The Right Heart International Network (RIGHT-NET)

Rationale, Objectives, Methodology, and Clinical Implications

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KEYWORDS

• Right heart • Pulmonary circulation • Pulmonary hypertension • Exercise doppler echocardiography

KEY POINTS

- Exercise Doppler echocardiography has been implemented for applications beyond coronary artery disease detection, but with a great variability of protocols to assess early stage pulmonary vascular disease and/or left heart failure.
- The RIGHT heart international NETwork ("RIGHT-NET") is a large prospective clinical and echocardiography observational multicenter study.
- Aims of the RIGHT-NET: a) define limits of normal in right heart function and pulmonary circulation hemodynamics during exercise in a large cohort of healthy individuals and elite athletes; b) investigate the impact of abnormal responses on clinical outcome in individuals with overt or at risk of developing pulmonary hypertension.

RATIONALE

Exercise stress testing of the pulmonary circulation to detect early-stage pulmonary vascular disease (PVD) or any cardiac condition associated with an increase in pulmonary venous pressure was part of the hemodynamic work-up in the early years of cardiac catheterization.[1] After years of doubt entertained due to insufficient knowledge of the limits of normal, variable methodologies, and limited validation, the advent of noninvasive exercise imaging of the pulmonary vasculature and cardiac function generated renewed interest.[2–7] Currently, there is emerging consensus to define exercise-induced pulmonary hypertension (PH) by the presence of a resting mean pulmonary artery pressure (mPAP) less than 25 mm Hg and of mPAP greater than 30 mm Hg at peak exercise, with total pulmonary vascular resistance (PVR) of more than 3 Wood units (WU).[8,9] However, these criteria are based on a limited number of studies with a mixture of invasive and noninvasive approaches and variable protocols. On the other hand, only limited information is available about right ventricular (RV) function indices during exercise testing of the pulmonary circulation,[10,11] so that the added value of these indices to measurements of the pulmonary circulation remains undefined. Thus, more methodologically robust noninvasive exercise stress tests of the pulmonary circulation and the right heart are needed. Transthoracic Doppler echocardiography (TTE) is the noninvasive method of choice because it is part of daily cardiology practice, is flexible, and relatively cheap, and is implemented anyway in the diagnostic work-up of any suspicion of PH.[12–15] Current preliminary experience with exercise TTE for detection or diagnosis of early PVD or left heart conditions with increased pulmonary venous pressure is promising.[16–18] However, the exact clinical relevance of abnormal responses in healthy patients with a known increased risk of developing PH and right heart failure remains unclear. The current state of knowledge based on reported exercise TTE studies of the pulmonary circulation and the RV in different populations are presented in **Tables 1–3**.[19–64] Thus, the available literature shows great disparities in sample sizes (from n = 8 to n = 113), exercise protocols (leg press, cycle, or treadmill ergometry), timing of measurements, selection of variables of interest, and different work rates (ranging from 23 ± 7 WU up to 175 ± 50 WU). Therefore, the need for standardization is evident. For this purpose, as recently

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Table 1
Pulmonary pressure response to exercise in normal subjects and athletes

	Subjects: Gender (M, F)	Age (y)	Baseline sPAP or mPAP[a] (mm Hg)	Peak sPAP or mPAP[a] (mm Hg)
Normal Subjects				
Himelman et al,[19] 1989[c]	12: 1 F, 11 M	27–68	22 ± 4	31 ± 7
Oelberg et al,[20] 1998[g]	10: 4 F, 6 M	52.3 ± 10.9	17 ± 8	19 ± 8
Bossone et al,[21] 1999[e]	14: 14 M	18.9 ± 0.9	9	21 CI 95%:9–19
Grünig et al,[22] 2000[c]	11: 11 M	37 ± 11	27 ± 4	36 ± 3
Kiencke et al,[23] 2008[c]	9/—	32 ± 3	17 ± 3	—
Grünig et al,[24] 2009[c]	191: 91 F, 100 M	32 ± 10	20.4 ± 5.3	35.5 ± 5.4
Mahjoub et al,[25] 2009[d]	70: 36 F, 34 M	48 ± 16	27 ± 4	51 ± 9
Möller et al,[26] 2010[c]	88: 49 F, 30 M	18.3 ± 3.5	21.8 ± 3.6	39 (17–63)
Argiento et al,[27] 2010[f]	25: 12 F, 13 M	36 ± 14	19 ± 5	46 ± 11
La Gerche et al,[28] 2010[c]	15/2 F/13 M	38 ± 6	21.6 ± 3.8	47.0 ± 6.5
D'Alto et al,[29] 2011[c]	88: 78 F, 10 M	55.3 ± 12.4	20.6 ± 3.7	25.9 ± 3.3
Argiento et al,[30] 2012[f]	124: 62 M, 62 F	37 ± 13	15.5 ± 2.6 M[a] 15.1 ± 2.9 F[a]	36.0 ± 5.9 M[a] 30.5 ± 7.2 F[a]
Lalande et al,[31] 2012[f]	24: 6 F, 18 M	25 ± 6	23 ± 3	61 ± 5
Simaga et al,[32] 2015[d]	30 Bl[b] 30 Wh[b]	—	16 ± 8[a] 16.6 ± 2.3[a]	34.7 ± 6.2[a] 38.5 ± 5.5[a]
Forton et al,[33] 2016[g,f,c]	30: 15 F, 15 M	23 ± 2	15.4 ± 1.2[a,g] 15.5 ± 1.3[a,f] 15.5 ± 0.8[a,c]	34.2 ± 3.6[a,g] 34.3 ± 3.8[a,f] 34.3 ± 3.2[a,c]
Faoro et al,[34] 2017[f]	38: 5 F, 33 M	38 ± 6	17.7 ± 2[a,sea level] 20 ± 2.8[a,altitude]	44.9 ± 4.4[a,sea level] 47.6 ± 4.9[a,altitude]
Motoji et al,[35] 2017[f]	26: 14 F, 12 M	22 ± 3	15.8 ± 1[a]	28.8 ± 3.2[a]
Athletes				
Bossone et al,[21] 1999[e]	26: 26 M	20.3 ± 1.7	21	41 CI 95%:21–41
La Gerche et al,[28] 2010[d]	40/4 F/36 M	36 ± 8	21.5 ± 3.8	60.7 ± 12.4
Bidart et al,[36] 2007[e]	15/—	38.7	19.4	54.8

Abbreviations: Bl, black; F, female subject; M, male subject; sPAP, systolic PAP; Wh, white; —, not available.
[a] mPAP (mm Hg) was calculated as 0.6 × sPAP + 2.
[b] 30 black subjects (age 27 ± 6 M, 25 ± 6 F) of sub-Saharan descent and 30 matched by age, sex, and body size European white subjects (age 27 ± 6 M, 27 ± 8 F).
[c] Exercise protocol: supine.
[d] Exercise protocol: semisupine.
[e] Exercise protocol: recumbent.
[f] Exercise protocol: semirecumbent.
[g] Exercise protocol: upright bicycle.

argued, a series of methodological requirements can be determined from sound physiologic principles and previously available experience[8,9,16]:

- Exercise must be dynamic (cycling, running) because resistive or static exercise (weight lifting, handgrip) is associated with increases in cardiac output (CO) too small to obtain a meaningful range of pulmonary vascular pressure-flow relationships.[35]
- Body position does not matter because the same slope of mPAP as a function of CO, maximum oxygen uptake (V_{O_2}), and maximum CO are estimated during incremental cardiopulmonary exercise testing in supine, semirecumbent or upright positions. Thus the body position allowing for the TTE approach can be used safely.[33,65]

Table 2
Pulmonary artery pressure response to exercise Doppler echocardiography in subjects with high risk for pulmonary hypertension

