DOI: 10.1111/echo.13401

WILEY Echocardiography

Acute effect of iloprost inhalation on right atrial function and ventricular dyssynchrony in patients with pulmonary artery hypertension

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Funding
This study was supported by grants from the Fondo Nacional de Desarrollo Científico y Tecnológico (Grant 1141198 to P.C.) and Fondo de Financiamiento de Centros de Excelencia en Areas Prioritarias (FONDAP) (Grant 15130011 to L.G; M.P.O.; H.E.V., S.L. and P.F.C.) from The Comisión Nacional de Investigación Científica Tecnológica (CONICYT).

Background: Right atrium function and ventricular function have significant prognostic value in pulmonary arterial hypertension patients. Acute changes in right ventricular synchrony and right atrium function postiloprost inhalation have not been evaluated.

Methods: Cross-sectional study. Consecutive pulmonary arterial hypertension patients (group I from Nice classification) were included. Echocardiographic right atrium and right ventricular function pre- and postiloprost inhalation, including a right ventricular dyssynchrony index and right atrium function using speckle tracking, were performed in all patients.

Results: Twenty pulmonary arterial hypertension patients, 44±7 years and 90% females, were included. After iloprost inhalation, we observed a significant increment in right ventricular fractional area change and a significant decrease in right ventricular dyssynchrony index (21.4±5.6% vs 26.1±4.0 %, P=.007 and 79±44 vs 32±22 msec-onds, P<.01, respectively), also an improvement in right atrium reservoir function (8.6±3.1% vs 11.7±3.5 %, P=.002).

Conclusions: Iloprost inhalation induces acute changes in right ventricular function, dyssynchrony, and right atrium performance that may add relevant clinical information in the management and risk stratification of pulmonary arterial hypertension patients.

KEYWORDS
pulmonary hypertension, right atrium, right ventricular function

1 | INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic and progressive disease characterized by remodeling of pulmonary vasculature leading to an increased pulmonary resistance and right ventricular (RV) failure.[1] RV function and remodeling have a significant prognostic value in PAH patients,[2,3] and novel imaging techniques allow for the evaluation of RV function and dyssynchrony.[4–6] Recently, RV dyssynchrony has been associated with RV adverse remodeling and function in idiopathic PAH patients.[7] Right atrial (RA) dilatation assessed by cardiac magnetic resonance imaging is also linked to important clinical outcome in PAH patients.[8] On the other hand, assessment of RA remodeling and function can be reproducibly performed with speckle tracking and three-dimensional echocardiography[9–11] in different clinical scenarios with proven clinical and functional outcome implications.[12,13]

Finally, inhaled iloprost has shown to improve hemodynamic profile and functional status in PAH patients.[14] Also a meta-analysis of iloprost, used as monotherapy or in combination, showed an increment in 6-minutes walk distance and a decrease in RA and pulmonary vascular resistance and pressure.[15] However, the effects on RV and RA function, which could in turn have prognostic implications, have not been extensively studied. In this study, we sought to evaluate the effects of inhaled iloprost by the determination of acute changes in RV function and dyssynchrony (see Fig. 1) and RA function using echocardiographic myocardial deformation imaging in PAH patients. This method could be a novel tool for risk stratification and clinical decisions in PAH patients, given the fact that not all patients with PAH respond to iloprost.

