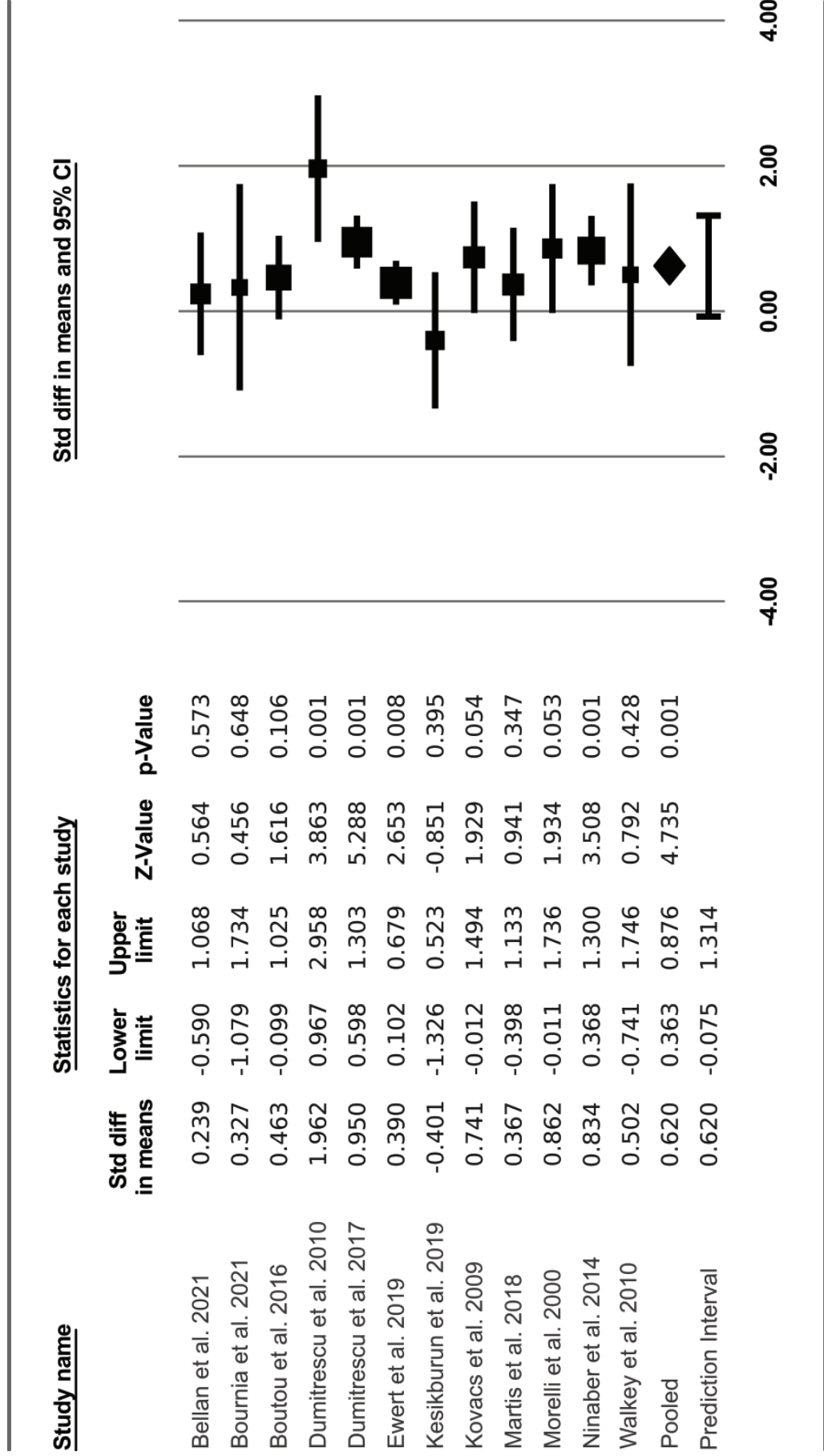


Figure 3-C. Forest plot of studies comparing peak VO₂ (expressed as %pred.) in systemic sclerosis patients between those with and without pulmonary hypertension.