Author, Year	Associated Disease Subjects: Gender	Age (y)	Baseline sPAP (mm Hg)	Peak sPAP (mm Hg)
Lung disease				
Himelman et al,[19] 1989[g]	COPD 36: 15 F, 21 M	32–80	46 ± 20 22 ± 4 (ctrl)	83 ± 30 31 ± 7
Rodrìguez et al,[37] 2017	COPD 81: 15 F, 66 M	68 ± 9	31 ± 27	57 ± 29
Congenital heart disease				
Oelberg et al,[20] 1998[k]	Asymptomatic ASD 10: 4 F, 6M	52.9 ± 11.2	31 ± 8 17 ± 8 (ctrl)	51 ± 10 19 ± 8
Möller et al,[26] 2010[g]	ASD and VSD 44: 25 F, 19 M	17.5 ± 3.3	20.7 ± 5.3 21.8 ± 3.6 (ctrl)	37 (24–76) 39 (17–63)
Ait Ali et al,[38] 2014[g]	Operated Fallot 123: 41 F, 82 M	26.2 ± 11.3	49 ± 22.4	79.4 ± 34.2
Brenner et al,[39] 2015[g]	HA dwellers PFO (n = 18) HA dwellers no PFO (n = 39)	54.2 ± 10.3 49.6 ± 10.7	24.4 ± 5.3 (HA PFO) 24.8 ± 3.6 (HA no PFO)	49.9 ± 9.6 40.3 ± 9.1
Van Riel et al,[40] 2015	ASD, VSD, PDA, other 76: 50 F, 26 M	43.2 ± 14.5	27.5 ± 5.2 37.1 ± 7.9	40.2 ± 6.6 59.3 ± 8.5
CMS				
Stuber et al,[41] 2010[g]	CMS subjects 30: —	47 ± 13	30.3 ± 8 (CMS) 25.4 ± 4.5 (ctrl)	56.4 ± 19 (CMS) 39.8 ± 8 (ctrl)
Groepenhoff et al,[42] 2012[g]	CMS subjects (13: 13 M) HA dwellers (15: 6 F, 9 M) L (15: 6 F, 9 M)	50 ± 3 41 ± 2 35 ± 3	**26 ± 2** (CMS) **23 ± 1** (HA) **20 ± 1** (L)$^{sea\ level}$	**56 ± 4** (CMS) **42 ± 3** (HA) **31 ± 2** (L)$^{sea\ level}$
Pratali et al,[43] 2013[g]	CMS subjects (n = 46) HA dwellers (n = 40)	51 ± 10 48 ± 8	30 ± 6 (CMS) 27 ± 5 (HA)	50 ± 12 (CMS) 38 ± 8 (HA)
HAPE-S				
Grünig et al,[22] 2000[g]	HAPE-S 9: —	45 ± 8	28 ± 4 27 ± 4 (ctrl)	55 ± 11 36 ± 3
Kiencke et al,[23] 2008[g]	HAPE-S 10: —	33 ± 2 NA	19 ± 4 17 ± 3 (ctrl)	23 ± 6 11 ± 5
Relative of iPAH				
Grünig et al,[22] 2000[g]	Relatives of iPAH cases 52: —	NA	24 ± 4 (nr) 23 ± 3 (ar)	37 ± 3 (nr) 56 ± 11(ar)
Grünig et al,[24] 2009[g]	Relatives of iPAH cases 291: 125 F, 166 M	37 ± 16	20.7 ± 5.4 20.4 ± 5.3 (ctrl)	39.5 ± 5.6 35.5 ± 5.4
Connective tissue disease				
Collins et al,[44] 2006[l]	Scleroderma 51: 49 F, 2 M	53.9 ± 12.0 NA	24 ± 8	38 ± 12
Alkotob et al,[45] 2006[l]	Scleroderma 65: 56 F, 9 M	51 ± 12 NA	25 ± 8	39 ± 8
Steen et al,[46] 2008[l]	Scleroderma 54: 51 F, 3 M	NA	34.5 ± 11.5	51.4

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Table 2
(*continued*)

Author, Year	Associated Disease Subjects: Gender	Age (y)	Baseline sPAP (mm Hg)	Peak sPAP (mm Hg)
Reichenberger et al,[47] 2009[g]	Scleroderma 33: 31 F, 2 M	54 ± 11 NA	23 ± 8	40 ± 11
Kovacs et al,[48] 2010[g]	Connective tissue disease 52: 42 F, 10 M	54 ± 11	27 ± 5[a] 23 ± 3[b]	55 ± 10[a] 29 ± 8[b]
D'Alto et al,[29] 2011[g]	Systemic sclerosis 172: 155 F, 17 M	51.8 ± 21.5	26.2 ± 5.3 20.6 ± 3.7 (ctrl)	36.9 ± 8.7 25.9 ± 3.3
Gargani et al,[49] 2013[h]	Systemic sclerosis 164: 150 F, 14 M	58 ± 13	—	TRV 332 cm/s Range 185–533
Grünig et al,[50] 2013[g]	PAH, CTPEH 124: 87 F, 37 M	54 ± 16	64 ± 17	98 ± 25
Codullo et al,[51] 2013[g]	Systemic sclerosis 170: 153 F, 17 M	55.2 ± 13 NA	23.7 ± 8.1[e] 29.5 ± 5.5[f]	33.1 ± 12.6[e] 47.7 ± 12.2[f]
Voilliot et al,[52] 2014[h]	Systemic sclerosis 45: 34 F, 11 M	54 ± 3	25 ± 7	46 ± 14
Nagel et al,[53] 2015[i]	Systemic sclerosis 76: 64 F, 12 M	58 ± 14 1.8 ± 0.2	25.6 ± 7.3[c] 52.0 ± 18.0[d]	49.9 ± 12.7[c] 83.9 18.9[d]
Kovacs et al,[54] 2017[j]	Systemic sclerosis 58: 56 F, 2 M	51.3 ± 11.5[m] 55.3 ± 11.6[n]	25.0 (22.0–27.0)[m] 25.0 (22.8–30.0)[n]	43.2 ± 11.7[m] 49.5 ± 10.7[n]

Bold type values indicate mPAP (mm Hg) calculated as 0.6 × sPAP + 2.

Abbreviations: ar, abnormal response to exercise; ASD, atrial septal defect; CMS, chronic mountain sickness; COPD, chronic obstructive pulmonary disease; ctrl, controls; HA, high altitude; HAPE-S, high altitude pulmonary edema susceptible; iPAH, idiopathic pulmonary arterial hypertension; nr, normal response to exercise; L, lowlanders; NA, not available; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.

[a] Exercise sPAP greater than 40 mm Hg.
[b] Exercise sPAP less than 40 mm Hg, peak V_{O_2} less than 75%.
[c] No PH group of 54 subjects (mPAP <25 mm Hg).
[d] 22 subjects with manifest PH (mPAP >25 mm Hg).
[e] Subjects (n = 164) with complete follow-up who did not develop PH.
[f] Subjects (n = 6) who did develop PH.
[g] Exercise protocol: supine.
[h] Exercise protocol: semisupine.
[i] Exercise protocol: recumbent.
[j] Exercise protocol: semirecumbent.
[k] Exercise protocol: upright bicycle.
[l] Exercise protocol: treadmill.
[m] Exercise protocol: baseline examination.
[n] Exercise protocol: follow-up ~4 y after their baseline examination.

