European Reference Network | Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

filière de santé maladies rares | AI²R filière | Centre de Référence des Maladies Auto-Immunes Systémiques Rares du Nord et Nord-Ouest

Nouvelle définition de HTAP associée à la sclérodermie : recommandations et conséquences pratiques

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Inserm

LIRIC
Lille Inflammation Research International Center
UMR 995

CHU LILLE

6th World Symposium on Pulmonary Hypertension

- 13 task forces
- 124 experts
- 1376 participants à Nice 2018

➔ Proceedings dans ERJ 2019

➔ Hemodynamic definition

One of the most significant (and controversial) recommendations from the 6th WSPH has been the proposal by the task force on haemodynamic definitions and clinical classification, to reconsider the haemodynamic definition of PH [5]. Based on data from normal subjects, the normal mean pulmonary arterial pressure

HTAP : nouvelle définition

Haemodynamic definitions and updated clinical classification of pulmonary hypertension

Gérald Simonneau[1,2], David Montani[1,2], David S. Celermajer[3], Christopher P. Denton[4], Michael A. Gatzoulis[5], Michael Krowka[6], Paul G. Williams[7] and Rogerio Souza[8]

Number 4 in the series
"Proceedings of the 6th World Symposium on Pulmonary Hypertension"
Edited by N. Galiè, V.V. McLaughlin, L.J. Rubin and G. Simonneau

Historique et explication

- depuis le 1er congrès mondial en 1973 : HTP est définie par PAPm ≥ 25 mmHg au KT droit
- Définition empirique et arbitraire à l'époque de l'HTAP « primitive » très sévère
- Maintenue ainsi essentiellement pour éviter des surdiagnostics et des surtraitements

Valeur normale de la PAPm

- 1187 KT de sujets normaux
- PAPm : 14.0 +/- 3.3 mmHg indépendante du sexe, un peu influencée par l'âge
- +2DS (>97.5 percentiles) : 20 mmHg

Une valeur anormale de PAPm ne définit pas un état pathologique

- La PAPm peut s'élever lors des hyperdébits, des shunts, des augmentations de la PAWP et hyperviscosité

➔ « Il faut donc introduire la notion de RVP (PAPm-PAWP)/CO) dans la définition de l'HTP précapillaire (quelque soit le groupe) »

➔ RVP ≥3UW car….. pronostic/utilisé dans les shunts

Nouvelles définitions de l'HTP

TABLE 1 Haemodynamic definitions of pulmonary hypertension (PH)

Definitions	Characteristics	Clinical groups[#]
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR ⩾3 WU	1, 3, 4 and 5
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR <3 WU	2 and 5
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩾3 WU	2 and 5

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. [#]: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.

Nouvelle classification de l'HTP

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

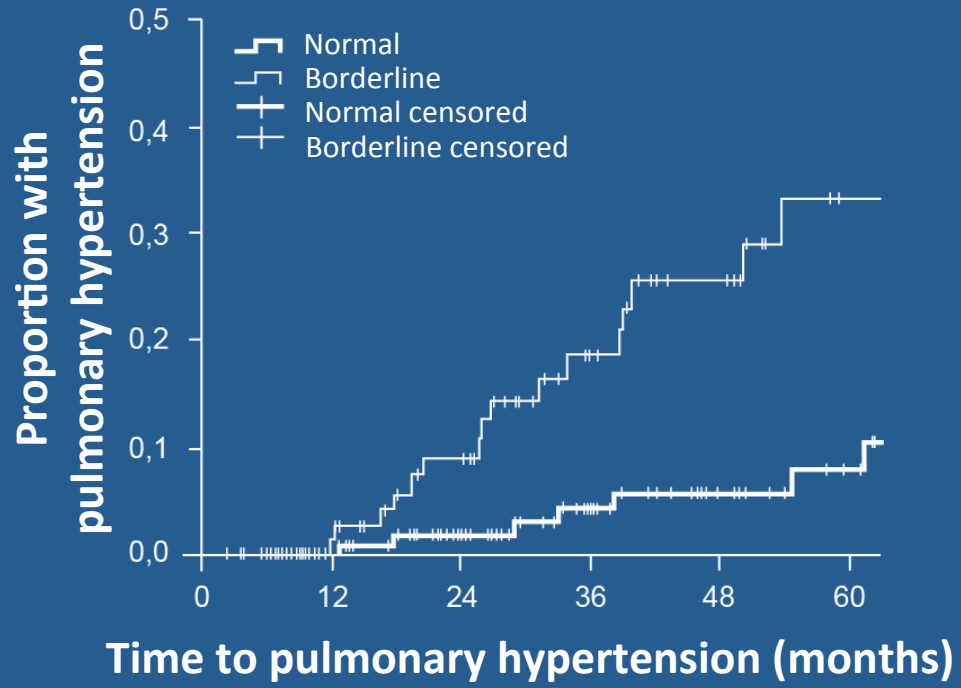
5 PH with unclear and/or multifactorial mechanisms (table 7)
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

Que sait-on des patients SSc entre 21 et 24 mmHg ?

228 patients SSc

- 823 cathétérisme cardiaque chez des patients SSc
- 86 patients ont une PAPm entre 21 et 24 mmHg : “borderline” ➔ 8 % vont développer une HTAP dans les 3 ans avec un pc de 82 % de survie à 3 ans



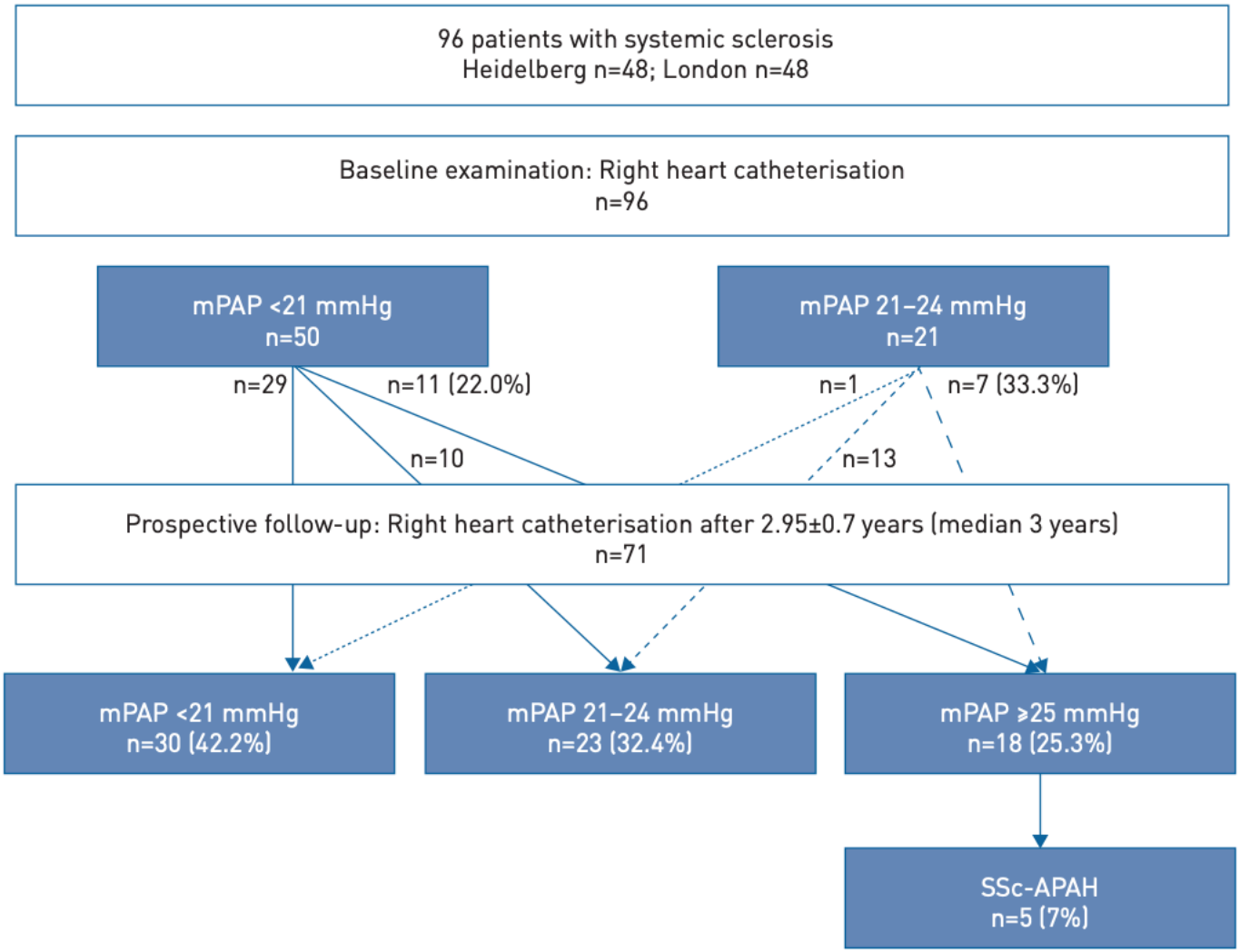
HR : 3.7 (1.7-8.0) de développer une HTAP dans le groupe “borderline” vs normal

5/16 décès dans le groupe qui développe une HTAP

Normal at risk n =	142	125	97	69	49	39
PH % ± SE	0	0	1.8 **± 1.2**	4.2 **± 2.1**	5.7 **± 2.5**	8.0 **± 3.3**
Borderline at risk n =	86	75	52	35	23	13
PH % ± SE	0	1.3 **± 1.3**	9.0 **± 3.5**	18.5 **± 5.1**	25.7 **± 6.1**	33.4 **± 7.5**

