A multicentric quality-control study of exercise Doppler echocardiography of the right heart and the pulmonary circulation

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Abstract

Purpose: This study was a quality-control study of resting and exercise echocardiography (EDE) variables measured by 19 echocardiography laboratories with proven experience participating in the RIGHT Heart International NETwork. Methods: All participating investigators reported the requested variables from ten randomly selected exercise stress tests. Intraclass correlation coefficients (ICC) were calculated to evaluate the inter-observer agreement with the core laboratory. Inter-observer variability of resting and peak exercise tricuspid regurgitation velocity (TRV), right ventricular outflow tract acceleration time (RVOT Act), tricuspid annular plane systolic excursion (TAPSE), tissue Doppler tricuspid lateral annular systolic velocity (S'), right ventricular fractional area change (RV FAC), left ventricular outflow tract velocity time integral (LVOT VTI), mitral inflow pulsed wave Doppler velocity (E), diastolic mitral annular velocity by TDI (e') and left ventricular ejection fraction (LVEF) was measured. Results: The accuracy of 19 investigators for all variables ranged from 99.7% to 100%. ICC was $>$ 0.80 for all observers. Inter-observer variability for resting and exercise variables was for TRV = 3.8 to 2.4%, E = 5.7 to 8.3%, e' = 6 to 6.5%, RVOT Act = 9.7 to 12, LVOT VTI = 7.4 to 9.6%, S'= 2.9 to 2.9% and TAPSE = 5.3 to 8%. Moderate inter-observer variability was found for resting and peak exercise RV FAC (15 to 16%). LVEF revealed lower resting and peak exercise variability of 7.6 and 9%. Conclusions: When performed in expert centers EDE is a reproducible tool for the assessment

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Abstract

Purpose: This study was a quality-control study of resting and exercise echocardiography (EDE) variables measured by 19 echocardiography laboratories with proven experience participating in the RIGHT Heart International NETwork. Methods: All participating investigators reported the requested variables from ten randomly selected exercise stress tests. Intraclass correlation coefficients (ICC) were calculated to evaluate the inter-observer agreement with the core laboratory. Inter-observer variability of resting and peak exercise tricuspid regurgitation velocity (TRV), right ventricular outflow tract acceleration time (RVOT Act), tricuspid annular plane systolic excursion (TAPSE), tissue Doppler tricuspid lateral annular systolic velocity (S'), right ventricular fractional area change (RV FAC), left ventricular outflow tract velocity time integral (LVOT VTI), mitral inflow pulsed wave Doppler velocity (E), diastolic mitral annular velocity by TDI (e') and left ventricular ejection fraction (LVEF) was measured. Results: The accuracy of 19 investigators for all variables ranged from 99.7% to 100%. ICC was > 0.80 for all observers. Inter-observer variability for resting and exercise variables was for TRV = 3.8 to 2.4%, E = 5.7 to 8.3%, e' = 6 to 6.5%, RVOT Act = 9.7 to 12, LVOT VTI = 7.4 to 9.6%, S'= 2.9 to 2.9% and TAPSE = 5.3 to 8%. Moderate inter-observer variability was found for resting and peak exercise RV FAC (15 to 16%). LVEF revealed lower resting and peak exercise variability of 7.6 and 9%. Conclusions: When performed in expert centers EDE is a reproducible tool for the assessment of the right heart and the pulmonary circulation.

Key words: right ventricle, pulmonary hypertension, exercise echocardiography

Background

Exercise Doppler echocardiography (EDE) is standard practice for the evaluation of patients with coronay artery disease. The procedure is now increasingly used for the assessment of right heart and the pulmonary circulation.[1-5] However, this technique may be limited, by its understudied inter-observer variability, which may impact on the quality and consistency of diagnostic results. The RIGHT Heart International NETwork (RIGHT-NET) study protocol incorporates a limited number of basic and generally accessible EDE measurements.[6,7] Echocardiography of the pulmonary circulation basically relies on estimates of the components of the pulmonary vascular resistance equation, that is pulmonary artery pressure (PAP) from the maximum tricuspid regurgitation velocity (TRV), or the right ventricular outflow tract (RVOT) acceleration time (Act) of PA flow, wedged PAP from the ratio of transmitral flow E and mitral annulus e' waves and cardiac output (CO) from the left ventricular outflow tract (LVOT) aortic flow. Echocardiography of the right heart relies on estimates of right ventricular surface areas, tricuspid annular plane systolic excursion