- Measurements should be made during, not after, the exercise stress because too-fast postexercise recovery of vascular pressures and flows normally occurs within minutes.[30,66]
- Exercise stress should be incremental, with stepwise increase in workload allowing for measurements in quasi-steady-state V_{O_2}, after 2 to 5 minutes of stabilization at each step and increments in workload individually tailored to obtain at least 3 (but preferably 5) pressure-flow coordinates in an exercise duration of less than 12 to 15 minutes.[4,5,9]
- It is important to estimate all the components of PVR, thus pulmonary artery pressure (PAP), wedged PAP (PAWP), and CO. Using workload or V_{O_2} as surrogates for CO greatly decreases the accuracy and precision of pulmonary vascular function as defined by mPAP–CO relationships. The relationships between CO, V_{O_2}, and workload are near-linear but with a plateauing at high levels of exercise, and prediction equations based on linear regression also fail due to the considerable variability of CO at any given level of workload or V_{O_2}.[30,33]

Noninvasive exercise stress testing of the pulmonary circulation using TTE is acceptable because exercise measurements are probably accurate.

Table 3
Pulmonary pressure response to exercise Doppler echocardiography in left heart diseases and valvular heart diseases

Author, Year	Subjects, Gender (M, F)	Age (y)	Baseline sPAP (mm Hg)	Peak sPAP (mm Hg)
Heart Failure				
Lancellotti et al,[55] 2003[d]	Survivors 89: 60 M	65 ± 11	26 ± 10	44 ± 18
	Nonsurvivors 9: 6 M	69 ± 9	22 ± 9	48 ± 16
Tumminello et al,[56] 2007[c]	46: —	66 ± 10	31 ± 11	52 ± 18
Ennezat et al,[57] 2008[d]	104: 29 F, 75 M	54 ± 12	29 ± 9	44 ± 18
Marechaux et al,[58] 2008[d]	85: 21 F, 64 M	57 ± 13	27 ± 8	43 ± 18
Bandera et al,[59] 2014[d]	136[a]: 50 F, 86 M	64 ± 11	—	—
	Group A[b] 36: 20 F	67 ± 10	37 ± 17	61 ± 19
	Group B[b] 100: 30 F	61 ± 12	33 ± 14	51 ± 18
Guazzi et al,[60] 2016[d]	97: 20 F, 67 M	64 ± 11	37 ± 16	59 ± 18
Degenerative Asymptomatic Mitral Regurgitation (at least moderate)				
Magne et al,[61] 2010[d]	78: 34 F, 44 M	61 ± 13	39 ± 11	62 ± 17
Kusunose et al,[62] 2013	196: 70 F, 126 M	56 ± 13	39 ± 8	56 ± 13
Asymptomatic Severe Aortic Stenosis				
Lancellotti et al,[63] 2012[d]	105: 53 F, 62 M	71 ± 9	38 ± 8	62 ± 16
Asymptomatic Mitral Stenosis				
Brochet et al,[64] 2011[c]	48: 32 F, 16 M	51 ± 14	36 ± 5	68 ± 7

[a] The underlying diseases were heart failure with reduced (n = 54, 40%) or preserved ejection fraction (n = 8, 6%), history of stable coronary artery disease (n = 18, 13%), high-risk subjects with hypertrophic cardiac remodeling (n = 33, 24%), hypertrophic or restrictive cardiomyopathy (n = 5, 4%), and mitral or tricuspid valvular regurgitation (n = 18, 13%).
[b] Δ oxygen consumption (V_{O_2})/Δ work rate: flattening (group A), not flattening (group B).
[c] Exercise protocol: semisupine.
[d] Exercise protocol: tilting bicycle.

The reliability of exercise TTE of the pulmonary circulation is still under discussion, although average responses and derived limits of normal seem to agree very well with those obtained during a right heart catheterization.[4,5,48] Bland-Altman analysis of PAP, PAWP, and CO measured at rest by TTE versus right heart catheterization show almost no bias, indicating excellent accuracy; however, limits of agreement are sometimes wide, indicating possible problems of insufficient precision for individual decision-making.[67] Echocardiographic estimates of PAP from the maximum velocity of tricuspid regurgitation (TR) compared with invasively measured PAP during exercise have recently also been shown by Bland-Altman analysis to be associated with only minimal bias, demonstrating acceptable accuracy; however, limits of agreement were broad, indicating limited precision.[11,68] Furthermore, the agreement between TTE and invasive measures of PAP during upright exercise is good among the subset of patients with high-quality TR Doppler signal.[68] There still is a concern that TTE might underestimate CO during exercise.[11] This can probably be overcome by intensive training of dedicated operators. Even so, a 5% underestimation remains, showing concomitant measurements of CO by the Innocor device (by rebreathing of nitrous oxide and sulfur hexafluoride) and TTE of the left ventricular outflow tract in 10 subjects reported by Forton and colleagues.[33]

At this stage, knowledge regarding limits of normal of exercise TTE indices of RV function is limited to measurements of tricuspid annular plane systolic excursion (TAPSE), tricuspid annulus S′, and stroke volume (SV), along with estimates of systolic PAP (sPAP) in 90 healthy young adults (45 male subjects).[10] Changes from rest to maximum workload were (Δ) 4 to 10 mm for TAPSE, 6 to 14 cm per second for S′, 12 to 57 mm Hg for sPAP, 0 to 96 mL for SV, and −0.6 plus or minus 0.3 (1.3 ± 0.4–0.7 ± 0.2) mm/mm Hg for TAPSE/sPAP.

THE RIGHT HEART INTERNATIONAL NETWORK

The Right Heart International Network (RIGHT-NET) is a large prospective observational multicenter clinical study, including resting and exercise TTE performed at different European

and American centers (ClinicalTrials.gov identifier: NCT03041337).

Aims

The aims of this study are

1. To evaluate the feasibility of exercise TTE for the noninvasive assessment of the right heart and pulmonary circulation in a large cohort of healthy subjects, elite athletes, and subjects with overt or at risk of PH.
2. To explore the physiologic spectrum of responses of the right heart and pulmonary circulation during an optimally standardized exercise TTE in a large cohort of healthy subjects, elite athletes, and subjects with overt PH or at risk of PH.
3. To systematically compare the morphologic and functional behavior of the right heart and pulmonary circulation to exercise in subjects with normal versus abnormal responses, and their clinical correlations.
4. To investigate the prognostic impact of an abnormal right heart and pulmonary circulation response to exercise during a long-term follow-up.

Methods

Study population

It is anticipated that the study population will comprise approximately 3000 subjects ($\geq$18 years old): 500 healthy subjects, 500 elite athletes, and about 2000 subjects with overt PH or at risk of PH.

Healthy subjects Healthy volunteers (or subjects for work ability assessment) with no structural heart disease on TTE and without a history of any cardiovascular disease and/or any systemic diseases known to affect the cardiovascular system will be prospectively recruited. Exclusion criteria will be systemic arterial hypertension, diabetes mellitus, coronary artery disease, significant (at least moderate) valvular heart disease, congenital heart disease, history of congestive heart failure, cardiomyopathies, sinus tachycardia, atrial fibrillation or flutter, use of illicit drugs, medical therapy with cardioactive drugs, chronic excessive alcohol consumption, elite athletes, pregnancy, obesity (body mass index $\geq$30 kg/m^2), pulmonary disease, renal disease, hepatic disease, significant endocrine alterations, cancer, and inadequate echocardiographic image quality.[69]

Elite athletes Cardiac adaptations in athletes mainly depend on the characteristics, intensity, and cumulative duration of training protocols, with a dose-effect relation.[70,71] In particular, isotonic (dynamic) exercise is associated with a substantial increase in CO and reduction in peripheral vascular resistance; therefore, endurance training mainly results in volume overload. Conversely, isometric (static) exercise is characterized by less increase in CO and by a transient increase in peripheral resistance; therefore, its training is characterized by a pressure overload.[71]