ANNEXES / SUPPLEMENTARY MATERIAL**Table S1. PRISMA 2020 Checklist**

| Section and Topic | Item # | Checklist item | Location where item is reported |
|-------------------------------|--------|--|---------------------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review. | Title |
| ABSTRACT | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Abstract |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Intro-paragraph 3 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Intro-paragraph 5 |
| METHODS | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Methods-section 1 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Methods-section 1 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Methods-section 1 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Methods-section 1 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Methods-section 2 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Methods-section 2 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Methods-section 2 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Methods-section 4 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Methods-section 4 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Methods-section 2 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Methods-section 4 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Methods-section 4 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Methods-section 4 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Methods-section 4 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Methods-section 4 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|--|--------|--|--|
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Methods-section 4 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Methods-section 4 |
| RESULTS | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Results-section 1 Figure 1 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Results-section 1 Figure 1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Results-section 1 Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Results-section 1 Figure 2 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Results-sections 2,3,4 Figures 3-A,B,C |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results-sections 2,3,4 Figures S2-A,B,C |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Results-sections 2,3,4 Figures 3-A,B,C Tables S4-A,B,C |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Results-sections 2,3,4 Tables S4-A,B,C |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Results-sections 2,3,4 Tables S5-A,B,C |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Results-sections 2,3,4 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Results-sections 2,3,4 Figures S1-A,B,C |
| DISCUSSION | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Discussion-section 1 |
| | 23b | Discuss any limitations of the evidence included in the review. | Discussion-section 5 |
| | 23c | Discuss any limitations of the review processes used. | Discussion-section 5 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Discussion-sections 2, 4 |
| OTHER INFORMATION | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Methods-section 2 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Methods-section 2 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Methods-section 2 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Support |
| Competing interests | 26 | Declare any competing interests of review authors. | Competing interests |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Methods-section 2 |

Table S2. Search algorithm and relevant research terms.

PubMed / Medline (last search 10/03/2024)

#1: "systemic sclerosis"[MeSH Terms] OR "sclerosis"[MeSH Terms]

AND

#2: "exercise test"[Title] OR "cardiopulmonary exercise testing"[Title]

No filter applied

→ 68 results

MedRxiv.org / ASAPbio.org (last search 10/03/2024)

"cardiopulmonary exercise testing" OR "exercise test" AND "systemic sclerosis"

Filter applied on "rheumatology"

→ 96 results

Cochrane database (last search 10/03/2024)

(cardiopulmonary exercise testing):ti,ab,kw OR (exercise testing):ti,ab,kw AND (systemic sclerosis):ti,ab,kw OR (scleroderma):ti,ab,kw

No filter applied

→ 49 results

ClinicalTrials.gov (last search 10/03/2024)

"cardiopulmonary exercise test" OR "exercise test" AND "systemic sclerosis" OR "scleroderma"

→ 42 results

Web of Science (last search 10/03/2024)

"cardiopulmonary exercise testing" OR "exercise test" OR "functional exercise test" AND "systemic sclerosis" OR "scleroderma" AND "prognosis" OR "outcome"

Filter applied on research field (ESI) for "clinical medicine"

→ 0 result

Table S3. The Newcastle-Ottawa Quality Assessment Scale

A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Is the case definition adequate?
 - a) yes, with independent validation*
 - b) yes, eg record linkage or based on self-reports
 - c) no description
- 2) Representativeness of the cases
 - a) consecutive or obviously representative series of cases*
 - b) potential for selection biases or not stated
- 3) Selection of Controls
 - a) community controls*
 - b) hospital controls
 - c) no description
- 4) Definition of Controls
 - a) no history of disease (endpoint)*
 - b) no description of source

Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis
 - a) study controls for pulmonary hypertension*
 - b) study controls for any additional factor (extra data provided by authors)*

Exposure

- 1) Ascertainment of exposure
 - a) secure record*
 - b) structured interview where blind to case/control status*
 - c) interview not blinded to case/control status
 - d) written self-report or medical record only
 - e) no description
 - 2) Same method of ascertainment for cases and controls
 - a) yes*
 - b) no
 - 3) Non-Response rate
 - a) same rate for both groups*
 - b) non respondents described
 - c) rate different and no designation
-

Table S4-A. Statistics associated with the forest plot of studies comparing VE/VCO₂(VeT) in systemic sclerosis patients between those with and without pulmonary hypertension.

| Model | Number studies | Point estimate | Effect size and 95% confidence interval | | | Test of null (2-tail) | | Prediction interval | | Between-study | | Other heterogeneity statistics | | | | |
|--------|----------------|----------------|---|----------|-------------|-----------------------|---------|---------------------|-------------|---------------|-------|--------------------------------|---------|--------|---------|-----------|
| | | | Standard error | variance | Lower limit | Upper limit | Z-value | P-value | Lower limit | Upper limit | Tau | TauSq | Q-value | df (Q) | P-value | I-squared |
| Fixed | 11 | -1.145 | 0.088 | 0.008 | -1.317 | -0.972 | -13.001 | <0.001 | | | | | 48.966 | 10 | <0.001 | 79.578 |
| Random | 11 | -1.233 | 0.220 | 0.048 | -1.664 | -0.802 | -5.605 | <0.001 | -2.705 | 0.238 | 0.612 | 0.375 | | | | |