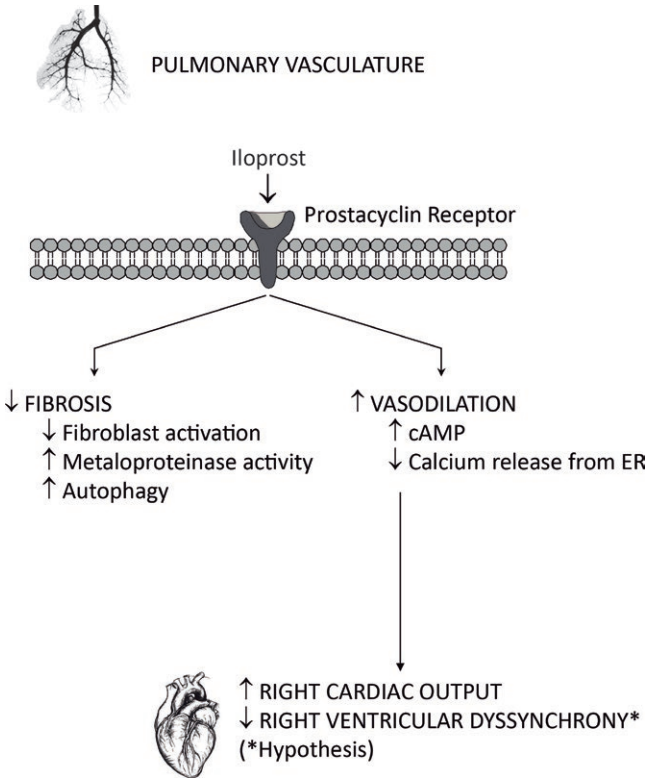

FIGURE 1 Iloprost effects on pulmonary vascular bed

2 | METHODS

2.1 | Study design and population

This was a cross-sectional study. Twenty consecutive PAH idiopathic patients (group I from Nice classification[16]) were included between January 2013 and May 2014. Patients were recruited from university tertiary care hospitals. Inclusion criteria were as follows: age 18 or older, sinus rhythm, mean pulmonary artery pressure >25 mm Hg at rest with a pulmonary capillary wedge pressure <15 mm Hg at the time of diagnosis right heart catheterization, stable clinical condition, stable medication with no prostanoids use (stable pulmonary vasodilator therapy and naive to prostanoids), no evidence of thromboembolic disease in a V/Q scan or computed tomographic pulmonary angiogram, and no evidence of pulmonary obstructive disease in a spirometric study (pulmonary function test). Exclusion criteria were iloprost or other prostanoid use, pregnancy, creatinine level 1.5 times upper normal level, autoimmune disease, acute or chronic inflammation, systemic hypertension, liver disease, use of anti-inflammatory or corticosteroids drugs, active smoker, QRS≥120 mseconds, PR segment >200 mseconds, use of pacemaker, any antecedent of pericardial disease. All participants signed an informed consent approved by our local ethics committee. In all patients, clinical variables were collected including age, gender, weight, height, heart rate, systemic arterial pressure, present medication and right heart catheterization measurements at diagnosis (diagnostic disease data, not at the time of study inclusion). Also a 6-minutes walking test was performed.

2.2 | Echocardiographic study

A two-dimensional echocardiographic study using a commercially available ultrasound scanner (Vivid-7, GE Healthcare, Milwaukee, WI, USA) with a 2.5-MHz phased array transducer (M4S) was performed in all subjects at baseline and 30 minutes postiloprost inhalation. Inhalation was performed with 20 mcg iloprost (Ventavis, Bayer) using MicroAir™ nebulizer (Omron Healthcare, Inc., Lake Forest, IL, USA).[17] Standard echocardiographic views were obtained, including parasternal long- and short-axis, as well as apical two- and four-chamber views. Special attention to the acquisition of apical right cardiac chamber images was taken. Only two-dimensional images with frame rates at least of 60 Hz were considered for analysis. Images were analyzed off line with commercially available software (EchoPac version 113.1.3, GE Healthcare). Blinded, experienced sonographers analyzed all data. Systolic pulmonary artery pressure was estimated from tricuspid regurgitation maximal velocity (TRVmax) (Bernoulli equation) plus RA atrial pressure estimation (using inferior vena cava diameter and degree of inspiratory collapse),[18] also pulmonary vascular resistance was estimated using TRVmax and time–velocity integral in right ventricular outflow tract (RVOT TVI) (formula: [TRVmax/RVOT TVI]×10 + 0.16).[19] LV and RV size measurements and volumetric function evaluations were made according to the recommendations of the American Society of Echocardiography;[20] RV

systolic and diastolic areas were measured using images acquired in the four-chamber view with special focus in adequate delineation of RV borders. RV diastolic function was evaluated using E/e′ ratio using lateral tricuspid annular tissue Doppler and transtricuspid pulse Doppler. LA volume was calculated from apical four- and two-chamber views using the biplane method summation of disks, and RA volume was measured from the apical four-chamber view at the frame just before tricuspid valve opening (end-systole) using the single plane area–length formula.[20]