In this study, protocol activity levels will be assessed by questionnaire, and subjects will be asked to describe and quantify exercise during a typical week during the preceding months. All the athletes will have been trained intensively for 15 to 20 hours per week for at least 4 years.[72] Based on their training protocol and the type of sports activity, they will be categorized into 2 groups: endurance-trained athletes and strength-trained athletes.[72–74] Endurance-trained athletes (long-distance and middle-distance swimming or running, cycling, rowing) will be defined as subjects actively engaged in endurance sports competition, subjected to intensive aerobic isotonic dynamic exercise at incremental workloads of 70% to 90% of maximal heart rate. In particular, they should have performed 3 hours per day of incremental long-distance swimming (7000 m per day divided into a series of 400–800 m) or 3 hours per day of long-distance running or cycling, and only 2 hours per week of weight-lifting at a low workload.[70] On the other hand, the strength-trained athletes group will include top-level competitive athletes (weight-lifting, martial arts, windsurfing) who should have undergone an aerobic isometric static exercise at incremental workloads of 40% to 60% of maximal heart rate. Their training protocol should have included 3 hours per day of short-distance running and/or 4 hours per day of weight-lifting at a high workload.[72–74]

Patients with overt pulmonary hypertension or at risk of pulmonary hypertension Patients with overt or at risk of PH will be classified according to European guidelines.[12]

1. Pulmonary arterial hypertension (PAH): idiopathic, heritable, healthy relatives of patients with PAH, healthy carriers of mutations of bone morphogenetic receptor 2 gene, associated with connective tissue disease, portal hypertension, schistosomiasis, congenital heart disease
2. PH due to left heart disease: left heart valve disease, heart failure with reduced or preserved ejection fraction, congenitally acquired inflow or outflow tract obstruction, and congenital cardiomyopathies
3. PH due to chronic lung diseases and/or hypoxia: chronic altitude exposure, chronic

obstructive pulmonary disease, interstitial lung diseases, sleep-disordered breathing
4. Chronic pulmonary thromboembolic disease and other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms: miscellaneous conditions such as histiocytosis-X or sarcoidosis.

Clinical data

Demographic characteristics, complete medical history, comorbidities, symptoms and signs, laboratory values, electrocardiogram (ECG) parameters, coronary angiography and other imaging results, medications, and in-hospital and long-term outcomes will be systematically collected for all patients via standardized forms to obtain as much information as possible (Table 4). Specific attention will be paid to excluding the presence of any pulmonary condition (apart from patients with PH due to chronic lung diseases and/or hypoxia) that may lead to a pathologic pulmonary hemodynamic response during exercise. Follow-up would be performed at 6 months and then once a year for at least 5 years during outpatient clinical visits or by telephone call. Events recorded will be death, major cardiovascular events (myocardial infarction, stroke, coronary revascularization, acute heart failure), hospitalization, and diagnosis of PH by invasive recording of an mPAP greater than 25 mm Hg at rest.

Resting echocardiographic Doppler examination

TTE examinations will be performed at rest with commercially available equipment on all subjects, according to standardized protocols.[75] A detailed case report form (CRF) will be used by all laboratories. All the measurements included in the CRF will be assessed by the operators and performed according to the recommendations for echocardiographic assessment of the left and right heart from the American Society of Echocardiography or the European Association of Cardiovascular Imaging[76–78] (Table 5).

Exercise echocardiographic Doppler examination

Exercise TTE will be performed according to the current recommendations on a semirecumbent cycle ergometer with an incremental workload

Table 4
Clinical data

Demographic and Lifestyle Data						
Age (y)	**Sex**	**Height (cm)**	**Weight (kg)**	**BMI (kg/m^2)**	**BSA (m^2)**	**Waist (cm)**
Systolic BP (mm Hg)	HR	Diastolic BP (mm Hg)	Physical activity	Coffee Alcohol	Smoker Drugs and toxins	Other lifestyle information

Cardiovascular Risk Factor				
Diabetes	**Arterial Hypertension**	**Dyslipidemia**	**Comorbidities**	**Medical Therapy**
Previous cardiovascular events or interventions	—	—	—	—

Laboratory Data					
Glycaemia (mg/dL)	**Cholesterol (mg/dL)**	**HDL (mg/dL)**	**Triglycerides (mg/dL)**	**Troponin**	**Hb (g/dL)**
CRP (m/dL)	Iron (μg /dL)	Creatinine (mg/dL)	NT-proBNP (pg/ml) BNP (pg/mL)	Other laboratory examination	

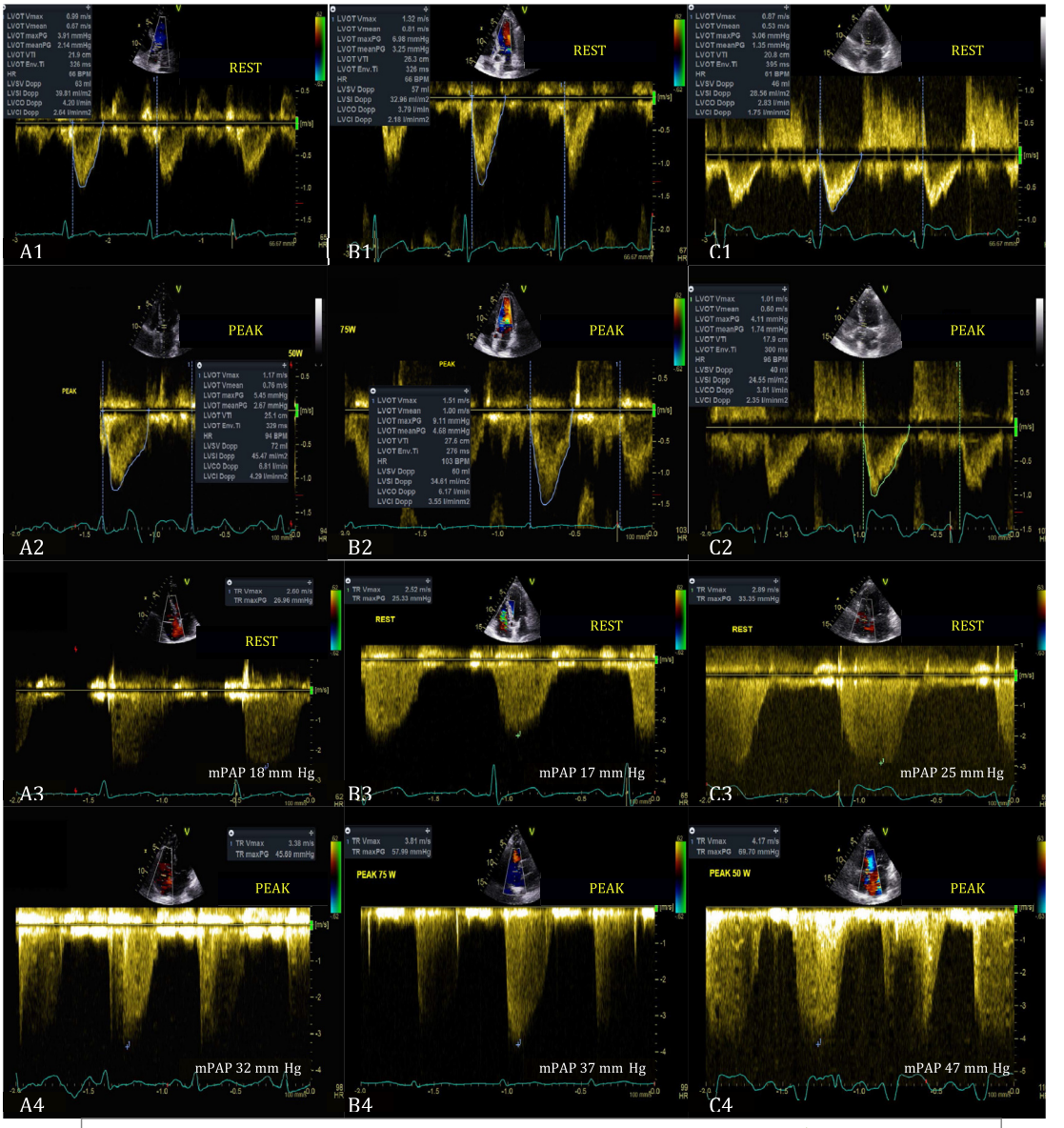
Other Data (if Available)		
Pulmonary Functional Test	**Capillaroscopy Pattern**	**Specific Antibodies for SSC**
6MWT (mt)	Other imaging data	Other useful information

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BSA, body surface area; CRP, C-reactive protein; Hb, hemoglobin; HDL, high-density lipoprotein; HR, heart rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; SSC, scleroderma; 6MWT, 6 minutes walking test.