Table S4-B. Statistics associated with the forest plot of studies comparing peak indexed VO₂ (mL/kg/mn) in systemic sclerosis patients between those with and without pulmonary hypertension

| Model | Number studies | Point estimate | Effect size and 95% confidence interval | | | Test of null (2-tail) | | Prediction interval | | Between-study | | Other heterogeneity statistics | | | | |
|--------|----------------|----------------|---|----------|-------------|-----------------------|---------|---------------------|-------------|---------------|-------|--------------------------------|---------|--------|---------|-----------|
| | | | Standard error | variance | Lower limit | Upper limit | Z-value | P-value | Lower limit | Upper limit | Tau | TauSq | Q-value | df (Q) | P-value | I-squared |
| Fixed | 11 | 0.620 | 0.084 | 0.007 | 0.454 | 0.785 | 7.335 | <0.001 | | | | | 40.829 | 10 | <0.001 | 75.508 |
| Random | 11 | 0.686 | 0.194 | 0.038 | 0.305 | 1.067 | 3.529 | <0.001 | -0.570 | 1.943 | 0.520 | 0.271 | | | | |

Table S4-C. Statistics associated with the forest plot of studies comparing peak VO₂ (%pred.) in systemic sclerosis patients between those with and without pulmonary hypertension

| Model | Number studies | Point estimate | Effect size and 95% confidence interval | | | Test of null (2-tail) | | Prediction interval | | Between-study | | Other heterogeneity statistics | | | | |
|--------|----------------|----------------|---|----------|-------------|-----------------------|---------|---------------------|-------------|---------------|-------|--------------------------------|---------|--------|---------|-----------|
| | | | Standard error | variance | Lower limit | Upper limit | Z-value | P-value | Lower limit | Upper limit | Tau | TauSq | Q-value | df (Q) | P-value | I-squared |
| Fixed | 12 | 0.617 | 0.083 | 0.007 | 0.453 | 0.780 | 7.393 | <0.001 | | | | | 20.424 | 11 | 0.040 | 46.143 |
| Random | 12 | 0.620 | 0.131 | 0.017 | 0.363 | 0.876 | 4.735 | <0.001 | -0.075 | 1.314 | 0.283 | 0.080 | | | | |

Table S5-A. Sensitivity analysis using the Newcastle-Ottawa scale subgroups (quality) for the analysis of VE/CO₂(VeT) studies

| Group | Number studies | Point estimate | Effect size and 95% confidence interval | | | Test of null (2-tail) | | Prediction interval | | Between-study | | | Other heterogeneity statistics | | | |
|--------------------------------|----------------|----------------|---|----------|-------------|-----------------------|---------|---------------------|-------------|---------------|-------|-------|--------------------------------|--------|---------|-----------|
| | | | Standard error | variance | Lower limit | Upper limit | Z-value | P-value | Lower limit | Upper limit | Tau | TauSq | Q-value | df (Q) | P-value | I-squared |
| Fixed effect analysis | | | | | | | | | | | | | | | | |
| Poor | 2 | -0.731 | 0.476 | 0.227 | -1.665 | 0.202 | -1.535 | 0.125 | | | | | 0.627 | 1 | 0.428 | <0.001 |
| Fair | 5 | -0.904 | 0.422 | 0.015 | -1.142 | -0.665 | -7.417 | <0.001 | | | | | 27.902 | 4 | <0.001 | 85.664 |
| Good | 4 | -1.461 | 0.132 | 0.017 | -1.720 | -1.720 | -11.047 | <0.001 | | | | | 10.059 | 3 | 0.018 | 70.176 |
| Random effects analysis | | | | | | | | | | | | | | | | |
| Poor | 2 | -0.731 | 0.476 | 0.227 | -1.665 | 0.202 | -1.535 | 0.125 | | | 0.000 | 0.000 | | | | |
| Fair | 5 | -1.076 | 0.399 | 0.160 | -1.859 | -0.293 | -2.693 | 0.007 | -3.952 | 1.801 | 0.811 | 0.657 | | | | |
| Good | 4 | -1.542 | 0.265 | 0.070 | -2.061 | -1.023 | -5.820 | <0.001 | -3.728 | 0.644 | 0.434 | 0.188 | | | | |