Valerio et al.
Arthritis Rheum 2013

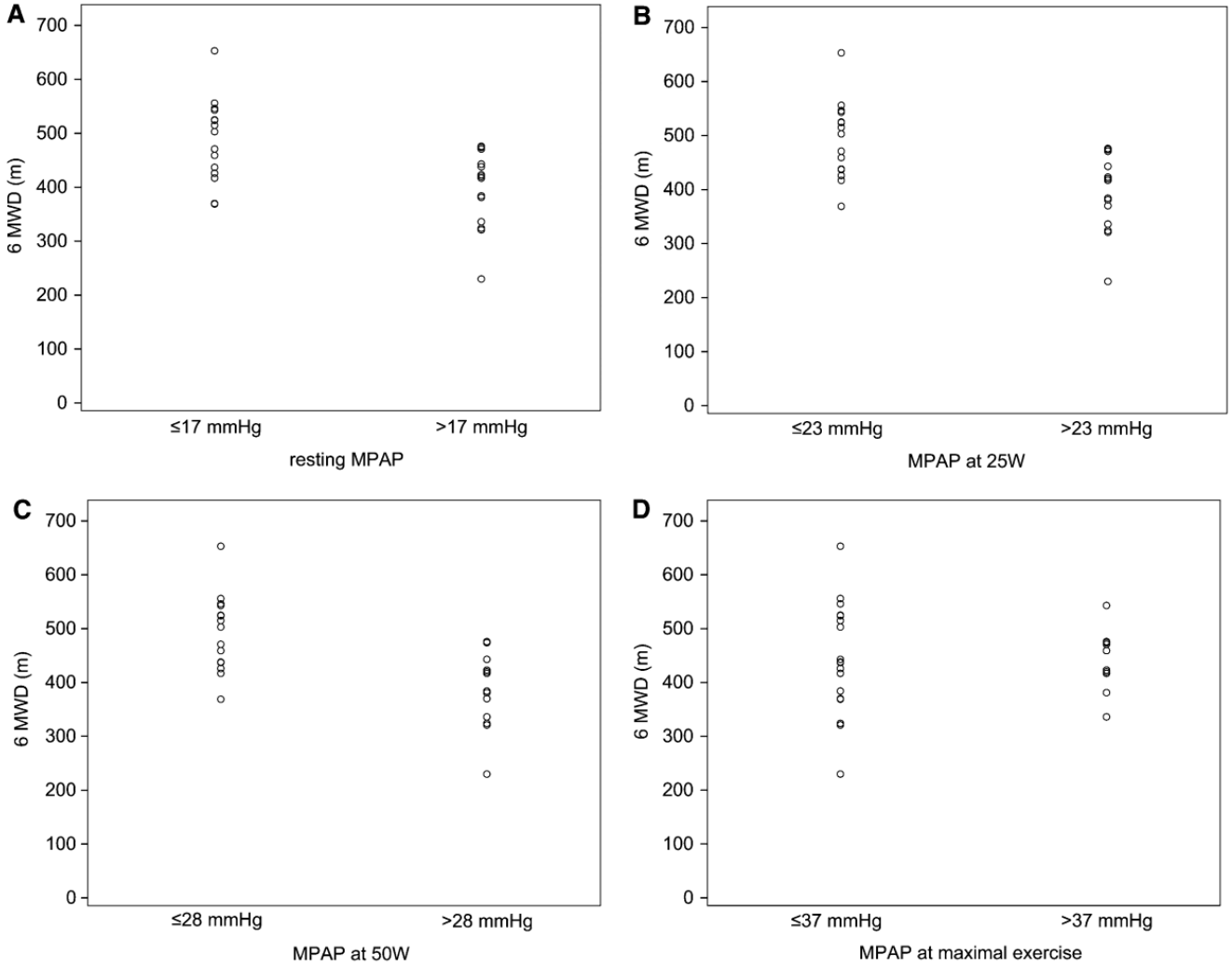
Coghlan et al. Eur Resp J 2018



7/21 développe une HTP dont 3 HTAP; 3 HTP-ILD et 1 HTP-LHD

Borderline Pulmonary Arterial Pressure Is Associated with Decreased Exercise Capacity in Scleroderma

Gabor Kovacs[1], Robert Maier[2], Elisabeth Aberer[3], Marianne Brodmann[4], Stefan Scheidl[1], Natascha Tröster[1], Christian Hesse[1], Wolfgang Salmhofer[3], Winfried Graninger[5], Ekkehard Gruenig[6], Lewis J. Rubin[7], and Horst Olschewski[1]



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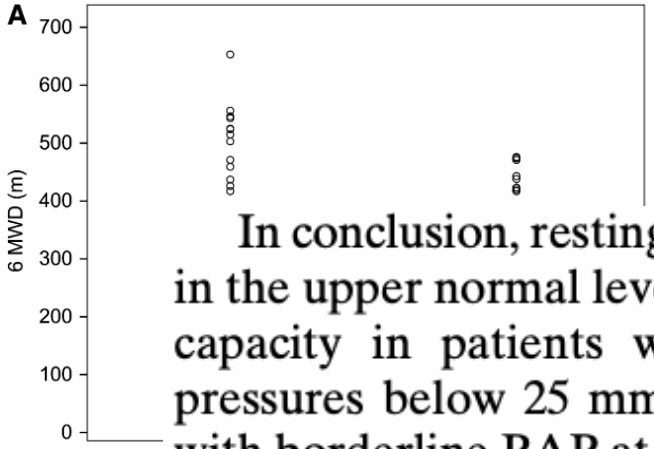
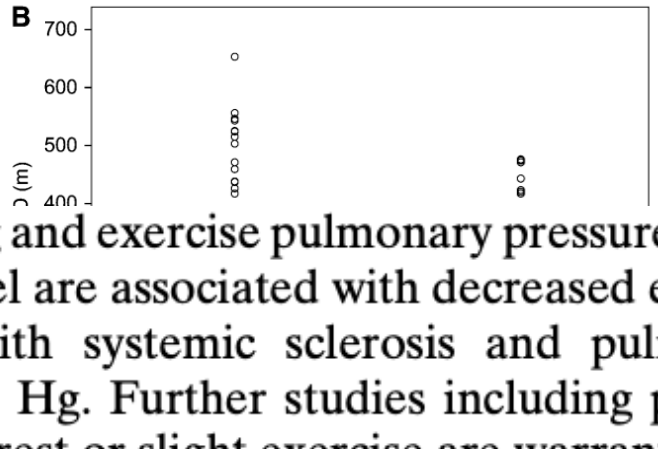
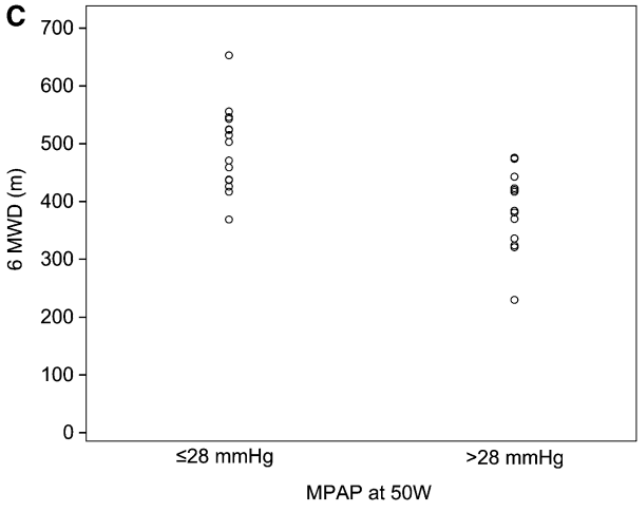
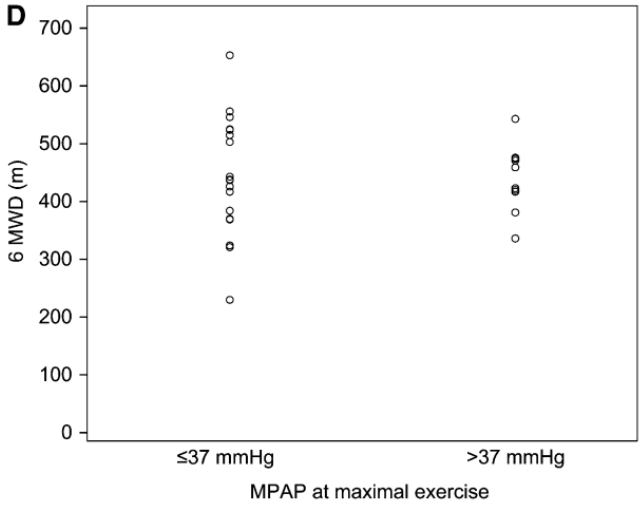




In conclusion, resting and exercise pulmonary pressure values in the upper normal level are associated with decreased exercise capacity in patients with systemic sclerosis and pulmonary pressures below 25 mm Hg. Further studies including patients with borderline PAP at rest or slight exercise are warranted.





Est-ce que la nouvelle définition de l’HTAP change quelque chose ?

EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

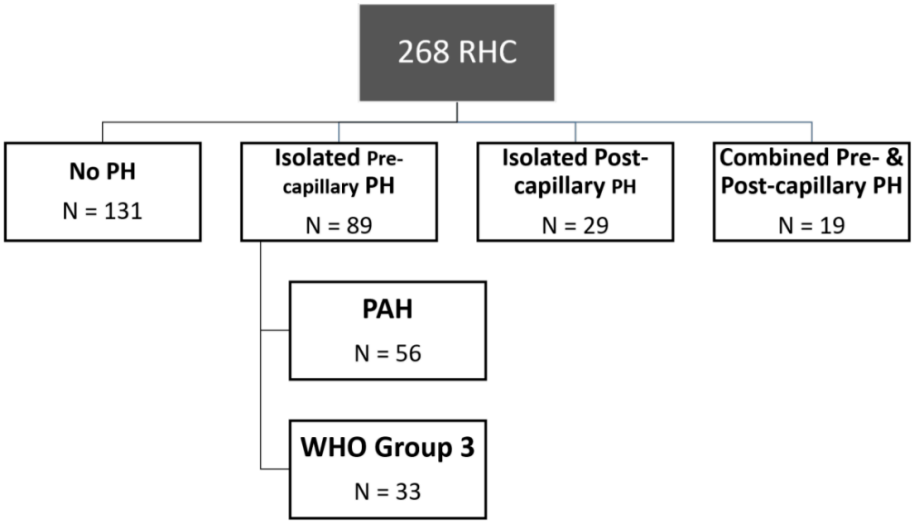
Original article

Impact of the Revised Hemodynamic Definition on the Diagnosis of Pulmonary Hypertension in Patients with Systemic Sclerosis