(TAPSE) and of tissue Doppler–derived tricuspid lateral annular systolic velocity (S').[2,3]The present report aims to validate the quality control process of the right heart and pulmonary circulation resting and exercise echo-Doppler variables and harmonize reading criteria among 19 echocardiography laboratories with proven experience participating in the RIGHT-NET study.[6,7]

Methods

The echo core Lab of the Institute of Clinical Physiology-CNR in Pisa (LG) coordinated the quality control procedure of all investigators at different centres participating in the RIGHT-NET study. Each center designated one operator that performed or reported at least 100 stress echocardiography studies per year. All readers were certified by national and/ or international societies. The quality control process was designed to be simple, repeatable, and sustainable. The Echo Core Lab issued a User Manual with a detailed description on how to measure each parameter, according to the most recent American and European Recommendations and Guidelines.[8-11] The User Manual was sent to all Participating Centers including the reference for transthoracic echocardiography assessment. All participating centers followed the recommended standard operational procedures in terms of data data storage (data format, transfer procedure), and data processing (software used and measurement procedures). All operators performing and reading echocardiographic exams adhered to the quality control protocol. The Echo Core Lab sent ten complete echocardiographic examinations in DICOM format through a safe file sharing platform (**Fig. 1)** . All participating investigators were invited by email to join the platform, which was protected by user-specific passwords. The platform includes also detailed instructions on how to start the training and allows downloading and uploading of external files. All images and videos were completely anonymized to protect patients' privacy, according to the new EU directive of protection of personal data (GDPR).[6]

Reading sessions

We randomly selected 10 cases including healthy subjects and at least one group of patients with overt and/or at risk of pulmonary hypertension (PH), according to clinical classification of PH**(Table 1)** .[12] Data were collected on patients undergoing EDE on a semi-recumbent cycle ergometer with an incremental workload of 25 Watts every 2 minutes up to the symptom-limited maximal tolerated workload including resting, 50 Watts, peak stress and recovery acquisition, as previously described.[6] All operators directly measured the requested parameters by uploading the same ten cases from the web platform to their echocardiography machine. The DICOM format enabled to perform assessment of variables in the respective centres. All operators were then asked to enter their measurements in a dedicated excel file, which was then sent to the Coordinating Center for analysis. T**able 2** provides the list of the left and the right heart parameters measured by all operators. The gold standard value for each measurement was established by the values measured by the Echo Core Lab.

Statistical analysis

Statistical analysis was performed using standard software (MedCalc version 14.8.1, MedCalc Software Ltd, Belgium; SPSS version 20.0, SPSS, Inc., Chicago, IL). Continuous variables were described by mean values $\pm$ standard deviation (SD). Accuracy (in %) for each observer was estimated by comparison with the reference standard (core lab reading). Intra-class correlation coefficient (ICC) was calculated along with the 95% confidence interval, in order to quantify the reliability of measurement process. An ICC of >0.8 indicated excellent agreement with the core lab. Inter-observer variability among 19 observers were examined for resting and peak exercise TRV, RVOT Act, TAPSE, S', right ventricular fractional area change (RV FAC), LVOT velocity time integral (VTI), mitral early inflow pulsed wave Doppler velocity (E), early diastolic mitral annular lateral and septal velocity by TDI (e'), left ventricular ejection fraction (LVEF). Data are presented as mean of the absolute and relative differences (in %) between measurements.

Intra-observer agreement was tested in 2 observers who volunteered to repeat the measurement session on 2 separate days and ICC was calculated.