Table S5-B. Sensitivity analysis using the Newcastle-Ottawa scale subgroups (quality) for the analysis of peak indexed VO₂ (mL/kg/mn) studies

| Group | Number studies | Point estimate | Effect size and 95% confidence interval | | | Test of null (2-tail) | | Prediction interval | | Between-study | | | Other heterogeneity statistics | | | |
|--------------------------------|----------------|----------------|---|----------|-------------|-----------------------|---------|---------------------|-------------|---------------|-------|-------|--------------------------------|--------|---------|-----------|
| | | | Standard error | variance | Lower limit | Upper limit | Z-value | P-value | Lower limit | Upper limit | Tau | TauSq | Q-value | df (Q) | P-value | I-squared |
| Fixed effect analysis | | | | | | | | | | | | | | | | |
| Poor | 3 | 0.504 | 0.335 | 0.112 | -0.153 | 1.161 | 1.504 | 0.133 | | | | | 0.928 | 2 | 0.629 | <0.001 |
| Fair | 4 | 0.257 | 0.120 | 0.014 | 0.021 | 0.493 | 2.138 | 0.033 | | | | | 6.738 | 3 | 0.081 | 55.479 |
| Good | 4 | 1.040 | 0.127 | 0.016 | 0.791 | 1.289 | 8.194 | <0.001 | | | | | 12.995 | 3 | 0.005 | 76.914 |
| Random effects analysis | | | | | | | | | | | | | | | | |
| Poor | 3 | 0.504 | 0.335 | 0.112 | -0.153 | 1.161 | 1.504 | 0.133 | | | 0.000 | 0.000 | | | | |
| Fair | 4 | 0.392 | 0.228 | 0.052 | 0.056 | 0.839 | 1.716 | 0.086 | -1.335 | 2.119 | 0.330 | 0.109 | | | | |
| Good | 4 | 0.955 | 0.282 | 0.080 | 0.401 | 1.508 | 3.380 | 0.001 | -1.465 | 3.374 | 0.486 | 0.236 | | | | |

Table S5-C. Sensitivity analysis using the Newcastle-Ottawa scale subgroups (quality) for the analysis of peak VO₂ (%pred.) studies

| Group | Number studies | Effect size and 95% confidence interval | | | | Test of null (2-tail) | | Prediction interval | | Between-study | | | | Other heterogeneity statistics | | | |
|--------------------------------|----------------|---|----------------|----------|-------------|-----------------------|---------|---------------------|-------------|---------------|-------|-------|---------|--------------------------------|---------|-----------|--|
| | | Point estimate | Standard error | variance | Lower limit | Upper limit | Z-value | P-value | Lower limit | Upper limit | Tau | TauSq | Q-value | df (Q) | P-value | I-squared | |
| Fixed effect analysis | | | | | | | | | | | | | | | | | |
| Poor | 3 | 0.009 | 0.335 | 0.112 | -0.647 | -0.665 | 0.027 | 0.978 | | | | | 1.558 | 2 | 0.459 | <0.001 | |
| Fair | 3 | 0.402 | 0.124 | 0.015 | 0.158 | 0.645 | 3.237 | 0.001 | | | | | 0.060 | 2 | 0.971 | <0.001 | |
| Good | 6 | 0.894 | 0.120 | 0.014 | 0.659 | 1.128 | 7.472 | <0.001 | | | | | 7.150 | 5 | 0.210 | 30.069 | |
| Random effects analysis | | | | | | | | | | | | | | | | | |
| Poor | 3 | 0.009 | 0.335 | 0.112 | -0.647 | 0.665 | 0.027 | 0.978 | | | 0.000 | 0.000 | | | | | |
| Fair | 3 | 0.402 | 0.124 | 0.015 | 0.158 | 0.645 | 3.237 | 0.001 | | | 0.000 | 0.000 | | | | | |
| Good | 6 | 0.889 | 0.157 | 0.025 | 0.582 | 1.197 | 5.664 | <0.001 | 0.167 | 1.611 | 0.207 | 0.043 | | | | | |