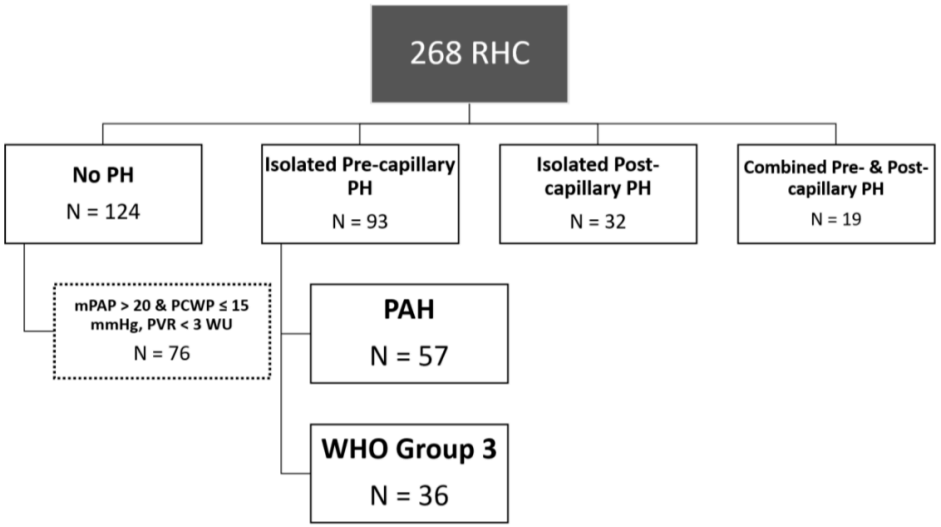
Sara Jaafar, Scott Visovatti, Amber Young, Suiyuan Huang, Paul Cronin, Dharshan Vummidi, Vallerie McLaughlin, Dinesh Khanna

Please cite this article as: Jaafar S, Visovatti S, Young A, *et al*. Impact of the Revised Hemodynamic Definition on the Diagnosis of Pulmonary Hypertension in Patients with Systemic Sclerosis. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00586-2019).

Figure 1a: Classification according to Prior Hemodynamic Definition of PH in the UM Cohort



PAPm ≥ 25 mmHg



PAPm > 20 mmHg
RVP ≥3

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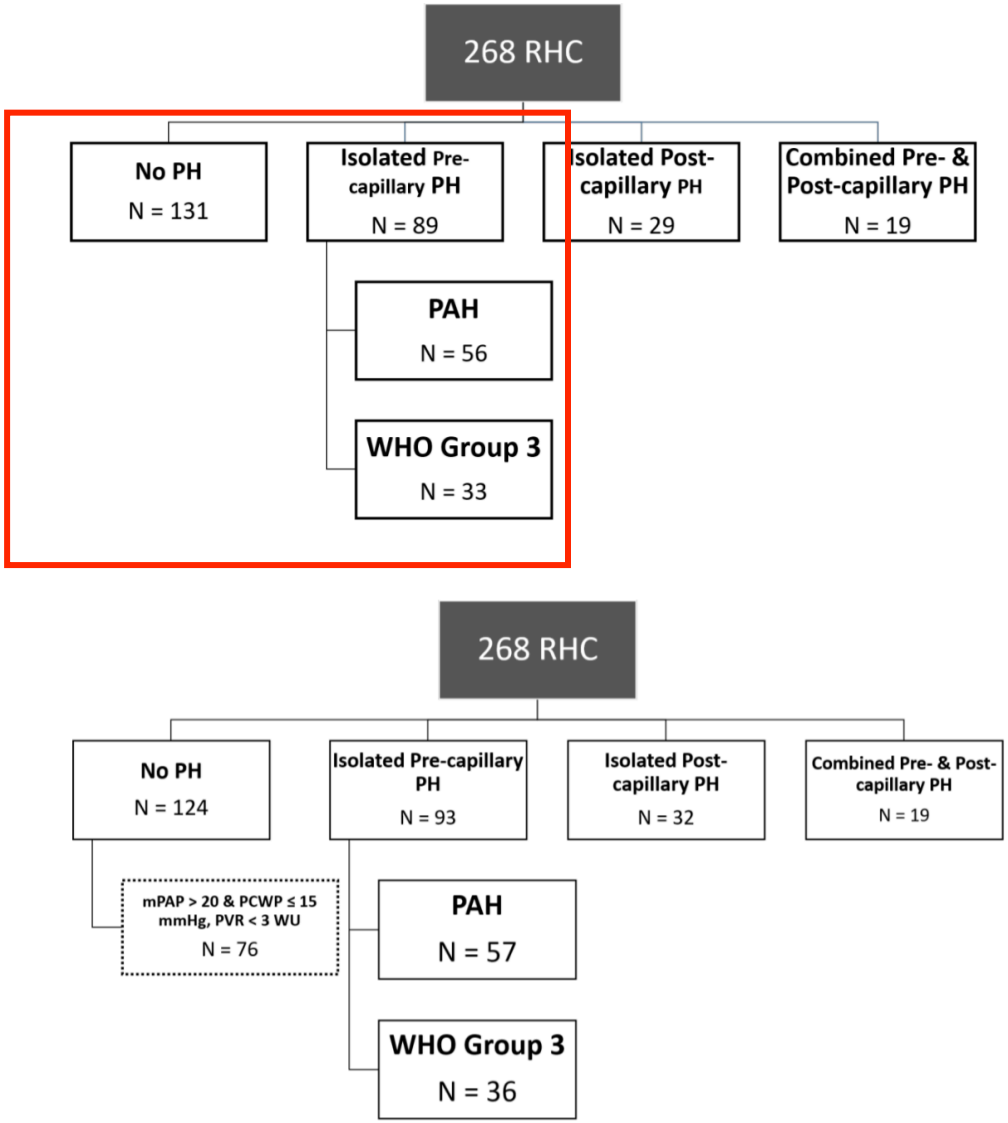

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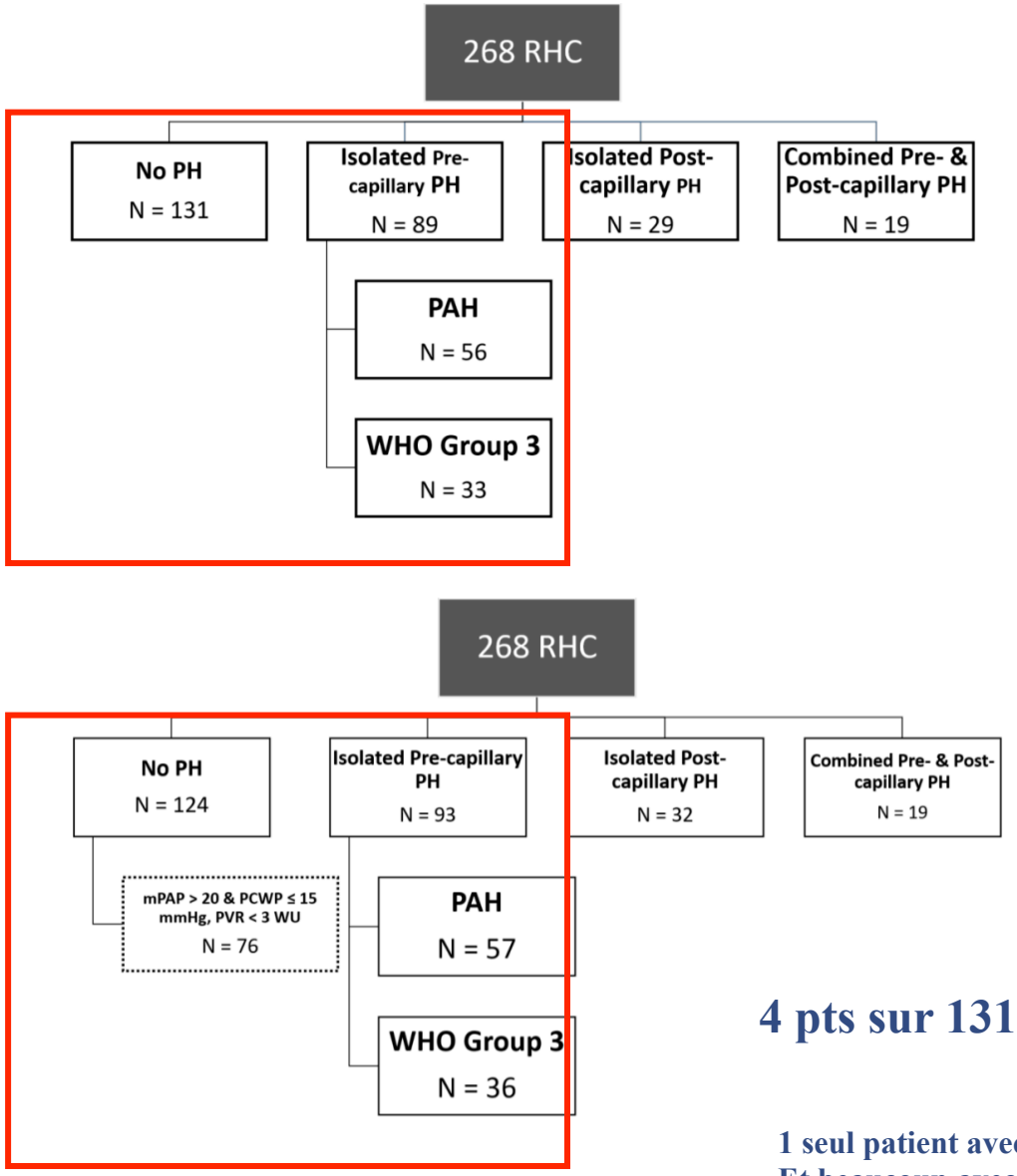

PAPm ≥ 25 mmHg

PAPm > 20 mmHg
RVP ≥3

4 pts sur 131 passe de no PH à precapillary PH

1 seul patient avec PAPm entre 21 et 24 mmHg, PCWP<15 et RVP>3
Et beaucoup avec PAPm entre 21 et 24 mmHg, PCWP<15 et RVP<3