Table 5
Key echocardiographic measurements at rest and during exercise

Echocardiographic View	Measurement
Parasternal long axes	• LV end-diastolic diameter • LV end-systolic diameter • Interventricular septum thickness (diastole) • Inferolateral wall thickness (diastole) • LVOT diameter (zoom) • Wall motion abnormalities • Aortic and mitral function • Pericardial effusion
Parasternal short axes	• RVOT diameter • Pulmonary artery diameter • RVOT acceleration time • RVOT TVI notch • PR early diastolic velocity • Peak tricuspid velocity • Wall motion abnormalities • Aortic, mitral, tricuspid and pulmonary valve function • Pericardial effusion
Apical 4-chamber	• LV end-diastolic volume • LV end-systolic volume • Wall motion abnormalities • LA volume • E, A, deceleration time • e' TDI lateral • e' TDI septal • S' systolic TDI • Mitral and tricuspid function • Pericardial effusion
Apical 5-chamber	• Peak aortic velocity • LVOT TVI • Aortic valve function
Apical 2-chamber	• LV end-diastolic volume • LV end-systolic volume • Wall motion abnormalities • LA volume • Mitral valve function • Pericardial effusion
Focused apical on the RV	• RV dimension 1 • RV dimension 2 • RV diastolic area • RV systolic area • RA volume • TAPSE • Peak tricuspid velocity • E, A • S' systolic TDI • e' TDI, a' TDI • Tricuspid valve function • Pericardial effusion
Subcostal	• IVC diameter • IVC collapse • RV free wall thickness • Pericardial effusion

Abbreviations: A, mitral inflow E velocity as measured by PW Doppler; E, mitral inflow E velocity as measured by PW Doppler; e', early diastolic velocity of the mitral annulus as measured by tissue Doppler; IVC, inferior vena cava; LA, left atrial; LV, left ventricular: LVOT, left ventricular outflow tract; PR, pulmonary regurgitation; RA, right atrial; RVOT, RV outflow tract; S' pulsed Tissue Doppler velocity of lateral tricuspid annulus; TDI, tissue Doppler imaging; TVI, time-velocity integral.



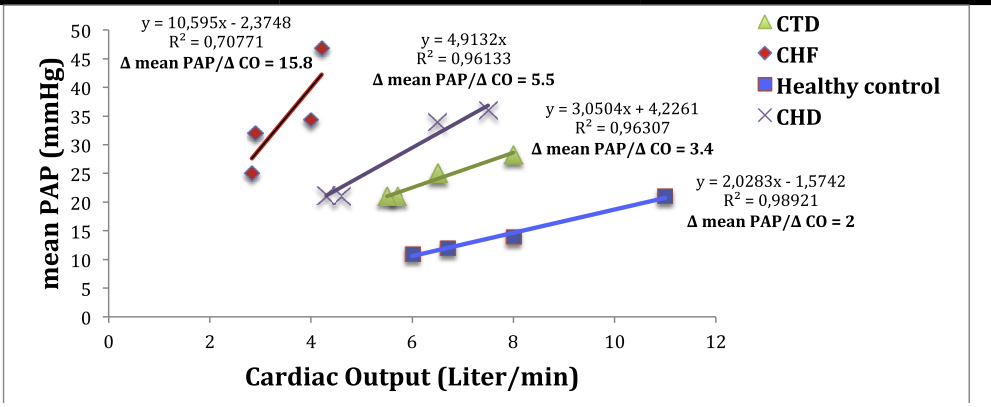


Fig. 1. Relationship between mPAP and CO at rest and during incremental exercise in 3 different diseases compared with normal response to exercise in an age-matched healthy control. (*A1–A4*) A 53-year-old woman with scleroderma (New York Heart Association [NYHA] class II). (*B1–B4*) A 64-year-old woman with patent ductus

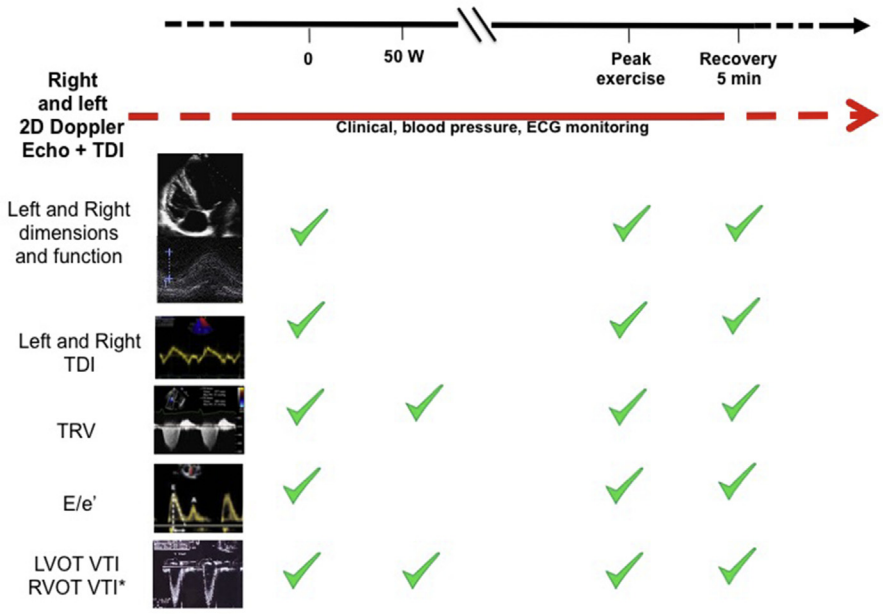


Fig. 2. Methodology of exercise stress echocardiography. Agitated saline may be used by mixing saline solution with room air (9:1 ratio) and vigorously agitating between 2 syringes using a 3-way stopcock, in cases of poor TR Doppler signals. A 5-mL bolus will be rapidly administered during exercise while simultaneously obtaining images of the right and left heart in the apical 4-chamber view. For each echocardiographic (echo)-Doppler parameter in case of poor and/or missing images it will be indicated not feasible and/or not assessed, respectively. Key echo-Doppler parameters that will be measured are specified in Tables 5 and 6. 2D, 2-dimensional; E, mitral inflow E velocity as measured by pulsed-wave Doppler; e', early diastolic velocity of the lateral mitral annulus and septal (average) as measured by TDI; LVOT, left ventricular outflow tract; PASP, pulmonary artery systolic pressure; RVOT, right ventricular outflow tract; TDI, tissue Doppler imaging (pulsed Doppler sample volume is placed at the tricuspid annulus, interventricular septum, and lateral mitral annulus in the apical 4-chamber view); TRV, tricuspid regurgitant velocity; VTI, velocity time integral; * RVOT VTI will be measured only at rest, peak exercise and after 5-minutes recovery.

of 25 every 2 minutes up to the symptom-limited maximal tolerated workload.[18,27,79] In subjects with reduced functional capacity, the exercise protocol may consist of lower incremental workload (10–20 WU every 2 minutes), and will be specified in the records. The exercise table will be tilted laterally by 20° to 30° to the left. Heart rate (ECG lead) will be continuously monitored, and blood pressure will be monitored by sphygmomanometer at baseline and during the last 15 seconds of each workload step. Termination criteria and/or positive test criteria for inducible myocardial ischemia will follow the current recommendations.[18,79] Key echocardiographic measurements will be acquired at baseline, at 50 WU, at peak exercise, and after 5-minutes recovery, including left ventricular and RV function, valvular and subvalvular gradients, regurgitant flows, left and right heart hemodynamics (sPAP, mPAP, PCWP, PVR, right atrial pressure [RAP] and CO) (Figs. 1 and 2, see Table 5; Table 6).