Table S6. Risk assessment in pulmonary arterial hypertension according to the ESC/ERS three-strata model [28]

| Determinants of prognosis (estimated 1-year mortality) | Low risk (<5%) | Intermediate risk (5–20%) | High risk (>20%) |
|--|---|--|--|
| Clinical observations and modifiable variables | | | |
| Signs of right HF | Absent | Absent | Present |
| Progression of symptoms and clinical manifestations | No | Slow | Rapid |
| Syncope | No | Occasional syncope ^a | Repeated syncope ^b |
| WHO-FC | I, II | III | IV |
| 6MWD ^c | >440 m | 165–440 m | <165 m |
| CPET | Peak VO ₂ >15 mL/min/kg (>65% pred.) VE/VCO ₂ slope <36 | Peak VO ₂ 11–15 mL/min/kg (35–65% pred.) VE/VCO ₂ slope 36–44 | Peak VO ₂ <11 mL/min/kg (<35% pred.) VE/VCO ₂ slope >44 |
| Biomarkers: BNP or NT-proBNP ^d | BNP <50 ng/L NT-proBNP <300 ng/L | BNP 50–800 ng/L NT-proBNP 300–1100 ng/L | BNP >800 ng/L NT-proBNP >1100 ng/L |
| Echocardiography | RA area <18 cm ² TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion | RA area 18–26 cm ² TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion | RA area >26 cm ² TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion |
| cMRI ^e | RVEF >54% SVI >40 mL/m ² RVESVI <42 mL/m ² | RVEF 37–54% SVI 26–40 mL/m ² RVESVI 42–54 mL/m ² | RVEF <37% SVI <26 mL/m ² RVESVI >54 mL/m ² |
| Haemodynamics | RAP <8 mmHg CI ≥2.5 L/min/m ² SVI >38 mL/m ² SvO ₂ >65% | RAP 8–14 mmHg CI 2.0–2.4 L/min/m ² SVI 31–38 mL/m ² SvO ₂ 60–65% | RAP >14 mmHg CI <2.0 L/min/m ² SVI <31 mL/m ² SvO ₂ <60% |

Abbreviations: 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO₂, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO₂, ventilatory equivalents for carbon dioxide; VO₂, oxygen uptake; WHO-FC, World Health Organization functional class.

^a Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient.

^b Repeated episodes of syncope even with little or regular physical activity.

^c Observe that 6MWD is dependent upon age, height, and burden of comorbidities.

^d To harmonize with the four-strata model, the BNP and NT-proBNP cut-off levels have been updated from the 2015 version based on data from the REVEAL registry, acknowledging that the European validation studies have used the original cut-off levels.

^e cMRI parameters

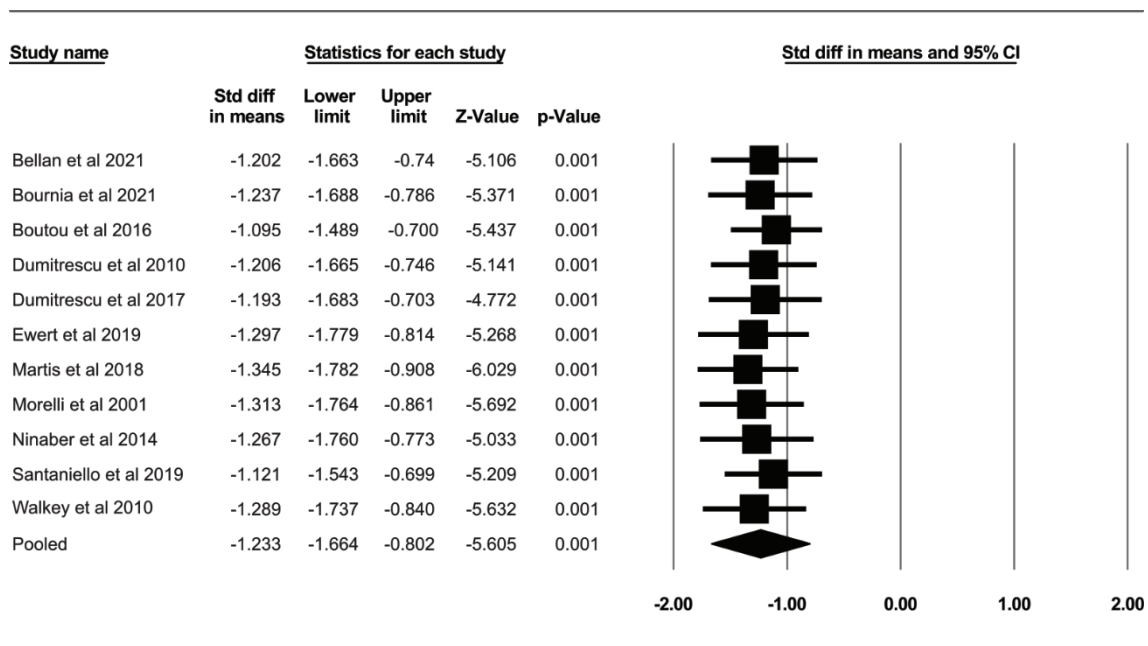


Figure S1-A. Leave-one-out meta-analysis performed on the set of studies comparing VE/VCO₂(VeT) between patients with and without SSc-PAH.