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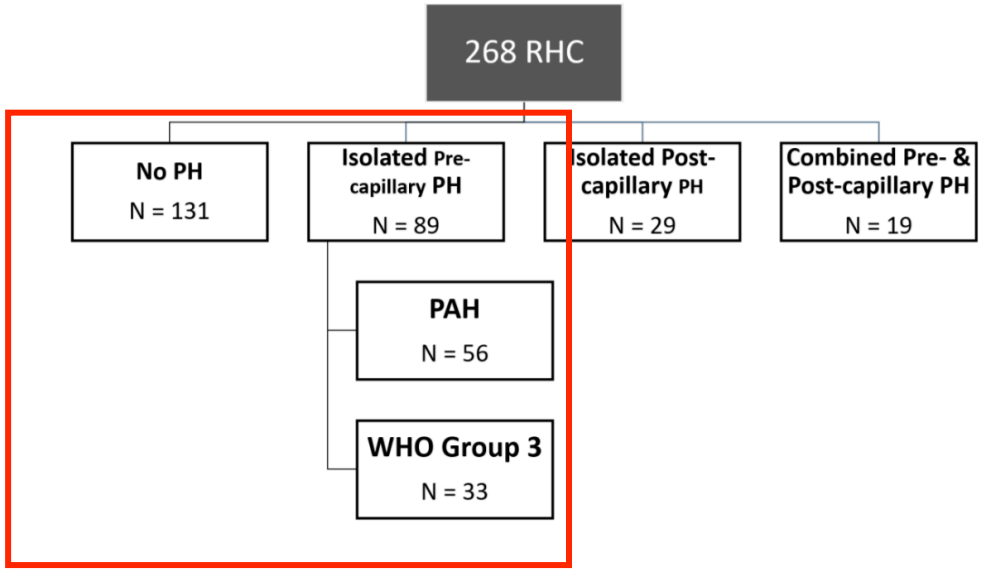
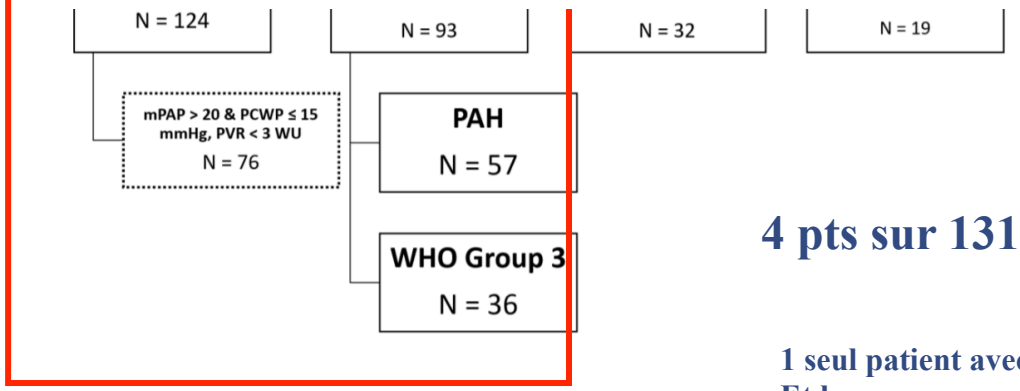


PAPm ≥ 25 mmHg

Conclusion: The updated PH definition does not appear to have a significant impact on the diagnosis of PH in 2 different screening cohorts.



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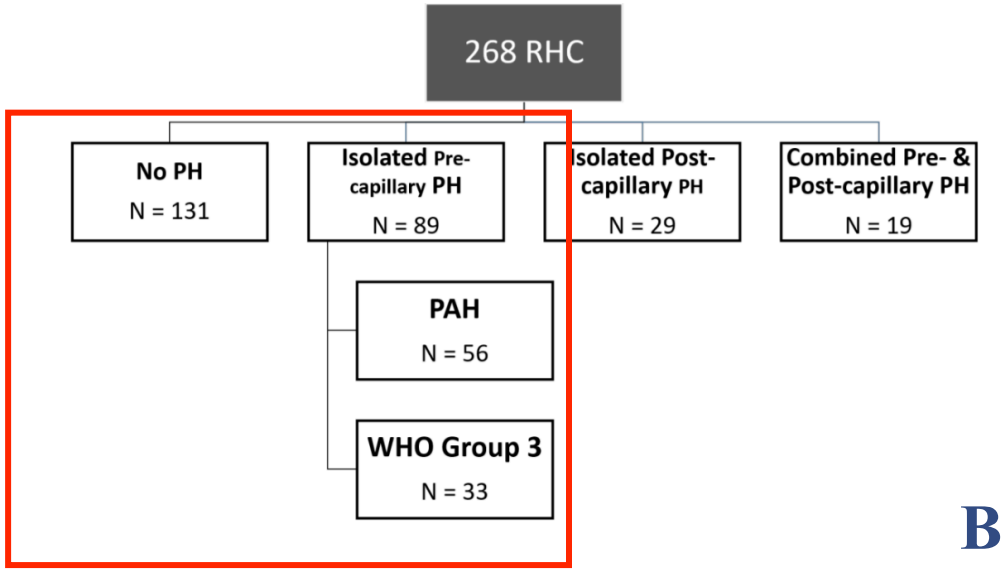

PAPm ≥ 25 mmHg

Because of RVP

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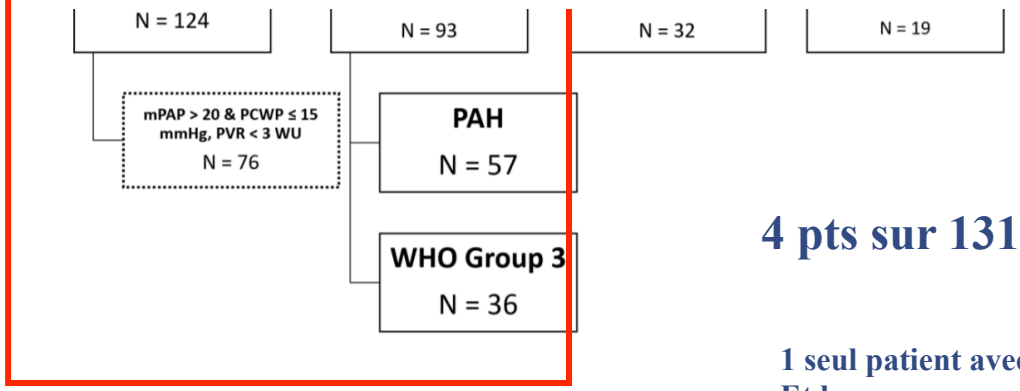

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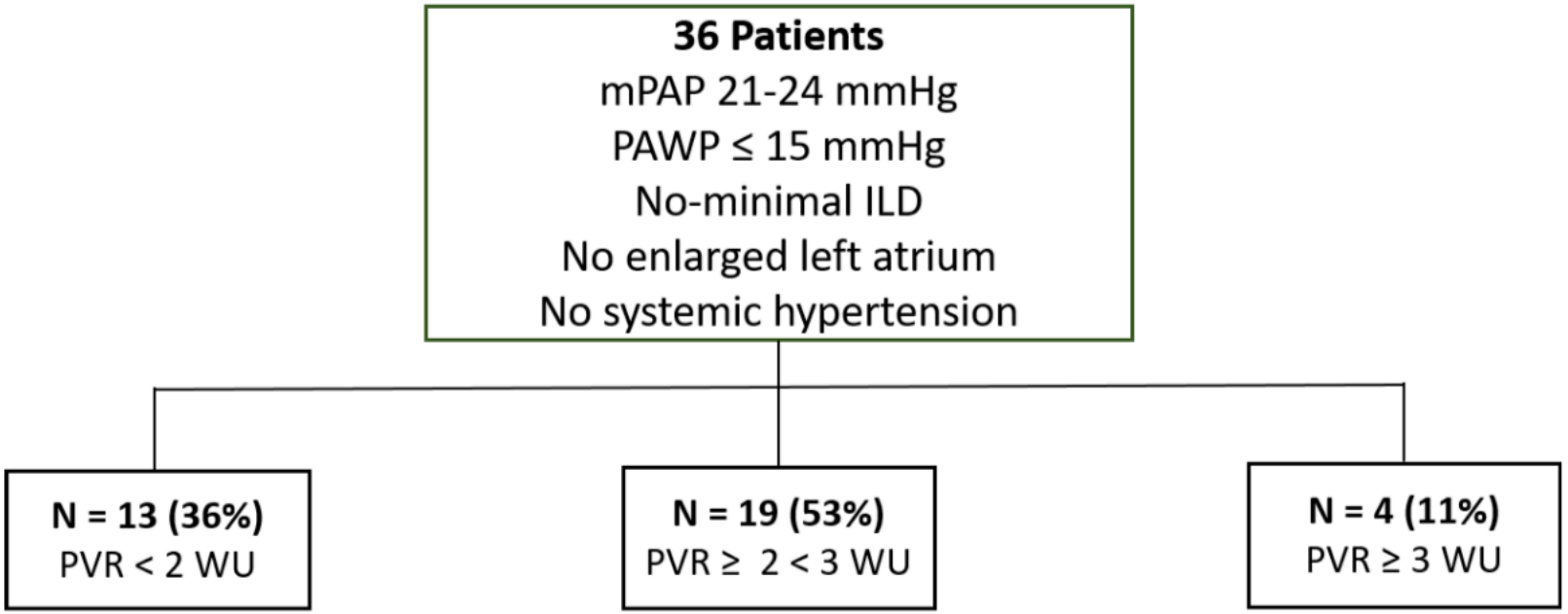
Figure 2 b Distribution of borderline mPAP (21-24 mmHg) in the DETECT study cohort, stratified by PVR