Oxygen saturation

Transcutaneous arterial oxygen saturation will be measured at a fingertip with a pulse oxymeter at baseline, 50 WU, peak exercise, and after 5-minutes recovery.

arteriosus, not corrected (NYHA class II). (*C1–C4*) A 75-year-old woman with diagnosis of heart failure (NYHA class III) with midrange reduced ejection fraction of 46%. The Δ mPAP/Δ CO of 3.4 mm Hg/L/min in patient with scleroderma (Δ), 5.5 mm Hg/L/min in patient with congenital heart disease (×), and 15.8 mm Hg/L/min in heart failure patient (◇) are indicative of an abnormal pulmonary vascular response to exercise compared with normal response in healthy control (□) (Δ mPAP/Δ CO of 2 mm Hg/L/min; normal ranges from 0.5 to 3.0). mPAP (mm Hg) = 0.6 × sPAP + 2; SV = π × (LVOT/2)2 × LVOT VTI; CO (L/min) = SV × HR. CHD, congenital heart disease; CHF, chronic heart failure; CTD, connective tissue disease; LVOT, left ventricular outflow tract; TVI, time-velocity integral. (*Courtesy of* Echo Lab Cava de' Tirreni and Amalfi Coast Division of Cardiology, University Hospital of Salerno, Italy.)

Table 6
Key echocardiographic indices for evaluation of the right heart pulmonary circulation unit at rest and during exercise

Key Echo-Doppler Indices	Cut-Off Value at Rest	Cut-Off Value at Peak Exercise	Pitfalls and Remarks	Reference
Pulmonary Hemodynamics				
sPAP (mm Hg) $4 \times TRV^2 + RAP$	TRV >2.8–2.9 m/s or not measurable sPAP >34–36 mm Hg	TRV >3.1 m/s sPAP >40 mm Hg for healthy patients sPAP >55–60 mm Hg for athletes	Signal acquisition may be difficult during exercise because of increased respiratory rate and excursion Postexercise is less reliable because sPAP is known to return to baseline quite quickly Sweep velocity should be at least 100 mm/s measuring only the well-defined dense spectral profile If there is a weak TR jet the intravenous use of agitated saline may provide a more complete TR envelope with attention to avoiding artifacts (fringes) and overestimation	12,18,21,30,68,76
RAP (mm Hg) IVC size and collapsibility	<2.1 cm, collapse >50%: RAP = 3–5 mm Hg	—	The baseline RA pressure is used for all calculations because of the difficulty of imaging the IVC and estimating RA pressure during exercise This assumption may result in underestimation of sPAP	18,76
mPAP (mm Hg) $(0.6 \times PASP + 2) + RAP$	≥25 mm Hg	34 mm Hg at a CO<10 L/min, 45 mm Hg at a CO<20 L/min and 52 mm Hg at a CO<30 L/min	mPAP–CO relationship is preferable for studying the pulmonary vascular response to exercise	30

(*continued on next page*)

Table 6
(*continued*)

Key Echo-Doppler Indices	Cut-Off Value at Rest	Cut-Off Value at Peak Exercise	Pitfalls and Remarks	Reference
CO (L/min) SV*HR/1000 SV = π•(LVOT/2)^2•LVOT VTI	SV = 60–120 mL CO = 4–8 L/min	Flow reserve = SV $\geq$20%	CO tends to be underestimated, mainly because of the underestimation of LVOT dimensions LVOT PW Doppler sample volume should be placed as much as possible at the same position in the LVOT during test	[18]
PVR TRV/VTI $_{RVOT}$ (cm) $\times$ 10 + 0.16	<1.5 WU normal PVR	>3 WU	Methods for estimating PVR are less well-validated Should not be used as a substitute for the invasive evaluation of PVR PVR at peak exercise is flow-dependent Dynamic PVR may better represent PVD than total PVR at peak exercise	[4,12,76]
AT_{RVOT}	<100 m/s	—	Heart rate should be in the normal range of 60 to <100 beats/min	[76]
FVE_{RVOT}	Midsystolic notching	—	Lack of data in wide population of PH subjects and during exercise; not specific for thromboembolic diseases	[76]
E/e' LAP = 1.9 + 1.24 E/e'	Average E/e'ratio <10 LAP >15 mm Hg	All the 3 conditions: Average E/e' >14 or septal E/e' ratio >15, peak TR velocity >2.8 m/s and septal e' velocity <7 cm/s	Angle-dependent; proper attention to the location of the sample size. Mitral inflow and annular early and late diastolic velocities are frequently fused at peak exercise it is preferable to acquire Doppler signal when the HR is slower than 100–110 beats/min	[78]

(*continued on next page*)

Table 6
(*continued*)

Key Echo-Doppler Indices	Cut-Off Value at Rest	Cut-Off Value at Peak Exercise	Pitfalls and Remarks	Reference
RV function				
TAPSE	<16 mm	Mean ± SD (range) 34 ± 2 (30–38) Δ = 7 ± 2 (3–11) <19 mm in primary MR	Angle- and load-dependent; not fully representative of RV global function There are no well-defined reference values to assess RV contractile reserve with exercise	10,18,69,76
RV FAC 100 × (EDA − ESA)/EDA	<35%	Mean ± SD (range) 53.7 ± 6.4 (40.9–66.5)[a]	Poorly reproducible in case of suboptimal image quality especially during exercise There are no well-defined reference values to assess RV contractile reserve with exercise	76
S′ TDI	<10 cm/s	Mean ± SD (range) 25 ± 4 (18–29) Δ = 10 ± 2 (6–14)	Angle-dependent; not fully representative of RV global function There are no well-defined reference values to assess RV contractile reserve with exercise	10,76
RV-PV coupling				
TAPSE/PASP ratio	<0.5 for healthy	Mean ± SD (range) 0.7 ± 0.2 (0.3–1.1) Δ = −0.6 ± 0.3 (−1.2–0)	Conceptually, the lower the ratio, the worse the association of PH and RV dysfunction	10,60,69
ΔmPAP/ΔCO mm Hg/L^{-1}/min^{-1}	—	>3 abnormal pulmonary vascular reserve	An increase in mPAP of 1–2 mm Hg/l/min of CO represents a normal pulmonary vascular response Does not clarify whether the abnormal pressure is attributable to PVD or upstream transmission of a high LAP	4,30

(*continued on next page*)

Table 6
(*continued*)

Key Echo-Doppler Indices	Cut-Off Value at Rest	Cut-Off Value at Peak Exercise	Pitfalls and Remarks	Reference
RVESPAR sPAP/RV end-systolic area	—	—	The ratio of peak exercise to resting RVESPAR may be a promising noninvasive index of RV contractile reserve. A ratio of 1.64 had respective sensitivity and specificity of 82% and 96% (AUC 0.94 [95% CI: 0.87–1.02]) for identifying CTEPH patients RVESPAR correlate strongly with data obtained by ExCMR	[11]

Abbreviations: AT, acceleration time (by PW Doppler); CTEPH, chronic thromboembolic PH; CO, SV*HR/1000; E, mitral inflow E velocity as measured by PW Doppler; e', early diastolic velocity of the mitral annulus as measured by TDI; EDA, end-diastolic area; ExCMR, exercise cardiac magnetic resonance; FAC, fractional area change; HR, heart rate; LAP, LA pressure; PASP, pulmonary artery systolic pressure; PV, pulmonary vascular; PW, pulsed-wave; RAP, RA pressure; RVESPAR, RV end-systolic pressure-area ratio; SV, stroke volume; TRV, TR peak velocity; VTI, velocity-time integral.
[a] Exercise stress test was performed to maximum exercise tolerance on a graded treadmill.