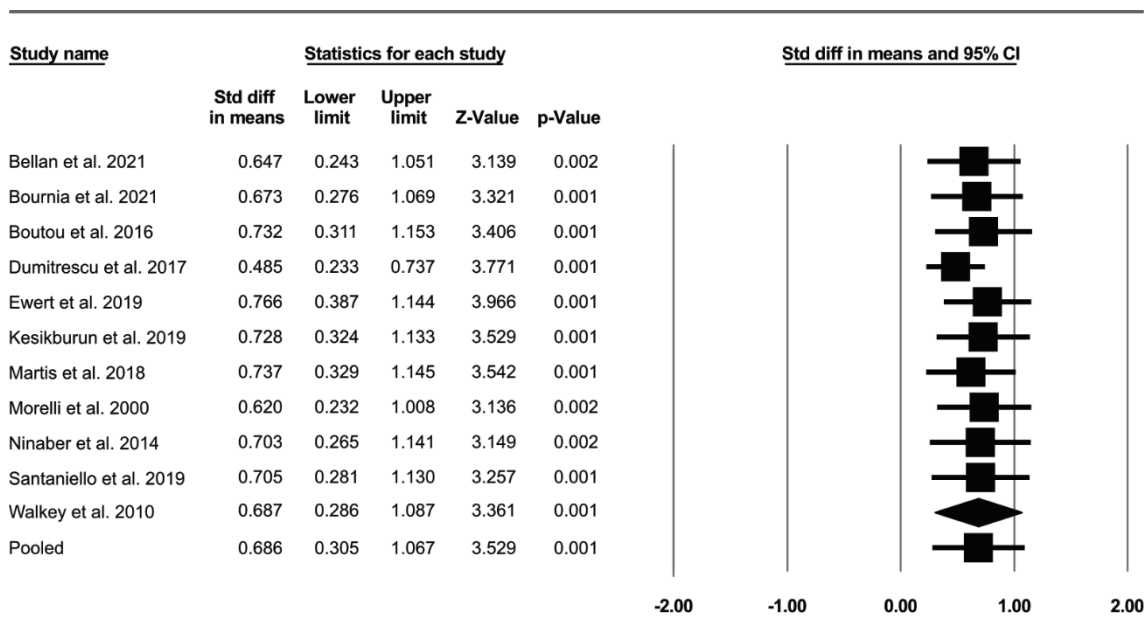


Figure S1-B. Leave-one-out meta-analysis performed on the set of studies comparing indexed peak VO₂ between patients with and without SSc-PAH.

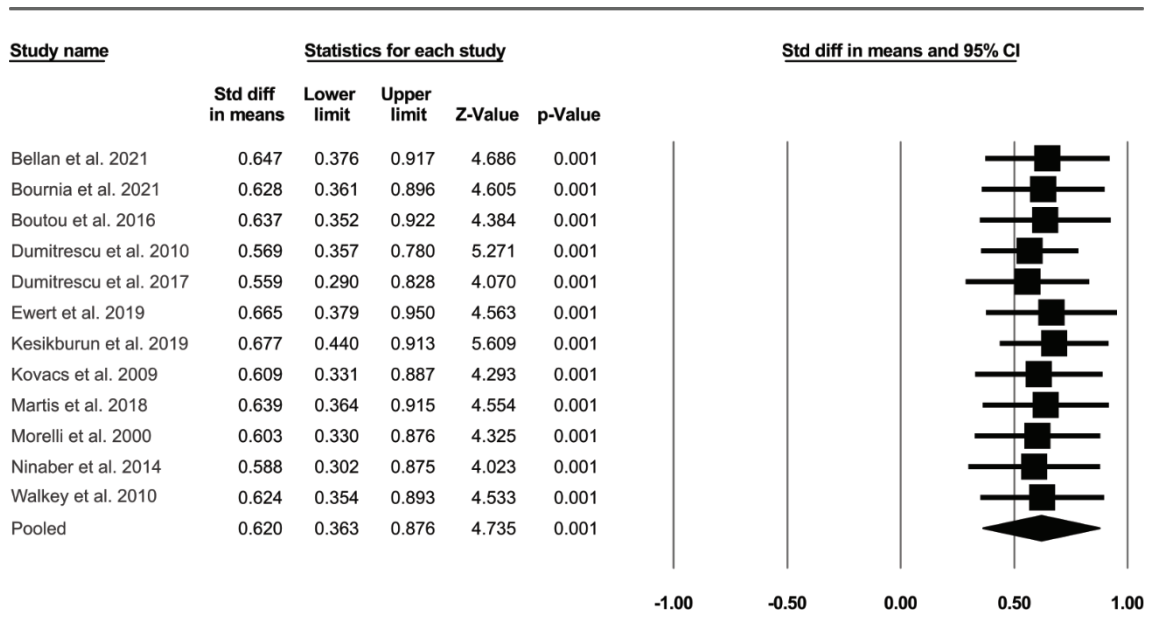


Figure S1-C. Leave-one-out meta-analysis performed on the set of studies comparing peak VO₂ (expressed as %predicted value) between patients with and without SSc-PAH.