2.3 | Right ventricular and right atrial strain analysis

Right ventricular and RA strains were analyzed off line with a commercially available software package (2Dstrain, EchoPac version 113.1.3, GE Healthcare) from images acquired in the four-chamber view. The endocardial border was manually traced using a point-and-click technique. For speckle tracking analysis, we selected images with at least 60 frames/s.[21] RV peak systolic strain dyssynchrony (PSSD) index was calculated using a RV six segments model from four-chamber view. The index was derived from the standard deviation of the times from QRS beginning to peak systolic strain of the six segments (Fig. 2). Also, interventricular dyssynchrony (IVD) index was measured (the difference in the timing, between QRS onset to onset of ejection of RV and left ventricle). RV global strain was determined with the RV lateral free wall mean value from images acquired in the four-chamber view.

Right atrial strains were calculated with the reference point set at the onset of the P-wave of the surface ECG,[21] which allowed identifying the peak negative strain (active shortening) during atrial contraction (RASa) and a positive peak strain wave representing RA reservoir function occurring during ventricular systole (RASs) (Fig. 3). The software divided the atrial wall into six segments, and the average was taken for analysis. Segments in which inadequate tracking was observed were excluded from further analysis, and the remaining segments were averaged. Time from the beginning of QRS to RASs peak wave was measured as a surrogate of RA compliance (Fig. 3).

2.4 | Statistical analysis

Normal distribution was assessed by the Kolmogorov–Smirnov test in each variable. Continuous baseline variables were expressed as mean±standard deviation (SD). Categorical variables were expressed as total number (percentages) and compared between groups using chi-square or Fisher's test when appropriate. Continuous variables were tested by unpaired *t*-test or Mann-Whitney U-test (unpaired data) and by paired *t*-test or Wilcoxon analysis (paired data). Pearson's or Spearman's methods were used to analyze the correlation between continuous variables when suitable.

For RV PSSD index, inter-rater reproducibility (observer A and observer B) and intra-rater reproducibility (same examiner A, repeated measurements) were determined by calculating the intra-class correlation coefficient. Absolute reproducibility was assessed using the Bland–Altman method with 95% confidence intervals. Statistical significance was established at $P<.05$. All data were analyzed using the SPSS version