Image analysis and quality control

All participating centers will be chosen according to recommended standard operational procedures in terms of data imaging acquisition (operational modes, machine settings), data storage (data format, transfer procedure), and data processing (software used and measurement procedures). All participating centers will fulfill established advanced standard criteria for echocardiographic laboratories.[80] All echocardiographic recordings, both at rest and exercise, will be reviewed and analyzed off line by certified operator experts in TTE. A quality control procedure will be set to reduce variability among laboratories and operators and to maintain and improve the quality of subsequent collections of data.[81] The Echo Core Lab will be established with 3 certified cardiologists, experts in TTE, and with specific documented experience in patients with PH. The Echo Core Lab will issue a user manual with a detailed description on how to measure each single parameter, according to the most recent American and European recommendations and guidelines.[76–81] The user manual will be sent to all participating centers and will be the reference for TTE assessment. All operators participating in the study who will be in charge of taking measurements on the echocardiographic examinations will undergo quality control consisting of 2 steps. For step 1 (**Fig. 3**), each year the Echo Core Lab will prepare 20 multiple-choice questions on a dedicated online questionnaire. All participating centers will be invited by email to access the questionnaire (password protected). Questions will address echocardiographic issues, especially about the right heart and noninvasive hemodynamics. At least 18 out of 20 correct answers are needed to proceed to step 2. The Echo Core Lab will provide dedicated personal feedback to the participating centers, when needed. For step 2 (**Fig. 4**), each year the Echo Core Lab will send a compact disc (CD) with 10 complete echocardiographic examinations in DICOM format, including resting, 50 W, peak stress, and recovery acquisition in the whole spectrum of enrolled subjects (healthy subjects, elite athletes and patients with overt and at risk of PH). All images and videos will be completely anonymized to protect subjects' privacy. All operators will be requested to measure a prespecified set of data, including all parameters listed in the CRF (see **Tables 4** and **5**). The operators will directly measure the requested parameters by uploading the 10 cases from the CD to their echocardiographic machine. The DICOM

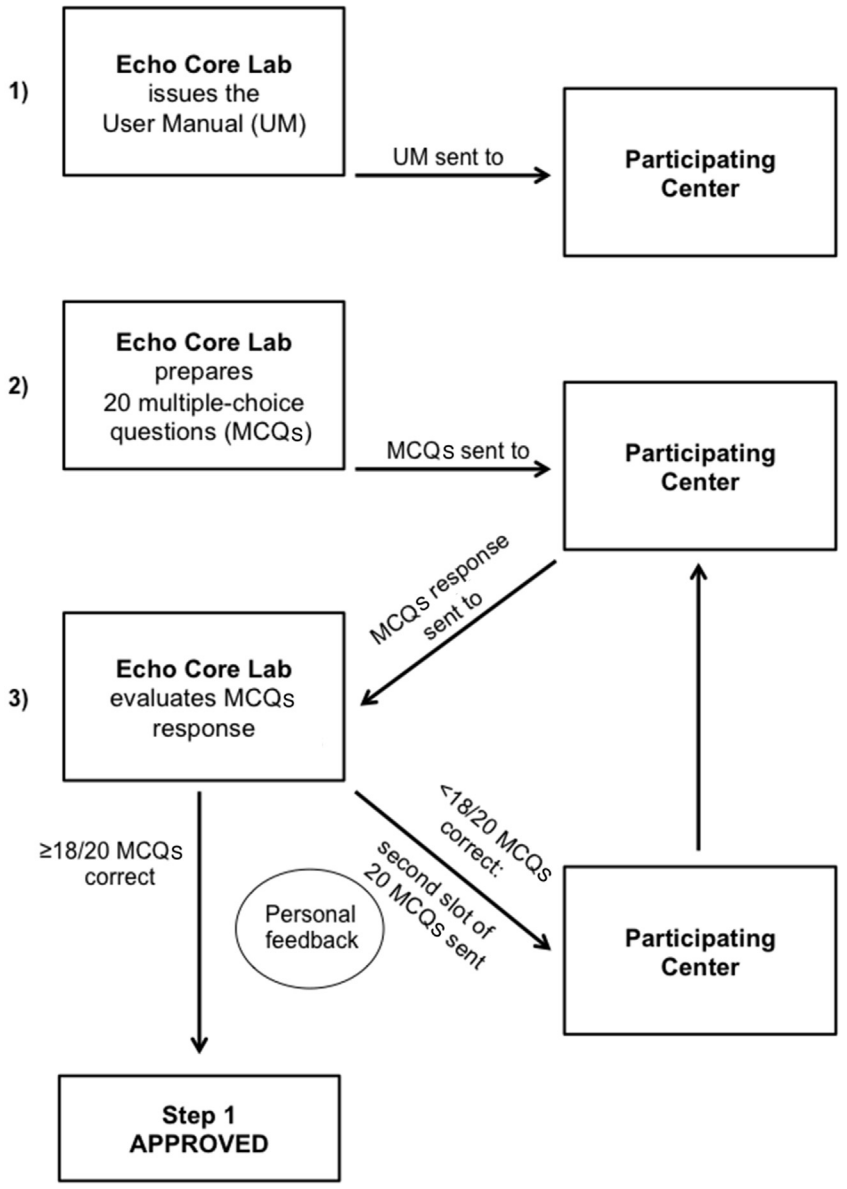


Fig. 3. Quality control step 1.

format will easily allow the measurement procedure. All operators will be then asked to enter their measurements in a dedicated Excel file, which will be then sent to the coordinating center for analysis. The gold standard value for each measurement will be established according to the reading of the Echo Core Lab (by unanimous approval). The Echo Core Lab will also establish acceptable ranges for correct measurement of continuous parameters, when appropriate. Intraobserver and interobserver variability will then be estimated. Intraclass correlation coefficient (ICC) will be calculated, and for those operators with an ICC less than 0.75, a second slot of measurements will be requested, until a proper agreement is reached. These operators will also be contacted by the Echo Core Lab for personal feedback aimed at understanding the reasons for discrepancy. If needed, operators from the Echo Core Lab will travel to the participating center site for retraining to guarantee robustness in data acquisition and analysis.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Patient data will be uploaded on a dedicated Web-based platform with secured access credentials