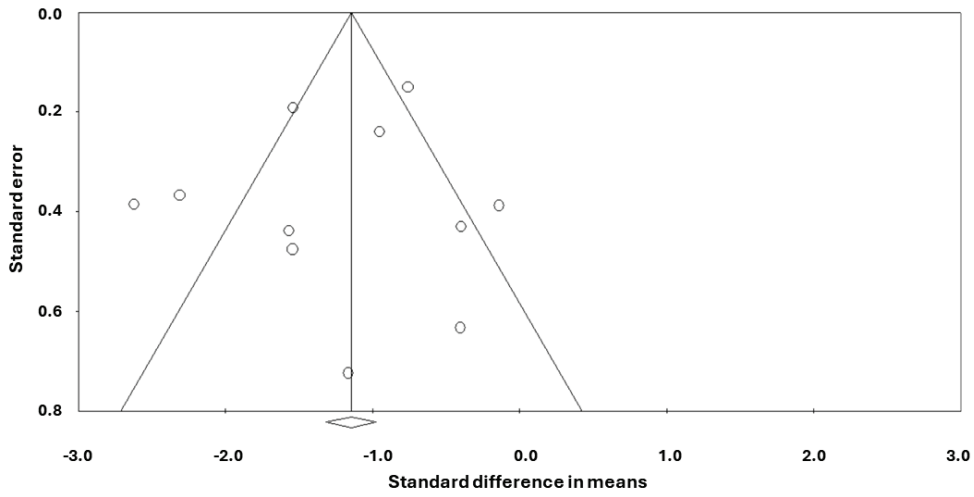


Figure S2-A. Funnel plot for studies recording VE/VCO₂(VeT)

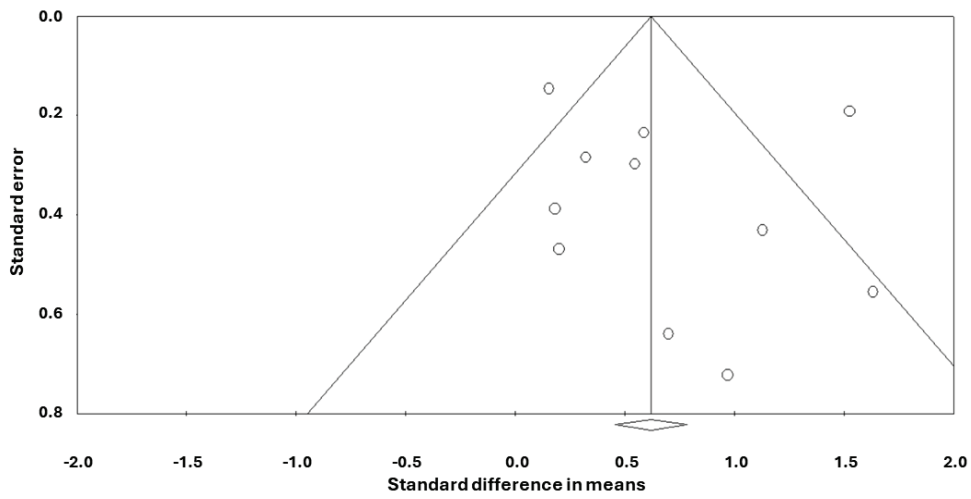


Figure S2-B. Funnel plot for studies recording peak indexed VO₂ (mL/kg/mn)