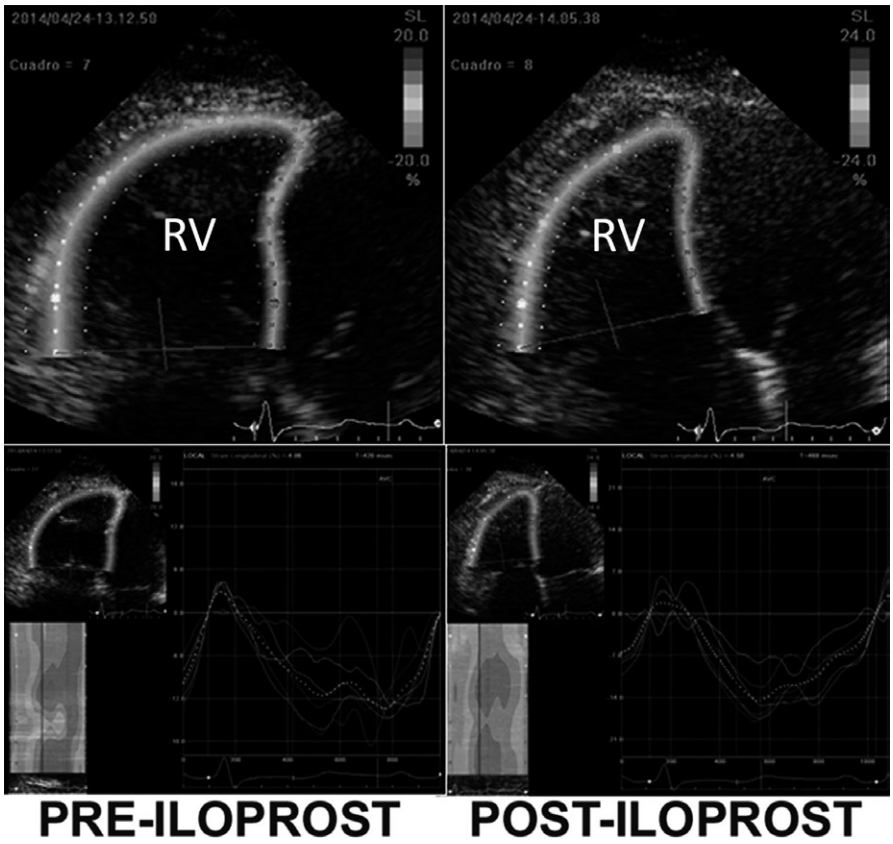

FIGURE 2 Right ventricular peak systolic strain dyssynchrony index. The index was calculated using a right ventricular six-segment model from four-chamber view. The index was derived from the standard deviation of the times from QRS beginning to peak systolic strain of the six segments

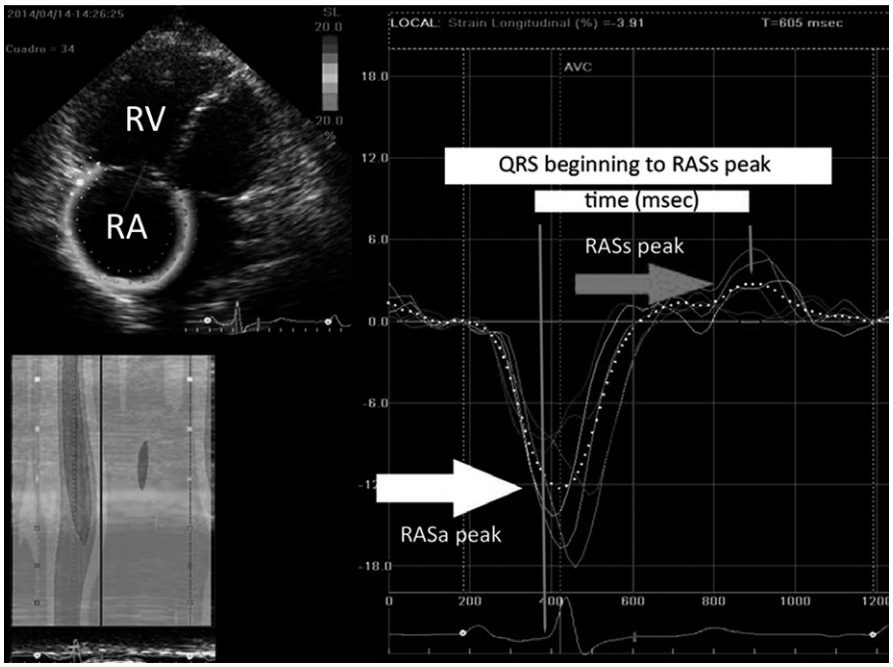

FIGURE 3 Right atrial strain analysis

15.0 (SPSS, Inc., Chicago, IL, USA) and RStudio (RStudio Team (2015) RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, USA).

3 | RESULTS

3.1 | Patient characteristics

Twenty PAH patients were included. Demographics characteristics, medical therapy, and the right heart catheterization data at the time of PAH diagnosis are shown in Table 1. At baseline, mean 6-minutes walking test distance was 339±144 m.

3.2 | Pre- and postiloprost inhalation study

Postiloprost inhalation, we did not observe any changes in systemic hemodynamic parameters (heart rate: 76±13 vs 80±15 bpm, *P*=.26; systolic blood pressure: 105±24 vs 102±26 mm Hg, *P*=.15; diastolic blood pressure: 67±8 vs 65±7 mm Hg, *P*=.39). Regarding echocardiographic parameters, we observed a significant reduction in estimated systolic pulmonary pressure, pulmonary vascular resistance, systolic RV area, and in RV E/e′ ratio. Table 2 shows volumetric and Doppler analysis pre- and postiloprost inhalation. After iloprost, a significant increase in RV contractile function was demonstrated according to the observed increase in RV fractional area change and increase in annular tricuspid S′-wave, TAPSE and global RV longitudinal strain. Also, RV filling improved with a decrease in E/e′ ratio. This was observed along with a significant reduction in RV PSSD and IVD index as shown after iloprost inhalation (Fig. 4A, B). Postiloprost inhalation, RV PSSD showed significant correlations between RV global strain (−0.68; *P*<.05), RV fractional area change (−0.62; *P*<.05), and RV stroke volume (−0.78; *P*<.05).