Results

Nineteen observers completed all reading sessions. **Figure 2**shows a summary of the accuracy (in %) of each center compared with the gold standard core lab for all parameters at rest and at peak of exercise. The average accuracy of 19 readers for all parameters was excellent in about 99.8% (range from 99.7% to 100%) **(Table 3)** . ICC was > 0.8 for all observers. The average agreement of the 19 readers for all parameters was excellent (ICC = 0.98). Moreover the average agreement among readers remained excellent at rest and at peak exercise for all measurements (ICC = 0.98 and 0.99, respectively) **(Table 4)** . Inter-observer variabilities for main exercise TTE measurements are reported in **table 5** . Close inter-observer variabilities were found for both resting and peak exercise TRV (3.8 and 2.4%), RV S' (2.9 and 2.9%), E (5.7 and 8.3%) and e' (6 and 6.5%). Inter-observer variabilities of the RVOT Act and LVOT VTI were of 9.7 and 7.4% at rest, 12 and 9.6% at peak exercise, respectively. TAPSE showed less resting (5.3%) than peak exercise variability (8%). Moderate inter-observer variability was found for resting and peak exercise RV FAC (15 and 16%, respectively). On the other hand LVEF revealed lower resting and peak exercise mean relative differences of 7.6 and 9%, respectively.

The intra-observer quality control analysis revealed an excellent ICC of 0.97 (95% Confidence Interval: 0.96 to 0.99).

Discussion

Before any acquisition of pooling echocardiographic data for research and clinical applications, a process of quality control and reading harmonization measurements should be undertaken.[13-16]The present results demonstrate that a rigorourly designed protocol with a strong focus on quality assurance and certification can yield very strong ICC and limited variability among the 19 participant experienced centers to a large prospective EDE study of the right heart and the pulmonary circulation.

Previous studies

The inter-observer variability during EDE right heart and pulmonary circulation studies may be not negligible. Few such studies have been previously reported and all were mono-centric.[3,17]Argiento et al reported in 124 healthy subjects (62 women and 62 men; age 37 ± 13 yrs) (single center study) an inter-observer variability for pulmonary artery systolic pressure (PASP) and cardiac output (CO) estimates of 1.9 % and 4.9 % at rest, and 7.9 % and 13.9 % at maximum exercise, respectively.[18] D'Alto et al reported in 90 healthy subjects (45 male, mean age 39 ±13 years) inter-observer variabilities between two readers at rest and peak exercise of 1.9% and 7.9% for PASP, 4.9% and 13.9% for stroke volume, 2.6% and 6.8% for TAPSE, and 5.4% and 8.7% for S', respectively.[19] Kusunose et al reported in a subgroup of 15 randomly selected subjects with isolated moderate to severe mitral regurgitation a close inter- and intra-observer variability for resting TAPSE (8.8%) and exercise TAPSE (9.5%).[20] As these data remain limited, more validation appeared necessary for a multi-centric study like the RIGHT-NET.

Uniqueness of the present study and clinical implications

To the best of our knowledge, this is the large EDE multicenter study that comprehensively provides a detailed quality control analysis of both the right heart and the pulmonary circulation measurements. One major finding was that the accuracy and agreement were remarkably high among 19 experienced investigators, with no significant differences between resting and exercise measurements. These results provide a valid evidence of reliability of TRV, E/e' ratio and LVOT VTI during exercise. The inter-observer variability of RVOT Act was higher than that of TRV. RVOT Act measurements were collected during exercise, in keeping with a recent report advocating its combination with TRV for the assessment of the pulmonary pressures both at rest and during exercise.[21] The interest of this combination is that the feasibility rate of RVOT Act may be higher than that of TRV.[22] Furthermore our findings suggested that exercise TAPSE and S' may be used as reproducible measures of the RV longitudinal systolic function. Larger resting and exercise variability of RV FAC may be caused by plane-dependency and reliance on difficult definition RV endocardial border.[23]