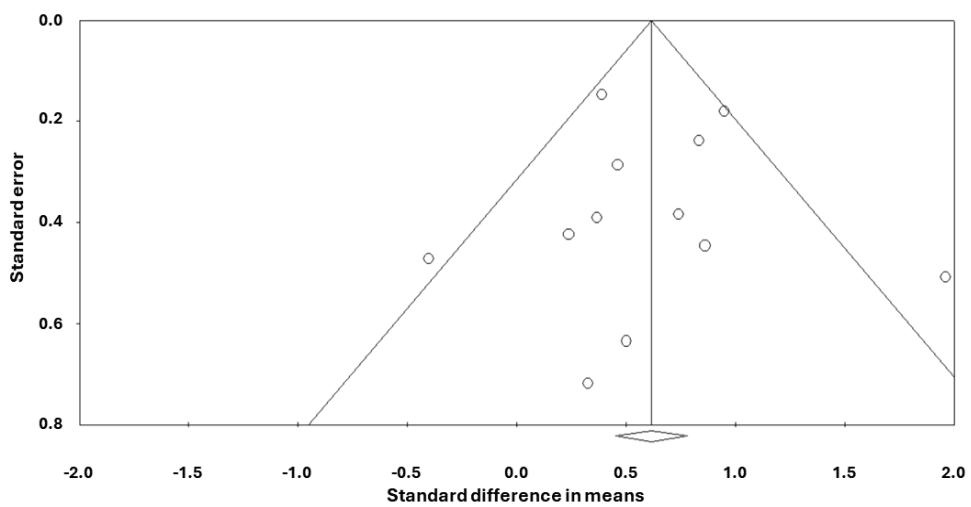


Figure S2-C. Funnel plot for studies recording peak VO₂ (%pred.)

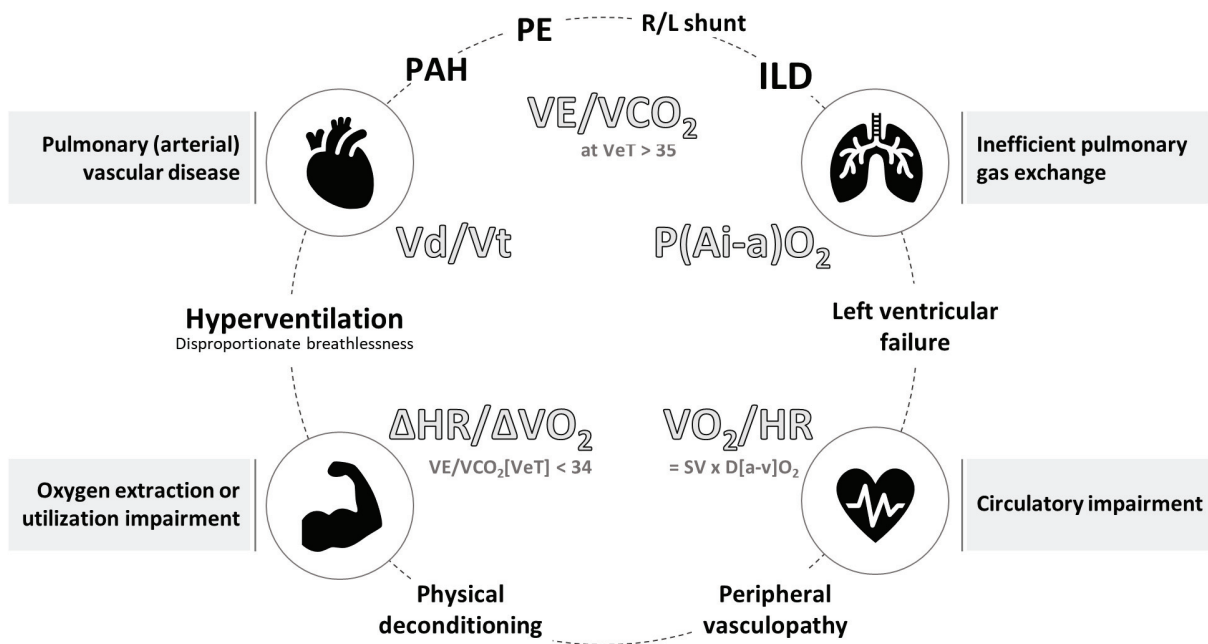


Figure S3. Simplified diagnostic approach based on principle CPET parameters defining general patterns of exercise impairment (adapted from Martis and Leroy [66]).

Abbreviations: $D[a-v]O_2$, difference in oxygen content between arterial and venous blood; $\Delta HR/\Delta VO_2$, defined as $HR[peak]-HR[rest]$ to $VO_2[peak]-VO_2[rest]$ ratio, with HR referring to heart rate; ILD, interstitial lung disease; $P(Ai-a)O_2$, peak oxygen alveolar–arterial pressure gradient; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; R/L shunt, right-to-left cardiac shunt; SV, stroke volume; VE/VCO_2 , ventilatory equivalent for carbon dioxide; VO_2/HR , O_2 -pulse; Vd/Vt , physiological dead space to tidal volume ratio; VeT , ventilatory threshold.

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.