Regarding the RA, iloprost inhalation induces a significant increase in RASs (Fig. 5A), while RASa was unchanged (−8.4±3.5% vs −8.5±3.9%, *P*=.834). The individual response regarding RA and RV function postiloprost inhalation is shown in Figure 5A–C. A significant shortening in the timing from QRS beginning to RASs peak was also observed after iloprost inhalation (Fig. 6).

TABLE 1 Clinical characteristics of the population

Clinical characteristic	
Age	44±7 years
Female	18 (90%)
Functional class	
I	2 (10%)
II	14 (70%)
III	4 (20%)
IV	0
Medical therapy	
Sildenafil	18 (90%)
Endothelin receptor antagonists	14 (70%)
Anticoagulation	16 (80%)
Aldosterone receptor antagonist	18 (90%)
Oxygen therapy	2 (10%)
Right heart cath	
sPAP	84±15 mm Hg
mPAP	52±9 mm Hg
dPAP	36±11 mm Hg
PWP	9±3 mm Hg
PVR	15±3 Wood units

sPAP, systolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; PWP, pulmonary wedge pressure; PVR, pulmonary vascular resistance.

TABLE 2 Echocardiographic characteristics pre- and postiloprost inhalation

	Pre-iloprost	Postiloprost	*P*-value
RV fractional area change (%)	21.4±5.6	26.1±4.0	.007
RV diastolic area, 4C (cm^2)	75±25	74±19	.200
RV systolic area, 4C (cm^2)	59±9	54±7	.030
Right outflow tract velocity–time integral (cm)	11.8±3.2	13.3±3.3	.018
Right E/e′ ratio	13±3	9±2	.028
TAPSE (mm)	12±3	14±3	.026
S′ tricuspid lateral wave (cm/s)	6.2±1.7	6.8±1.7	.026
sPAP (mm Hg)	90±19	76±17	.002
PVR (Wood units)	5.1±1.8	3.3±0.9	.004
RV preejection time (ms)	104±17	85±14	.001
LV preejection time (ms)	93±18	89±18	.044
RV global strain (%)	−12.8±2.8	−14.8±3.3	<.001
RA volume 4C (mL)	140±42	109±29	.008

Data are shown as mean±SD. RV, right ventricle; 4C, four chambers; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; PVR, pulmonary vascular resistance; LV, left ventricle; RA, right atrium.

3.3 | Reproducibility for PSSD index

Intra-rater reproducibility was excellent (ICC 0.995, CI 95% 0.984-0.998), (Fig. 7C). Bland–Altman plots showed that all differences were within the 95% limits of agreement with a very low mean difference between the two raters (Fig. 7A-E). Inter-rater reproducibility was also very high (ICC 0.989, CI 95% 0.962-0.997), and all differences were within the 95% limits (Fig. 7D, E, F); inter-rater differences were minimal (Fig. 7F).

RA atrial strain variability for our laboratory has been reported in detail elsewhere.[21,22]

4 | DISCUSSION

The main findings of this study were (1) iloprost inhalation induces an acute reduction in PAH and PVR with an acute improvement in RV function with increase in systolic and diastolic function and reduction in dyssynchrony. (2) No acute effects on RA contractile function were observed, inhaled iloprost acutely reduces RA size, and RV E/e′ also significantly increases the magnitude of RA deformation during ventricular systole, as well as making it occur earlier in RA filling phase. This last finding could reflect the better RV performance.

During recent years, an improvement in the clinical evolution and survival in PAH patients has been shown.[23] The use of pulmonary-selective therapy reduces pulmonary artery smooth muscle cell proliferation, reduces oxidative stress, and improves cardiac function,[17] and these changes have been associated with quality-of-life improvement.[24] Despite this progress, not all PAH patients have the same response to this specific treatment and the clinical evolution and survival of some of these patients are still poor.[25] For this reason, it seems important that the inclusion of new data would help to differentiate potential responders from nonresponders patients in the treatment strategy, in terms of intensity and timing of pulmonary transplant consideration.