Study limitations

The present study did not validate the echocardiographic measurements against invasive gold standard evaluation of the pulmonary circulation by PAP, wedged PAP and cardiac output, and right ventricular function by indices derived from pressure-volume loops. Thus accuracy and precision were defined by comparison only with the core laboratory measurements. The number of patients studied was relatively small (n = 10). However, each of the 19 participating centers provided a total of 35 left and right heart echo-Doppler variables at rest, peak exercise and after 5 minutes of recovery. Finally, it should be underlined that contrast and/or agitated saline enhancement for tricuspid regurgitation (TR) Doppler signal was not performed. The additional use of contrast and/or agitated saline may further improve the reliability, particularly in less experienced centers.

Conclusions

When protocols for acquisition and analysis are provided upfront and in experienced echocardiography laboratories EDE represents a reproducible tool to comprehensively assess the right heart and pulmonary circulation. This quality control study represents a solid bedrock for future RIGHT-NET studies, aiming to evaluate the diagnostic and prognostic role of EDE in the clinical settings of patients with cardiorespiratory diseases.

Figure Legend

Figure 1. Quality control procedure

Figure 2. Accuracy of each center compared with the gold standard core lab for all, right and left parameters (A), for all parameters at rest and peak (B), for right paramaters at rest and at peak (C) and for left parameter at rest and at peak (D).

Appendix

The RIGHT Heart International NETwork (RIGHT-NET)

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References:

1. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, Rubenfire M. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. Vol. 128, Circulation 2013; p. 1470–9.
2. Naeije R, Saggar R, Badesch D, Rajagopalan S, Gargani L, Rischard F, Ferrara F, Marra AM, D' Alto M, Bull TM, Saggar R, Grünig E, Bossone E. Exercise-induced pulmonary hypertension. Translating pathophysiological concepts into clinical practice. Chest 2018 Jan 31.
3. Rudski LG, Gargani L, Armstrong WF, Lancellotti P, Lester SJ, Grunig E, D'Alto M, Aneq MA, Ferrara F, Saggar R, Saggar R, Naeije R, Picano E, Schiller NB, Bossone E. Stressing the Cardiopulmonary Vascular System: The Role of Echocardiography. JASE 2018; 31(5):527-550.
4. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, Cittadini A, Rubenfire M, Naeije R. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc Echocardiogr. 2013 Jan;26(1):1-14.
5. Ferrara F, Gargani L, Ostenfeld E, D'Alto M, Kasprzak J, Voilliot D, Selton-Suty C, Vriz O, Marra AM, Argiento P, Stanziola AA, Cittadini A, D'Andrea A, Bossone E. Imaging the right heart pulmonary circulation unit: Insights from advanced ultrasound techniques. Echocardiography. 2017 Aug;34(8):1216-1231.
6. Ferrara F, Gargani L, Armstrong WF, Agoston G, Cittadini A, Citro R, D'Alto M, D'Andrea A, Dellegrottaglie S, De Luca N, Di Salvo G, Ghio S, Grünig E, Guazzi M, Kasprzak JD, Kolias TJ, Kovacs G, Lancellotti P, La Gerche A, Limongelli G, Marra AM, Moreo A, Ostenfeld E, Pieri F, Pratali L, Rudski LG, Saggar R, Saggar R, Scalese M, Selton-Suty C, Serra W, Stanziola AA, Voilliot D, Vriz O, Naeije R, Bossone E. The Right Heart International Network (RIGHT-NET): Rationale, Objectives, Methodology, and Clinical Implications. Heart Fail Clin. 2018 Jul;14(3):443-465.
7. Bossone E, Gargani L. The RIGHT Heart International NETwork (RIGHT-NET): A Road Map Through the Right Heart-Pulmonary Circulation Unit. Heart Fail Clin. 2018 Jul;14(3)
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28:1–39.
9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016 Apr;29(4):277-314.
10. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the

Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.
11. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, Edvardsen T, Garbi M, Ha JW, Kane GC, Kreeger J, Mertens L, Pibarot P, Picano E, Ryan T, Tsutsui JM, Varga A. The Clinical Use of Stress Echocardiography in Non-Ischaemic Heart Disease: Recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2017 Feb;30(2):101-138.
12. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barberà J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol Ç, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Völler H, Luis Zamorano J. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119.
13. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 2015;20:1021-41.
14. Popescu BA, Stefanidis A, Nihoyannopoulos P, Fox KF, Ray S, Cardim N, Rigo F, Badano LP, Fraser AG, Pinto F, Zamorano JL, Habib G, Maurer G, Lancellotti P, Andrade MJ, Donal E, Edvardsen T, Varga A. Updated standards and processes for accreditation of echocardiographic laboratories from The European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014 Jul;15(7):717-27.
15. Patton DM, Enzevaie A, Day A, Sanfilippo A, Johri AM. A quality control exercise in the echo laboratory: Reduction in inter-observer variability in the interpretation of pulmonary hypertension. Echocardiography. 2017 Dec;34(12):1882-1887.
16. Armstrong AC, Ricketts EP, Cox C, Adler P, Arynchyn A, Liu K, Stengel E, Sidney S, Lewis CE, Schreiner PJ, Shikany JM, Keck K, Merlo J, Gidding SS, Lima JA. Quality Control and Reproducibility in M-Mode, Two-Dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year 25 Examination Experience. Echocardiography. 2015 Aug;32(8):1233-40.
17. D'Andrea A, Stanziola AA, Saggar R, Saggar R, Sperlongano S, Conte M, D'Alto M, Ferrara F, Gargani L, Lancellotti P, Bossone E; RIGHT Heart International NETwork (RIGHT-NET) Investigators. Right Ventricular Functional Reserve in Early-Stage Idiopathic Pulmonary Fibrosis: An Exercise Two-Dimensional Speckle Tracking Doppler Echocardiography Study. Chest. 2019 Feb;155(2):297-306.
18. Argiento P, Vanderpool RR, Mulè M, Russo MG, D'Alto M, Bossone E, et al. Exercise Stress Echocardiography of the Pulmonary Circulation: Limits of Normal and Sex Differences. Chest. 2012 Nov 26;142(5):1158–65.
19. D'Alto M, Pavelescu A, Argiento P, Romeo E, Correra A, Di Marco GM, et al. Echocardiographic assessment of right ventricular contractile reserve in healthy subjects. Echocardiography 2017;34: 61-8.
20. Kusunose K, Popović ZB, Motoki H, Marwick TH. Prognostic significance of exercise-induced right ventricular dysfunction in asymptomatic degenerative mitral regurgitation. Circ Cardiovasc Imaging. 2013 Mar 1;6(2):167-76.
21. Wierzbowska-Drabik K, Picano E, Bossone E, Ciampi Q, Lipiec P, Kasprzak JD. The feasibility and clinical implication of tricuspid regurgitant velocity and pulmonary flow acceleration time evaluation for pulmonary pressure assessment during exercise stress echocardiography. Eur Heart J Cardiovasc Imaging. 2019 Sep 1;20(9):1027-1034.
22. Naeije R, Torbicki A. More on the noninvasive diagnosis of pulmonary hypertension: Doppler echocardiography revisited. Eur Respir J. 1995 Sep;8(9):1445-9.

23. Ling LF, Obuchowski NA, Rodriguez L, Popovic Z, Kwon D, Marwick TH. Accuracy and interobserver concordance of echocardiographic assessment of right ventricular size and systolic function: a quality control exercise. J Am Soc Echocardiogr. 2012 Jul;25(7):709-13.

Table 1. Demographic and clinical characteristics of 10 subjects included in quality control procedure.