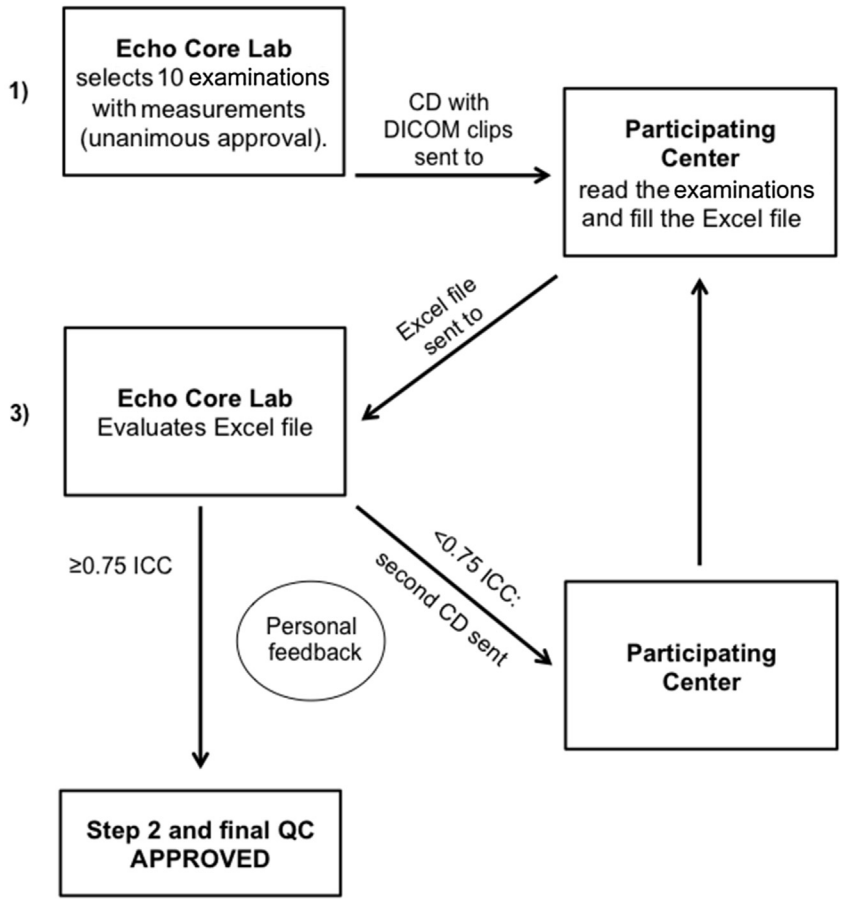


Fig. 4. Quality control step 2. CD, compact disc; ICC, intraclass correlation coefficient QC, quality control.

and protocols transporter layer security (TLS)/HyperText Transfer Protocol over Secure Socket Layer (HTTPS) and will be completely anonymized before the processing phase by using a hashing function (a noninvertible algorithm capable of mapping the identification data in a unique alphanumeric string). Dedicated technical staff with specific expertise will ensure the correct operative functioning of the platform and the safety of data will be guaranteed. Data management and statistical analyses will be carried out at the Institute of Clinical Physiology–consiglio nazionale delle ricerche (CNR) in Pisa, Italy. Descriptive statistics will comprise of the usual scale and frequency statistics. Data will be presented as mean plus or minus standard deviation, or median and interquartile ranges, as appropriate. Different clinical conditions will be compared by 2-sided student's t-tests or Wilcoxon rank sum tests, as appropriate. Correlation analysis will be performed with Pearson or Spearman correlation analysis. Cox regression analysis and Kaplan-Meier survival estimation will be used to analyze mortality and time-to-clinical-worsening or time-to-event data. *P*-values less than 0.05 will be considered as statistically significant.

All analyses will be performed by the SPSS/PC software package (SPSS, Chicago, IL, USA) and GraphPad Prism (GraphPad Software Inc, San Diego, CA, USA).

LEGAL AND ETHICAL ASPECTS

The study will be performed in accordance with the Declaration of Helsinki in its current version (2013). Subjects of the prospective cohort will be informed of the nature and scope of the proposed study, in particular about the possible benefits for their health and potential risks. They will be informed verbally and with a special written document before inclusion to the study. Their consent will be documented by signing the consent form. Participation of subjects in the study is voluntary; the consent to participate may be withdrawn at any time. In case of withdrawal from the study, the subject can require his or her already obtained data to be deleted. The protocol will be submitted to the ethics

committee of each participating center. Other cooperating centers will apply for approval at their local ethics committees. Subjects will be included after the committee has stated no objections against the proposed study. The name of the subject and other confidential information that are subject to medical confidentiality are subject to the provisions of the Federal Data Protection Act and the Data Protection Law of Baden-Württemberg, according to the new European Union directive of protection of personal data (GDPR). Transfer for analysis will be performed with pseudonym-coded data. Personal data that may lead to identification of the subject will not be transferred.

SIDE EFFECTS AND RISKS

The risks of this study are limited to the risks associated with a stress echocardiography, which are very rare. Studies unanimously show the excellent safety profile of stress echocardiography, especially with exercise.[79] Leg muscle aching might occur the day after the diagnostic test. In some rare cases, a transient ischemia with consequent chest pain or ECG abnormalities could occur. Drug administration is rarely medically indicated to resolve this side effect. In some cases, hypotension may occur that could lead to dizziness and sweating. In the case of premature interruption of the test, the subjects will be asked to lie with legs elevated to restore arterial pressure rapidly. In rare cases, life-threatening arrhythmias might occur.

SAFETY MEASURES

During the study procedure, an ECG will be recorded and the blood pressure on the right arm will be measured every 2 to 3 minutes. These measures will be performed until the subject is exhausted or if symptoms such as chest pain or shortness of breath occur, or if the doctor performing the examination considers it necessary to halt the procedure due to changes in the ECG or blood pressure. Subjects will be told to inform the doctor immediately if any symptoms or chest pain, dyspnea, pain in the legs, or other discomfort occurs during the examination. All necessary equipment needed to perform cardiopulmonary resuscitation, as well as medications required to manage major medical events (eg, myocardial ischemia, syncope, arrhythmias, lung insufficiency) will be present in the room where the stress echocardiography will be performed. All the medical staff performing the study will be able to treat possible complications and to behave properly in the very rare occurrence of life-threatening arrhythmias. Subjects will be supervised at least 30 minutes after finishing the test and written informed consent will be obtained for each subject.

CLINICAL IMPLICATIONS

As recently reviewed,[8] exercise-induced PH defined by an abnormally high mPAP alone or in combination with elevated PAWP and CO, measured invasively or noninvasively, has been reported in subjects susceptible to high altitude pulmonary edema, healthy family members of patients with idiopathic PAH, systemic sclerosis, chronic obstructive pulmonary disease or interstitial lung diseases, heart failure with decreased or preserved ejection fraction, mitral valve disease, aortic stenosis, late closure of atrial septal defects, and chronic thromboembolism (see **Tables 1–3**).[19–64] Exercise-induced PH has been typically diagnosed in patients referred for shortness of breath and exercise intolerance without obvious pulmonary or cardiac cause.[82] In these patients, there is an inverse relationship between the slope of mPAP–CO and V_{O_2} max, suggesting RV afterload-related limitation of maximum CO, such as that observed in patients with manifest PH[83] and, in fact, in healthy subjects in normoxia or in hypoxia.[32,42] Thus, modulation of aerobic exercise capacity by the afterload-sensitive RV seems to be a universal phenomenon; however, of course, it is exacerbated in exercise-induced PH or manifest PH compared with healthy controls. Exercise-induced PH has been shown to be a major risk factor for the development of resting PH in patients with systemic sclerosis[53,54,84,85] and in healthy carriers of a BMPR2 mutation.[86] Exercise-induced PH has been shown by limited size studies to be of prognostic relevance in systemic sclerosis[84,87] and in valvular heart diseases, such as mitral regurgitation[61,62] or aortic stenosis.[63] Thus, at this stage, it remains to be defined whether noninvasively diagnosed exercise-induced PH with updated rigorous methodology as prespecified in the RIGHT-NET predicts later development of manifest PH, clinical deterioration, or decreased survival. It is unclear whether exercise-induced changes in RV function increase the prognostic relevance of exercise TTE in evaluating the pulmonary circulation. The RIGHT-NET protocol is expected to answer to these questions.

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APPENDIX
The Right Heart International Network (RIGHT-NET)

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