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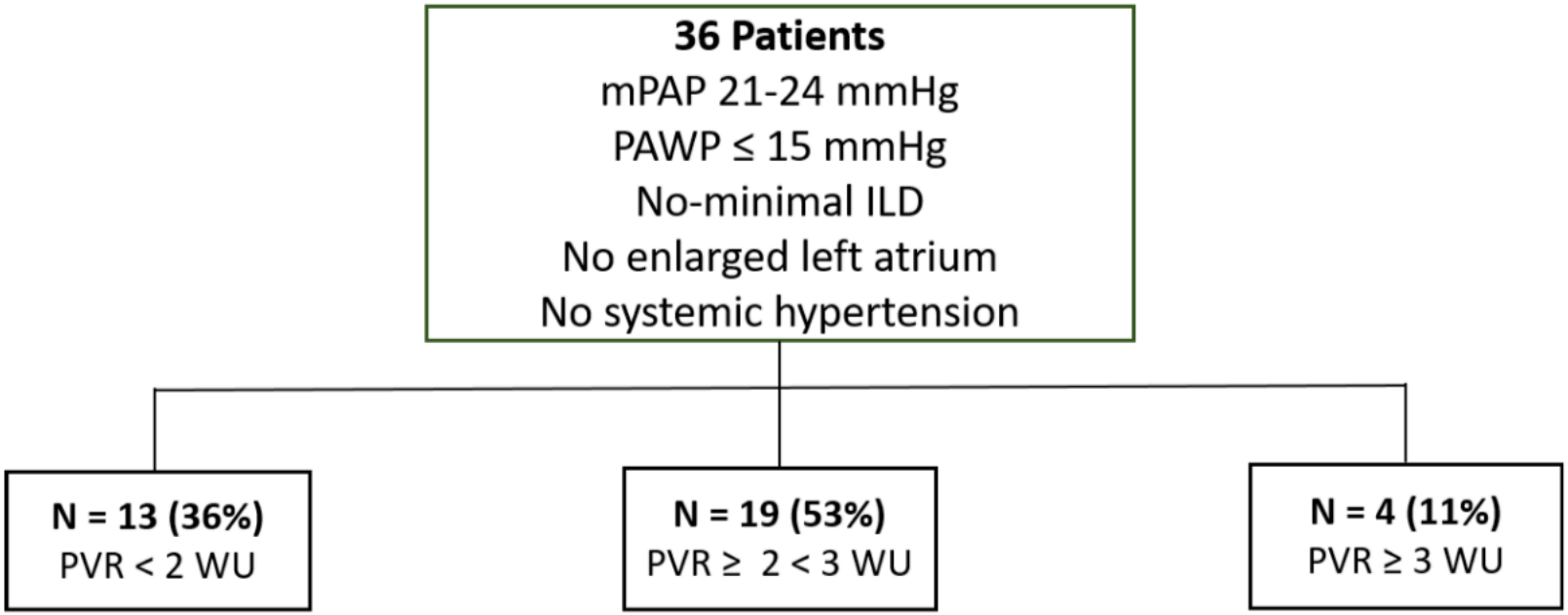


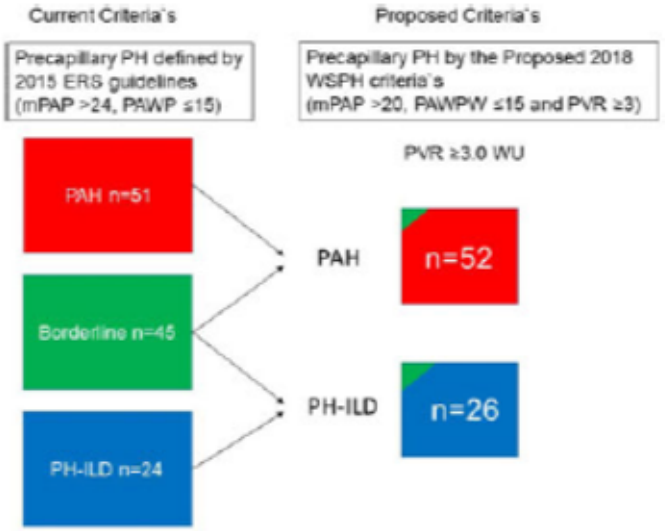
Conclusion: The updated PH definition does not appear to have a significant impact on the diagnosis of PH in 2 different screening cohorts.

Because of RVP

Abstract Number: 0718

Diagnosing Pulmonary Hypertension Using the Proposed 6th World Symposium on Pulmonary Hypertensions New Definitions

Håvard Fretheim,[1] Øyvind Midtvedt,[2] Torhild Garen,[2] Arne Kristian Andreassen,[2] Einar Gude,[2] Øyvind Molberg,[3] and Anna Maria Hoffmann-Vold[4], [1]Oslo University Hospital, Oslo, [2]Oslo University Hospital, Oslo, Norway, [3]University Hospital Oslo, Oslo, Norway, [4]Department of Rheumatology, Oslo University Hospital, Oslo, Norway, Oslo, Norway



Results: Of the 191 SSc patients, 150/191 (79%) were female, 143/191 (75%) had limited cutaneous SSc and 85/191 (45%) were anti-centromere antibody positive. Mean age of the patients was 57 years and mean time from SSc diagnosis to PH diagnosis was 6 years. Using the current PH criteria 51/191 (27%) SSc patients were diagnosed with PAH, 36/191(19%) patients with PH-ILD and 45 (24%) patients with borderline PH. Using the newly proposed definitions the frequency of PAH and PH-ILD changed as shown in Figure 1. 24 patients had an mPAP ≥ 21 mmHg and a PVR value 2.0-2.9 WU. The mean mPAP in these 24 patients was 23.8 mmHg, the mean PAWP 10.1 mmHg, 20/26 (77%) were female and 16/26 (62%) were anti-centromere antibody positive.

Conclusion: Lowering the mPAP to ≥ 21 mmHg and including PVR ≥ 3.0 WU did not substantially change the PH prevalence in our cohort due to the PVR cut-off value. We still need more knowledge about the long-term outcome of SSc patients with pre-capillary PH when changing definitions for pre-capillary PH. Also, it will be important to decide how and when to treat these patients.

Disclosure: H. Fretheim, GSK, 9, Actelion, 9; **Ø. Midtvedt**, ACHIM, 4; **T. Garen**, None; **A. Andreassen**, Actelion, 8; **E. Gude**, Actelion, 8; **Ø. Molberg**, None; **A. Hoffmann-Vold**, Actelion, 5, 8, Boehringer Ingelheim, 2, 5, 8, GSK, 5, 8.

Because of RVP

TABLE 1 Proportion of patients who would be included in the proposed definition of pre-capillary pulmonary hypertension (PH) at the authors' institutions, based on existing referral criteria

PH centre	All patients submitted to RHC	Patients with mPAP 21–24 mmHg	Patients with mPAP 21–24 mmHg and PAWP ⩽15 mmHg	Patients with mPAP 21–24 mmHg and PAWP ⩽15 mmHg and PVR ⩾3 Wood units
Medical Center for Postgraduate Education, ECZ-Otwock, Otwock, Poland	1242	152 (12.2%)	135 (10.8%)	29 (2.3%)
Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK	2111	133 (6.3%)	101 (4.8%)	23 (1.1%)

Note that the referral patterns might change if the new definition of PH is adopted. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance.

Because of RVP

Eur Respir J 2019; 53: 1900197

Qu’en penser ?

- **Révolutionnaire ?**
- **Pertinent ?**
- **Problème des RVP**
- **Problème des PAPm entre 21 et 24 mmHg, PCWP<15 et RVP<3**
- **Problème du screening**
- **Traitement ?**

Debating the new haemodynamic definition of pulmonary hypertension: much ado about nothing?

Gabor Kovacs[1,2] and Horst Olschewski[1,2]

Eur Respir J 2019; 54: 19012

Debating the new haemodynamic definition of pulmonary hypertension: much ado about nothing?

Gabor Kovacs[1,2] and Horst Olschewski[1,2]

Proposed new pulmonary hypertension definition: is 4 mm(Hg) worth re-writing medical textbooks?

J. Simon R. Gibbs [1,3] and Adam Torbicki [2,3]

Eur Respir J 2019; 53: 1900197

Eur Respir J 2019; 54: 19012

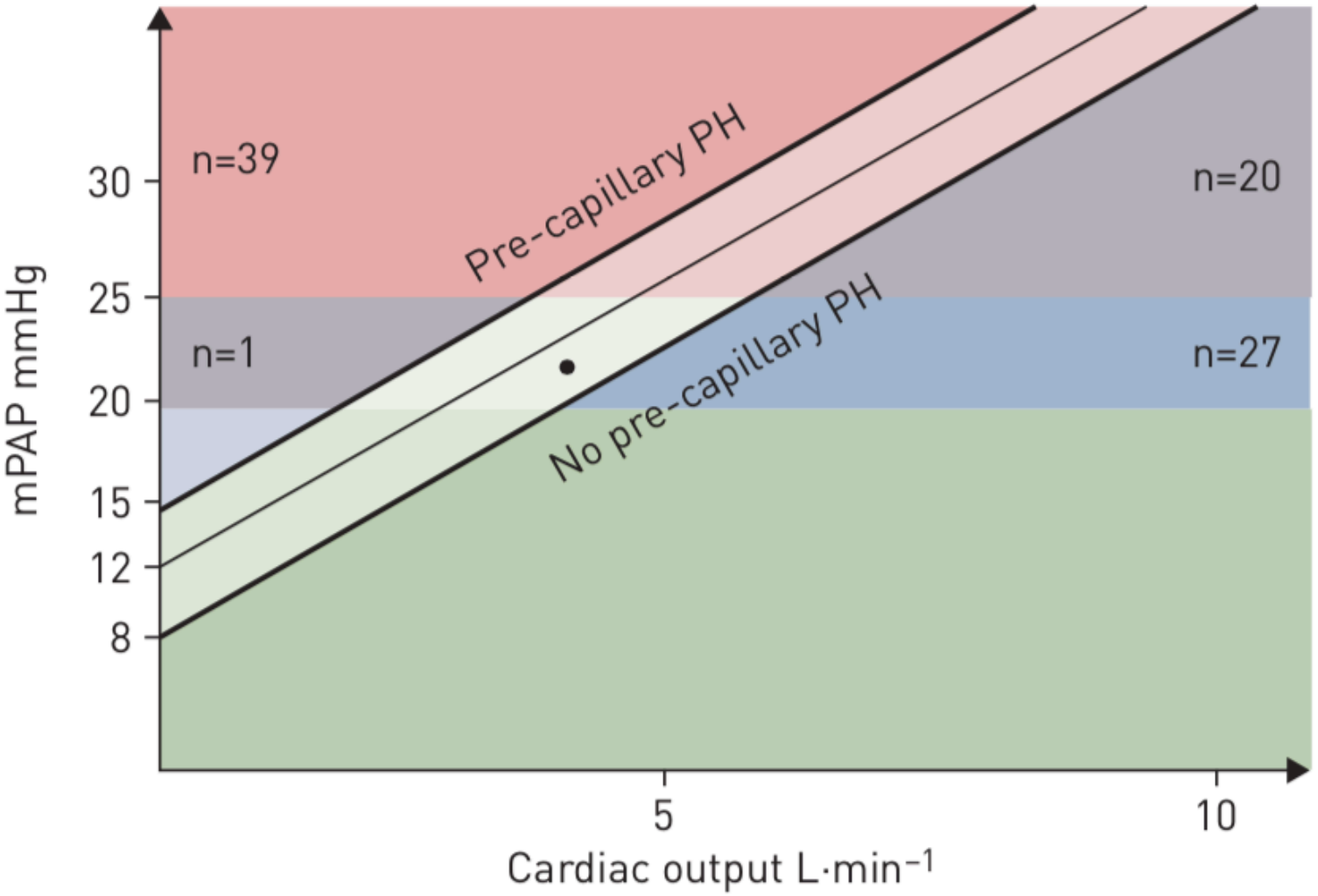
Debating the new haemodynamic definition of pulmonary hypertension: much ado about nothing?