Variable	**Value** Mean ± SD
Age (years)	67.2 ± 11.3
Sex (male/female)	2/8
BSA (m^2)	1.7 ± 0.2
BMI (Kg/m^2)	25.2 ± 2.2
Systolic blood pressure (mmHg)	129 ± 24
Diastolic blood pressure (mmHg)	77 ± 12
Heart rate (bpm)	74 ±11
Diagnosis	
Healthy subjects	1
PAH	1
CTD	1
CHD	1
Patients with CAD risk factors	2
LHD	2
Lung disease	1
Post-PE	1

BSA, body surface area; BMI, Body Mass Index; CAD, coronary artery disease; CHD, congenital heart disease; CTD, connective tissue disease; LHD, left heart disease (coronary artery disease and heart failure); PAH, pulmonary arterial hypertension; Post-PE, post-pulmonary embolism; risk factors (hypertension, dyslipidaemia); SD, standard deviation. Data are expressed as number, mean ± SD.

Table 2. List of parameters measured in the quality control procedure

Left Chambers Parameters

	Parameters	**Rest**	**50 W**	**Peak**	**Rec 5min**	**Images**
M-Mode Echocardiography	LVEDD(mm) IVS (mm) PWT(mm) LVESD (mm) LVOT (mm)					
2D-Echocardiography	LVEDV 4-CH (ml) LVESV 4-CH (ml) LVEDV 2-CH (ml) LVESV 2-CH(ml) LA volume 4-CH (ml) LA volume 2-CH (ml)					

	Parameters	Rest	50 W	Peak	Rec 5min	Images
Doppler-Echocardiography	Mitral E and A (cm/s), DT (ms) Mitral lateral and septal e', a', s' TDI (cm/s) Aortic Peak Vel (cm/s) LVOT VTI (cm)					

B. Right Chambers Parameters

	Parameters	Rest	50W	Peak	Rec 5 min	Images
M-Mode Echo-cardiography	TAPSE (mm)					
2D- Echo-cardiography	RV basal and mid diameter (mm) RVED area (cm^2) RVES area (cm^2) RA area (cm^2)and Volume(ml) RVOT(mm) PA diameter (mm) IVC(mm)and collassability					
Doppler-Echocardiography	RVOT AcT (m/s) RVOT VTI (cm) RV E and A (cm/s) RV e', a', S' TDI TRV (cm/s) RV-RA gradient (mmHg)					

AcT, acceleration time; ED, end-diastolic; ES, end-systolic; IVC, inferior vena cava; PA, pulmonary artery; RA, right atrial; Rec, recovery; RV, right ventricular; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane excursion; TDI, tissue Doppler imaging; TRV, trans-tricuspid valve regurgitation velocity;

VTI, velocity time integral.

Table 3. Accuracy, ICC and 95% Confidence Interval of each Center for all parameters.

Centers	Accuracy (%)	*ICC*	*95% Confidence Interval Lower bound*	*95% Confidence Interval* Upper bound
Center 1	100	0.99	0.999	1.000
Center 2	99.9	0.99	0.991	0.997
Center 3	99.7	0.99	0.991	0.998
Center 4	99.8	0.99	0.992	0.998
Center 5	99.9	0.99	0.992	0.997
Center 6	99.7	0.99	0.993	0.998
Center 7	99.9	0.99	0.987	0.995
Center 8	99.6	0.99	0.988	0.996
Center 9	99.9	0.98	0.975	0.990
Center 10	99.7	0.98	0.975	0.996
Center 11	99.9	0.99	0.988	0.995
Center 12	99.7	0.99	0.990	0.997
Center 13	100	0.99	0.994	0.998
Center 14	100	0.99	0.999	1.000
Center 15	99.8	0.99	0.993	0.998
Center 16	100	0.99	0.999	1.000
Center 17	100	0.99	0.999	1.000
Center 18	100	0.99	0.999	1.000
Center 19	99.9	0.96	0.935	0.973

ICC= Intraclass Correlation Coefficient.

Table 4. Accuracy, ICC and 95% Confidence Interval of each Center for all parameters at rest and peak.