Gabor Kovacs[1,2] and Horst Olschewski[1,2]

4/131 patients (3.1%) passe de no PH à precapillary PH dans l'étude de Jaafar et al. ➔ « rare condition »

27 des 28 patients avec PAPm 21-24 Hg ont des PVR<3UW

Eur Respir J 2019; 54: 19012



Pour avoir des RVP >3, le plus souvent PAPm>25 mmHg

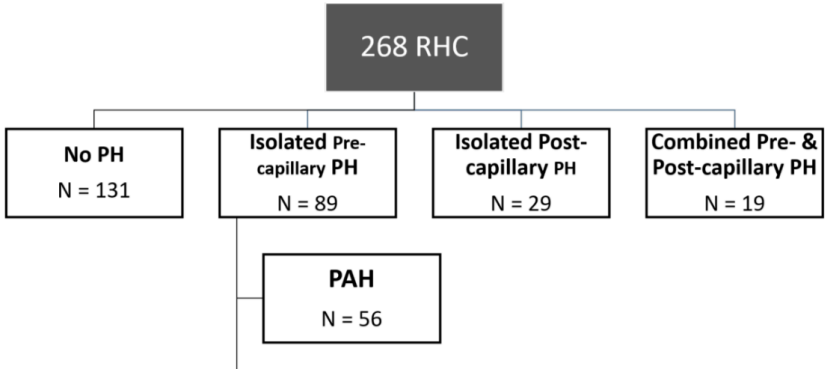
Eur Respir J 2019; 54: 19012

RVP>3 : trop stringent ?

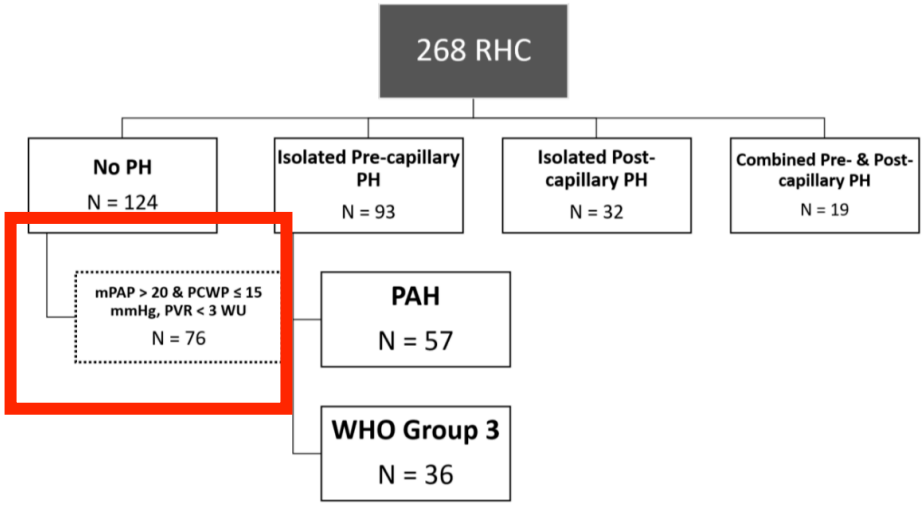
- **RVP>2 UW**
- **On passe de 1 patient à 9 patients n'ayant pas d'HTP à ayant une HTAP précapillaire**

Problème des PAPm entre 21 et 24 mmHg, PCWP<15 et RVP<3

Figure 1a: Classification according to Prior Hemodynamic Definition of PH in the UM Cohort



PAPm ≥ 25 mmHg



PAPm > 20 mmHg

Hyperdébit ?

Screening

1. **DLCO<80% : DETECT-2015 ESC/ERS guidelines ou FVC/DLCO>1.6**
2. **DLCO>80% : ETT**

Table 8A Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Table 8B Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement in *Table 8A*

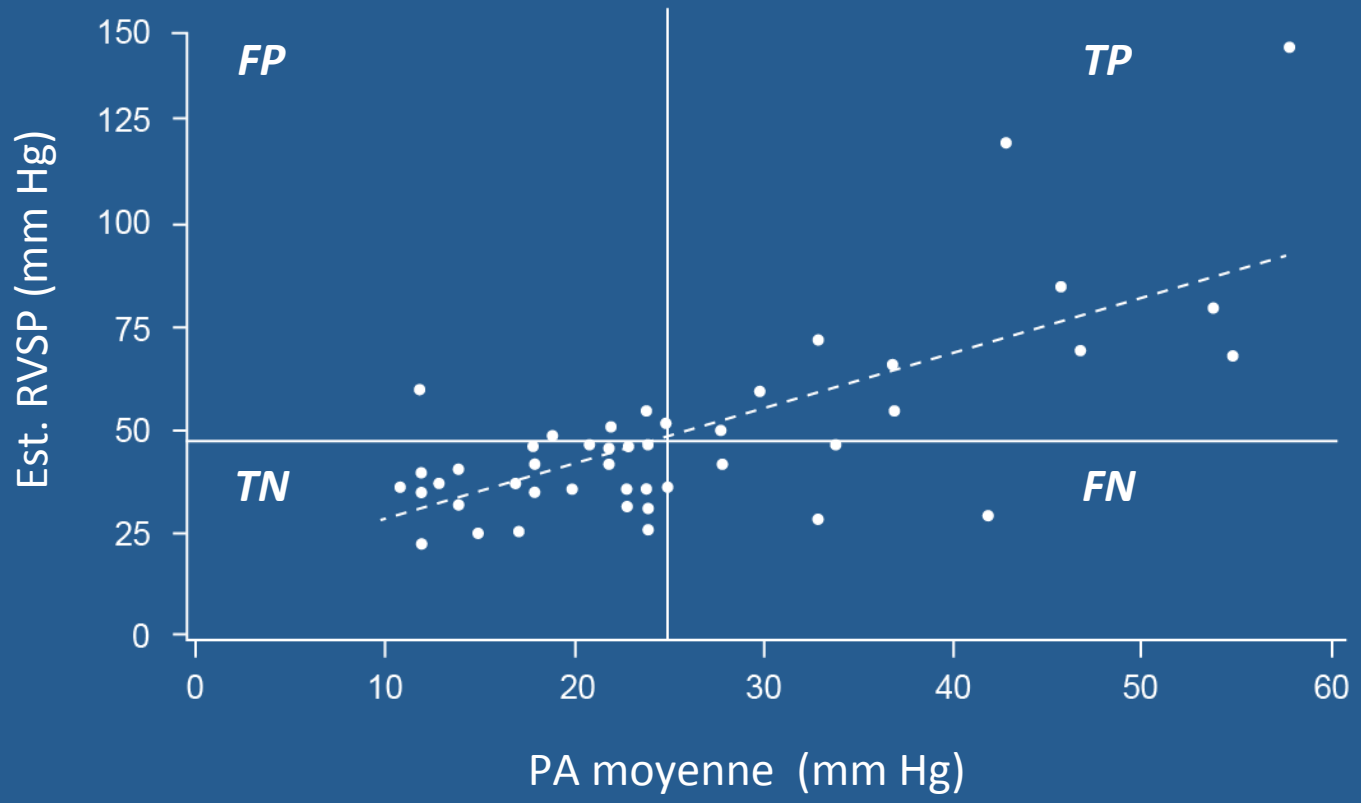
A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm²
	PA diameter >25 mm.	

Les signes et symptomes n'apparaissent pas dans cet algorithme différent de ESC-ERS 2009

Guidelines ERS/ESC 2015

Mais…

- Peu de données invasives sont disponibles chez les patients ayant une VIT < 2.5 m/s
- La corrélation entre la VIT et la PAPs mesurée en cathétérisme n'est pas parfaite



Hsu et al. J Rheumatol 2008

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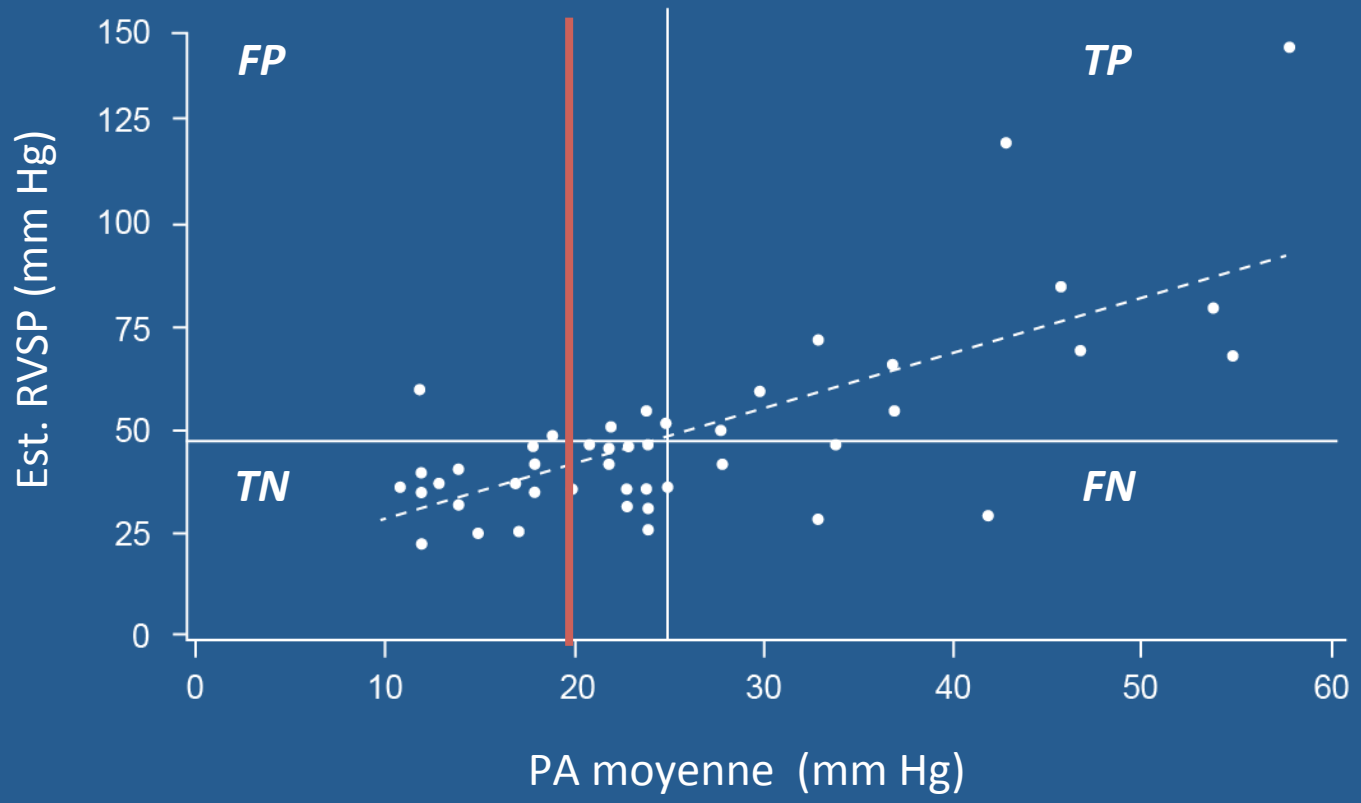

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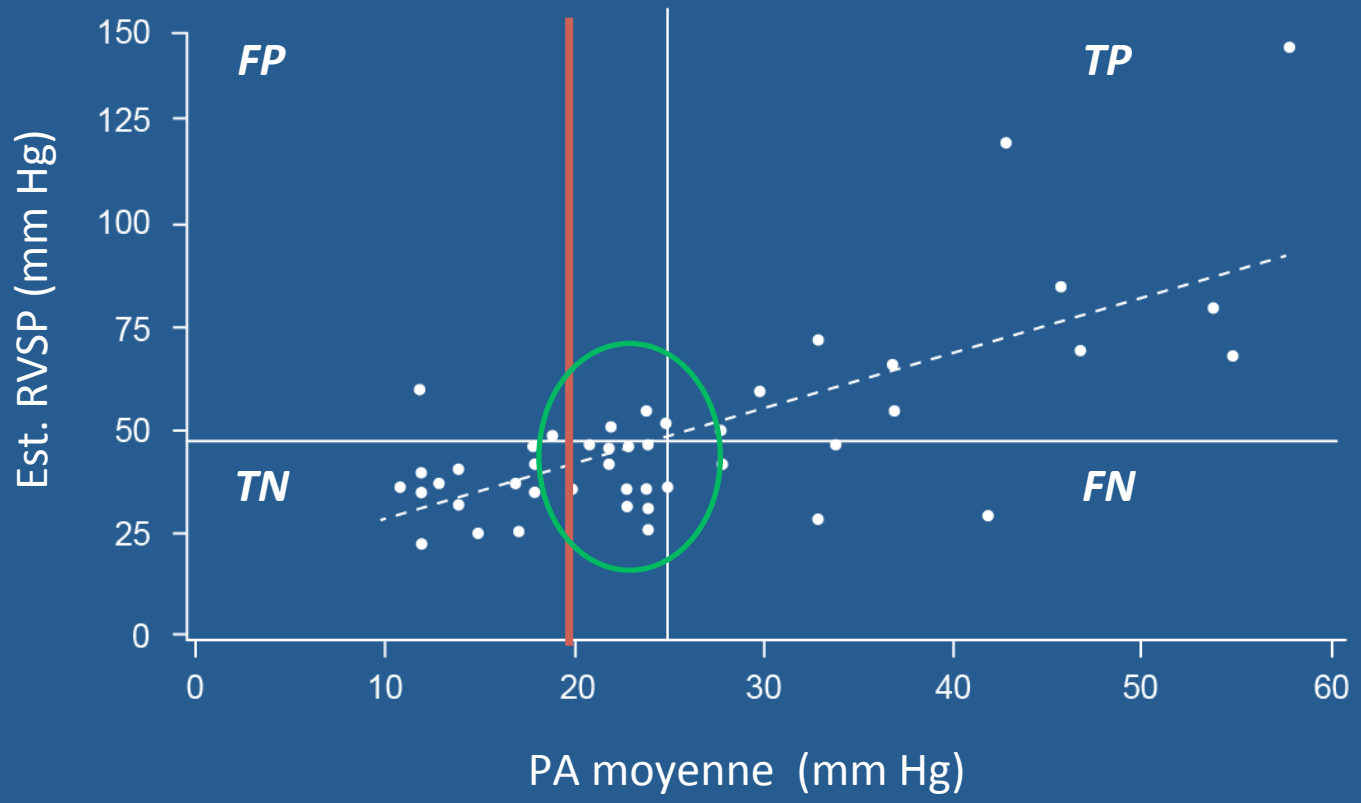
Pertinence du dépistage ?



Hsu et al. J Rheumatol 2008

Screening

1. **Toutes les études de screening ont été faites avec l'ancienne définition**
2. **Est-ce que ces patients existent et si oui, comment les screener ?**

Traitement

1. **Tous les traitements sont indiqués avec l'ancienne définition mais pas la nouvelle…**

Pan *et al. Arthritis Research & Therapy* (2019) 21:217
https://doi.org/10.1186/s13075-019-1981-0

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Early treatment with ambrisentan of mildly elevated mean pulmonary arterial pressure associated with systemic sclerosis: a randomized, controlled, double-blind, parallel group study (EDITA study)

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- (1) resting mPAP 21–24 mmHg, pulmonary arterial wedge pressure (PAWP) < 15 mmHg, transpulmonary gradient (TPG = mPAP- PAWP) > 11 mmHg, or
- (2) exercise-induced elevated mPAP values > 30 mmHg, PAWP < 18 mmHg, and TPG > 15 mmHg which occurred at low workloads (cardiac output (CO) < 10 l/min) [21] without significant left heart or severe lung disease. Inclusion of patients was based on pulmonary pressures and not on PVR

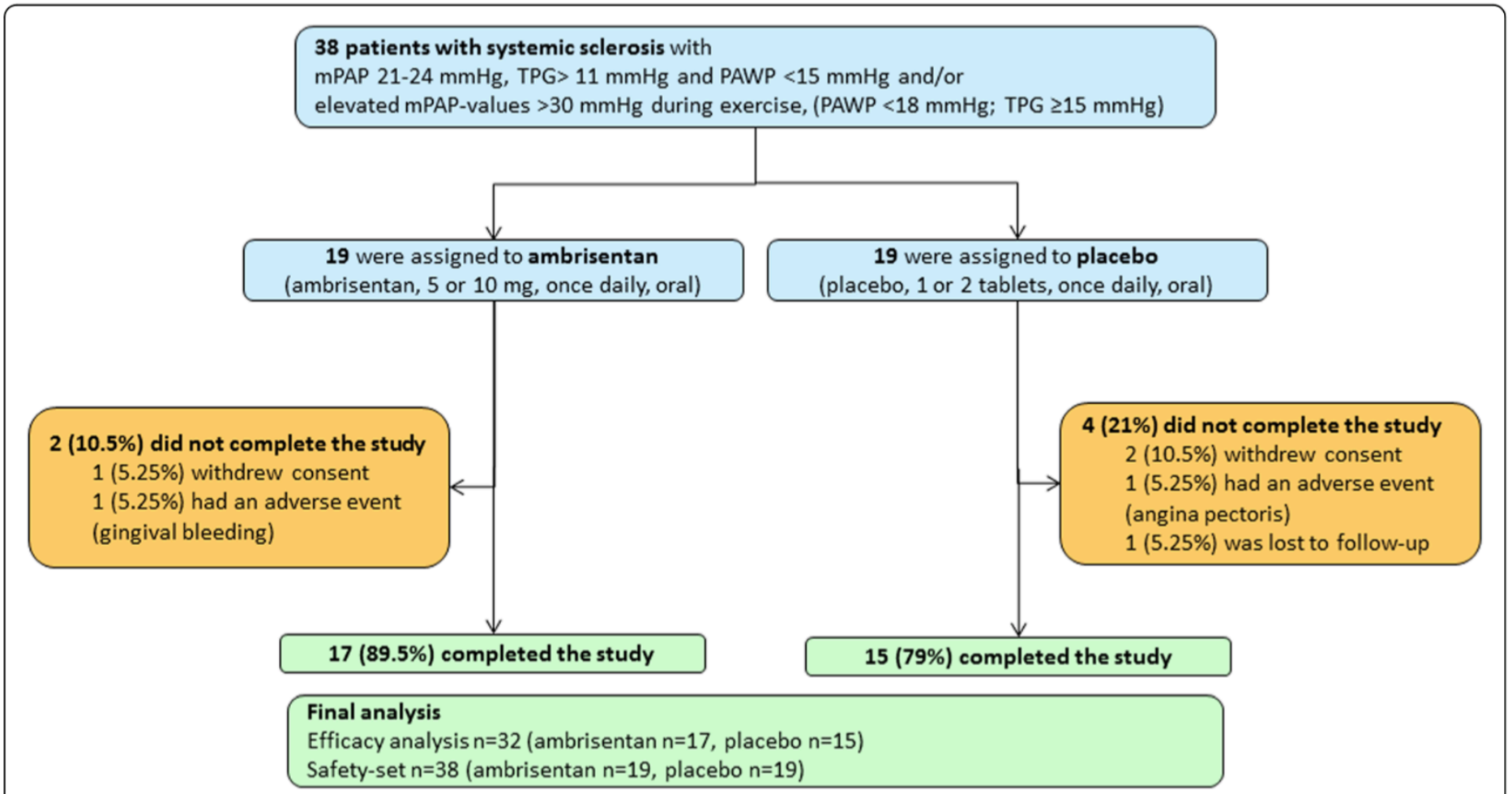


Fig. 1 Study flowchart. A total of 38 patients were enrolled into our study and randomly assigned to be treated with ambrisentan 5 or 10 mg/day or to receive placebo. After 6 months, 32 patients completed the study, 17 in the ambrisentan group, and 15 in the placebo group. Among the 6 dropout patients, 1 in the ambrisentan group and 2 in the placebo group withdrew their written informed consents. One in each group quit because of adverse events, one in the ambrisentan group for gingival bleeding, and one in the placebo group for angina pectoris. One patient in the placebo group was lost to follow-up