Centers	*Rest* Accuracy (%)	*Rest ICC*	*Rest 95% Confidence Interval Lower bound*	*Rest 95% Confidence Interval* Upper bound	*Peak* Accuracy (%)	*Peak ICC*	*Peak 95% Confidence Interval Lower bound*	*Peak 95% Confidence Interva* Upper bound
Center 1	100	0.99	0.999	1.000	100	0.99	0.999	1.000
Center 2	99.8	0.99	0.978	0.993	99.8	0.99	0.990	0.999
Center 3	99.4	0.99	0.982	0.997	99.9	0.99	0.994	0.999
Center 4	99.8	0.99	0.983	0.997	99.9	0.99	0.993	0.999
Center 5	99.7	0.99	0.984	0.995	99.9	0.99	0.994	0.999
Center 6	99.8	0.99	0.994	0.999	99.9	0.99	0.993	0.999

Center 7	99.9	0.99	0.991	0.997	99.9	0.99	0.993	0.999
Center 8	99.6	0.99	0.981	0.995	100	0.99	0.998	0.999
Center 9	99.8	0.98	0.972	0.991	100	0.99	0.979	0.996
Center 10	99.6	0.98	0.973	0.986	99.8	0.99	0.978	0.996
Center 11	99.9	0.99	0.990	0.997	100	0.99	0.975	0.996
Center 12	99.6	0.99	0.982	0.997	99.9	0.99	0.990	0.998
Center 13	100	0.99	0.995	0.999	100	0.99	0.996	0.999
Center 14	99.9	0.99	0.998	0.999	100	0.99	0.998	0.999
Center 15	99.8	0.99	0.990	0.997	99.9	0.99	0.991	0.999
Center 16	100	0.99	0.999	1.000	99.9	0.99	0.998	0.999
Center 17	99.9	0.99	0.998	0.999	100	0.99	0.998	0.999
Center 18	100	0.99	0.999	1.000	100	0.99	0.998	0.999
Center 19	99.9	0.99	0.975	0.992	100	0.99	0.992	0.999

ICC= Intraclass Correlation Coefficient.

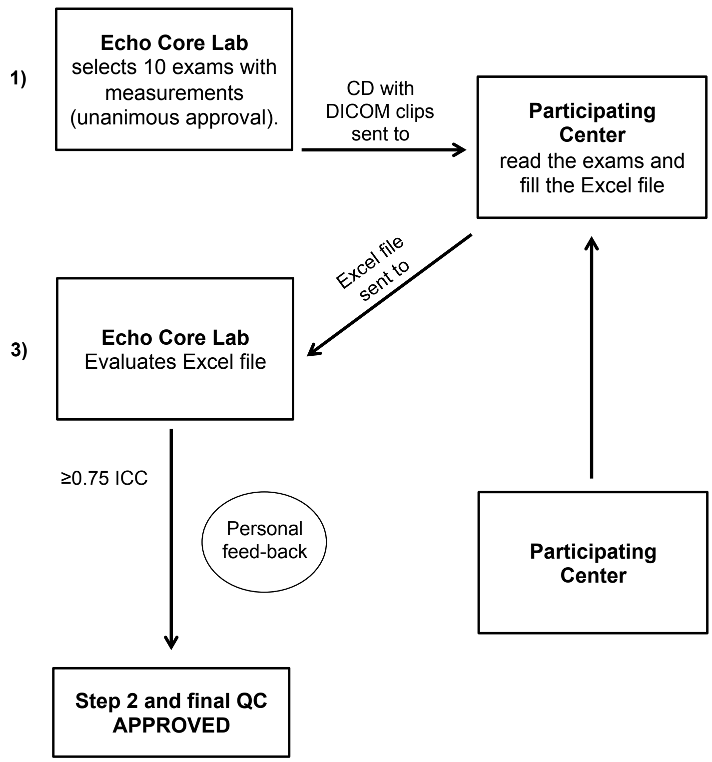
Table 5. Interobserver variability of main echocardiographic measurements of all participating centers at rest and at peak exercise.

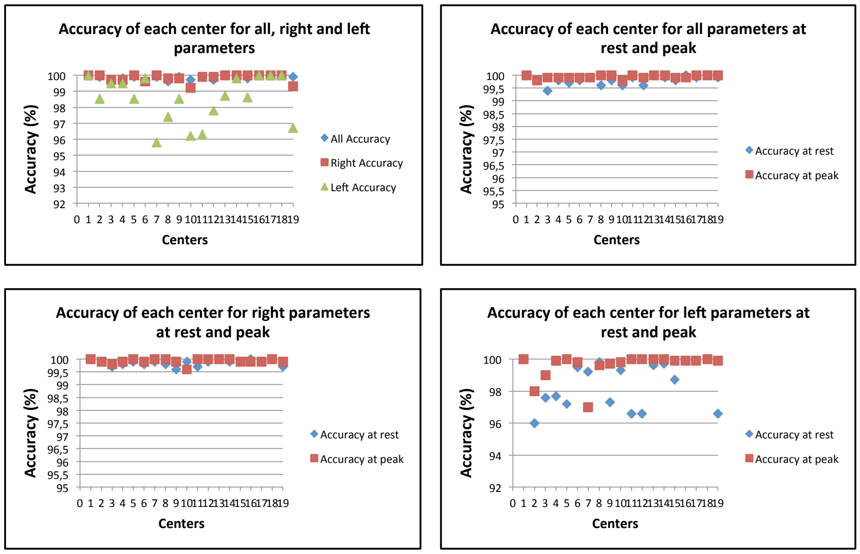
	TRV (cm/s)	**RVOT Act (msec)**	**TAPSE (mm)**	**RV S' (cm/s)**	**RV FAC (%)**	**LVOT VTI (cm)**	**E (cm/s)**	**e' (cm/s)**	**LV (% M**
Rest									
Mean	282±22	128±28	20.2±2.2	12.2±0.5	58±8	20.5±1.8	59.7±5.3	12.0±1.1	50:
Mean absolute difference	10.6±10.8	13±14	1.1±1.2	0.4±0.5	9.5±7	1.6±1.7	3.5±4.2	0.7±0.9	3.9
Mean relative difference, %	3.8±4	9.7±9	5.3±5.5	2.9±3.9	15±10	7.4±7	5.7±6.6	6.0±6.9	7.6
Peak exercise									
Mean	322±16	92±16	24.2±4.3	20.9±1	59±11	22.0±2.8	82±6.4	21±1,6	57:

	TRV (cm/s)	**RVOT Act (msec)**	**TAPSE (mm)**	**RV S' (cm/s)**	**RV FAC (%)**	**LVOT VTI (cm)**	**E (cm/s)**	**e' (cm/s)**	**LV (% M**
Mean absolute difference	7.7±7.4	11±11	1.5±3	0.6±0.8	9.2±7.7	2.2±2.4	7.3±6.4	1.4±1.2	5±
Mean relative difference, %	2.4±2.3	12±13	8±14	2.9±3.4	16±14	9.6±10	8.3±7.0	6.5±5.1	9±

Legend: Act, acceleration time; CH, chamber; E, mitral early inflow velocity; e', early diastolic mitral annular lateral velocity; EF, ejection fraction; FAC, fractional area change; LVOT, left ventricular outflow tract; MOD, biplane method of disks (modified Simpson's rule); RV, right ventricle; RVOT, right ventricular outflow tract; S', tissue Doppler–derived tricuspid lateral annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity; VTI, velocity time integral.

Quality Control Procedure





Accuracy of each center for all, right and left parameters
Accuracy (%)
Centers
All Accuracy
Right Accuracy
Left Accuracy
Accuracy of each center for all parameters at rest and peak
Accuracy (%)
Centers
Accuracy at rest
Accuracy at peak
Accuracy of each center for right parameters at rest and peak
Accuracy (%)
Centers
Accuracy at rest
Accuracy at peak
Accuracy of each center for left parameters at rest and peak
Accuracy (%)
Centers
Accuracy at rest
Accuracy at peak