Tous ont des PVR<3….. Et ne remplissent donc pas les nouveaux critères d'HTAP

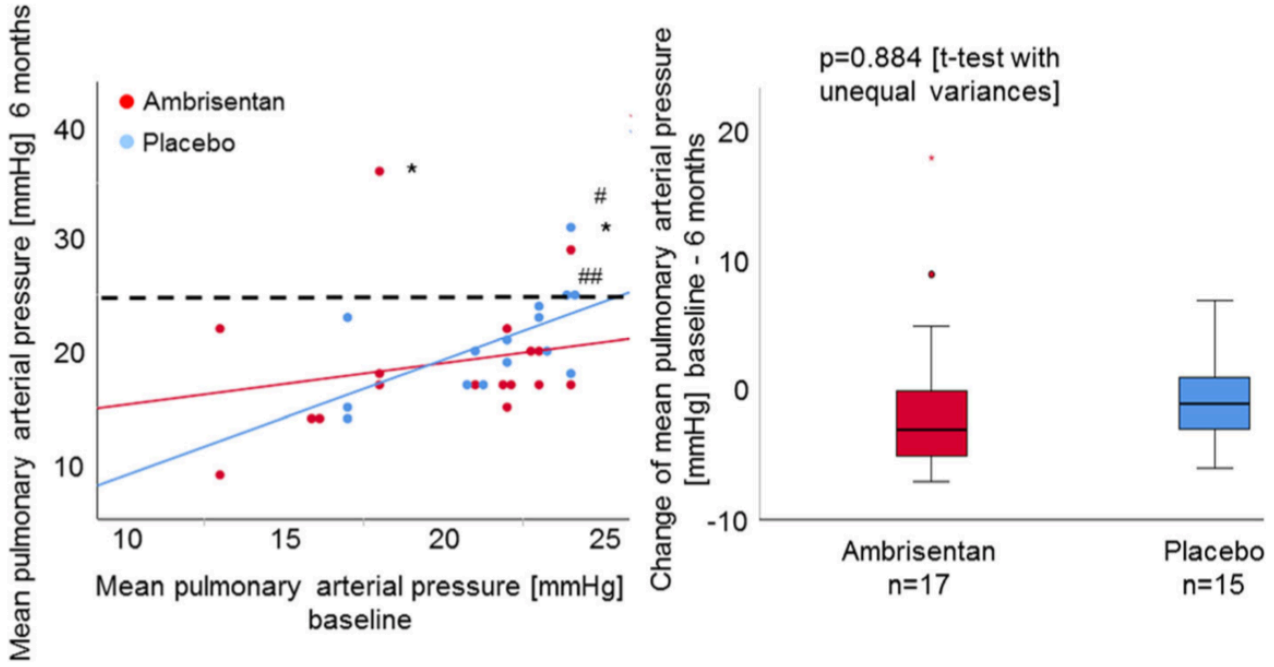


Fig. 2 Changes of mPAP over 6 months. No patients at baseline had a resting mPAP of ≥ 25 mmHg. After 6 months, 2 patients in the ambrisentan group developed a resting mPAP of > 25 mmHg. The dotted line indicates a resting mPAP of 25 mmHg. *: Two patients in the ambrisentan group had a resting PAWP of > 15 mmHg after 6 months; they were reclassified as PH due to left heart disease. #: Three patients in the placebo group developed a resting mPAP of ≥ 25 mmHg at month 6 with a resting PAWP of ≤ 15 mmHg; thus, they were diagnosed as having SSc-APAH after 6 months. The mean change of resting mPAP over 6 months in the ambrisentan group was − 1 ± 6.4 mmHg, and that in the placebo group was − 0.73 ± 3.59 mmHg. The changes between the two groups were not significantly different ($p = 0.884$). Ambrisentan did not significantly decrease the mPAP at rest over 6 months compared to placebo

Change in mPAP : Primary endpoint not met

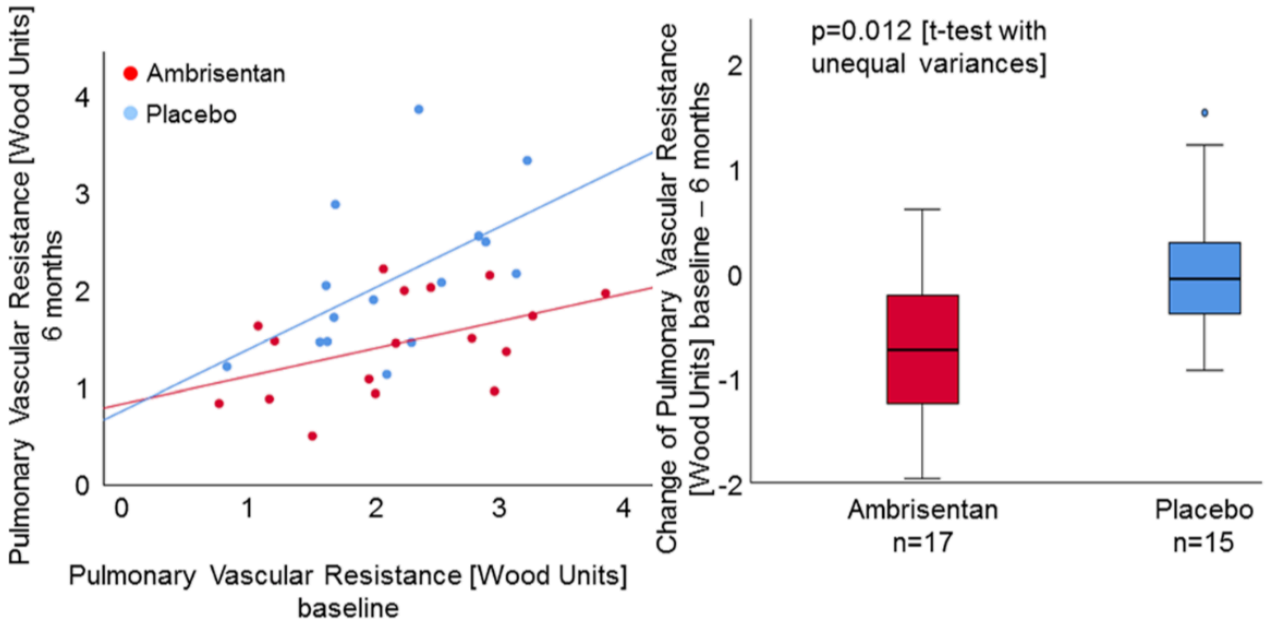
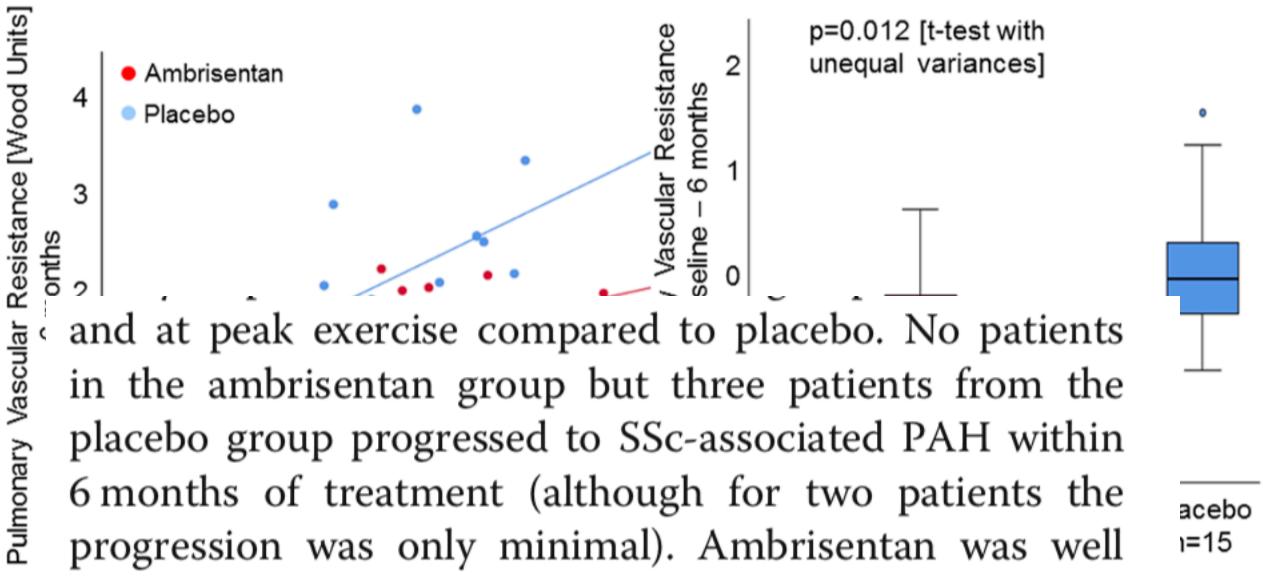


Fig. 4 Changes of PVR at rest over 6 months. Ambrisentan patients had on average a lower PVR at 6 months compared to placebo. The mean change of PVR at rest over 6 months in the ambrisentan group was -0.70 ± 0.78 WU and that in the placebo group was 0.01 ± 0.71 WU. Ambrisentan significantly decreased the PVR at rest over 6 months compared to placebo ($p = 0.012$)

Change in PVR : secondary endpoint met



and at peak exercise compared to placebo. No patients in the ambrisentan group but three patients from the placebo group progressed to SSc-associated PAH within 6 months of treatment (although for two patients the progression was only minimal). Ambrisentan was well tolerated, with a favorable safety profile.

Fig. 4 Changes of PVR
change of PVR at rest o
Ambrisentan significant
l to placebo. The mean
as 0.01 ± 0.71 WU.

Change in PVR : secondary endpoint met

Conclusion

- Nouvelle définition : coup de pied dans la fourmilière ?
- Les vraies HTAP selon la nouvelle définition semblent rares dans la SSc……mais
- Les programmes de screening n'ont pas été designés pour cela : DETECT 2 ?
- Quid du traitement ?
- Etiqueter quelqu'un HTAP et ne pas le traiter…. : un problème ?
- Il faut de futures étude avant d'être affirmatif