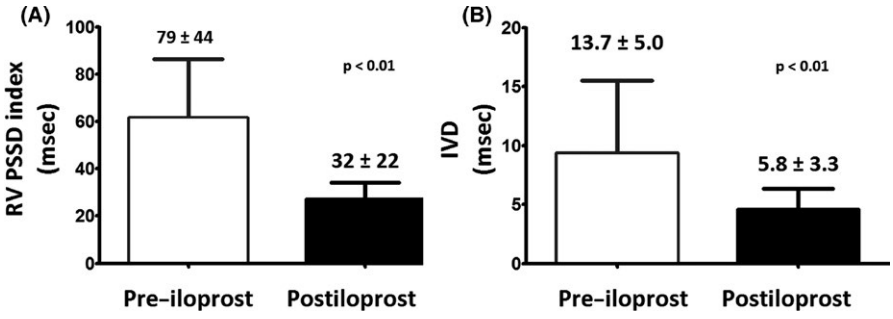

FIGURE 4 Right ventricular dyssynchrony index and interventricular dyssynchrony index pre- and postiloprost inhalation

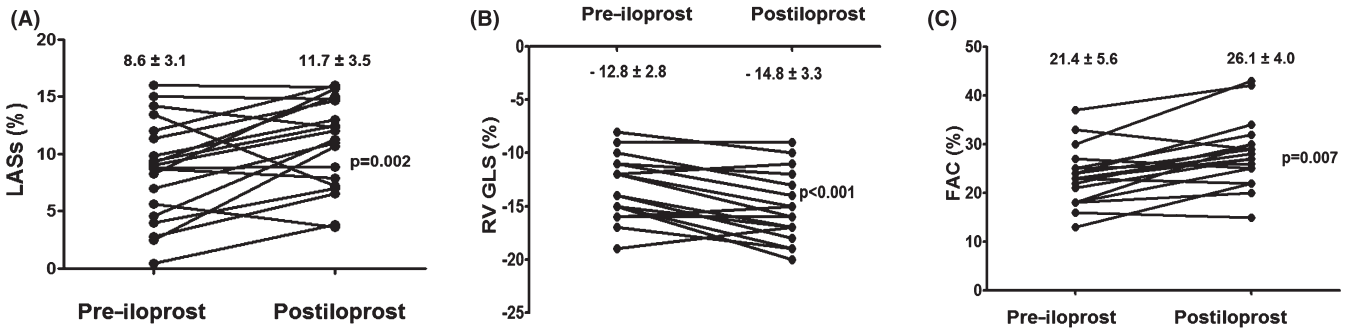

FIGURE 5 **A.** Individual right atrial reservoir function (RASs); **B.** right ventricular global longitudinal strain; **C.** right ventricular fractional area change pre- and postiloprost inhalation

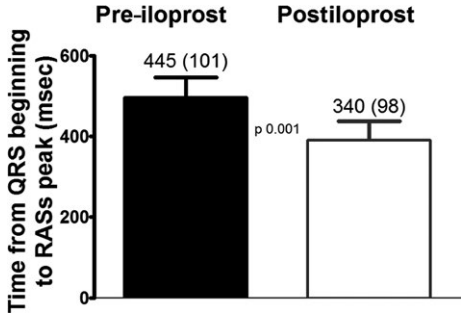

FIGURE 6 Timing from QRS beginning to RASs peak pre- and postiloprost inhalation

4.1 | RV function

Right ventricular function has been shown as an important prognostic factor in PAH.[26] In patients with PAH, the primary cause of death is RV dysfunction.[26] RV dysfunction can be reversed with pulmonary transplantation, and the current guidelines indeed recommend repeated assessment of RV function in the clinical follow-up of patients with PAH.[27] The time onset of chronic RV failure after the diagnosis of PAH is highly variable between patients; for this reason, a comprehensive echocardiography assessment remains an important tool at diagnosis moment and follow-up. Recently, novel echocardiographic techniques including strain analysis by speckle tracking allowed the analysis of

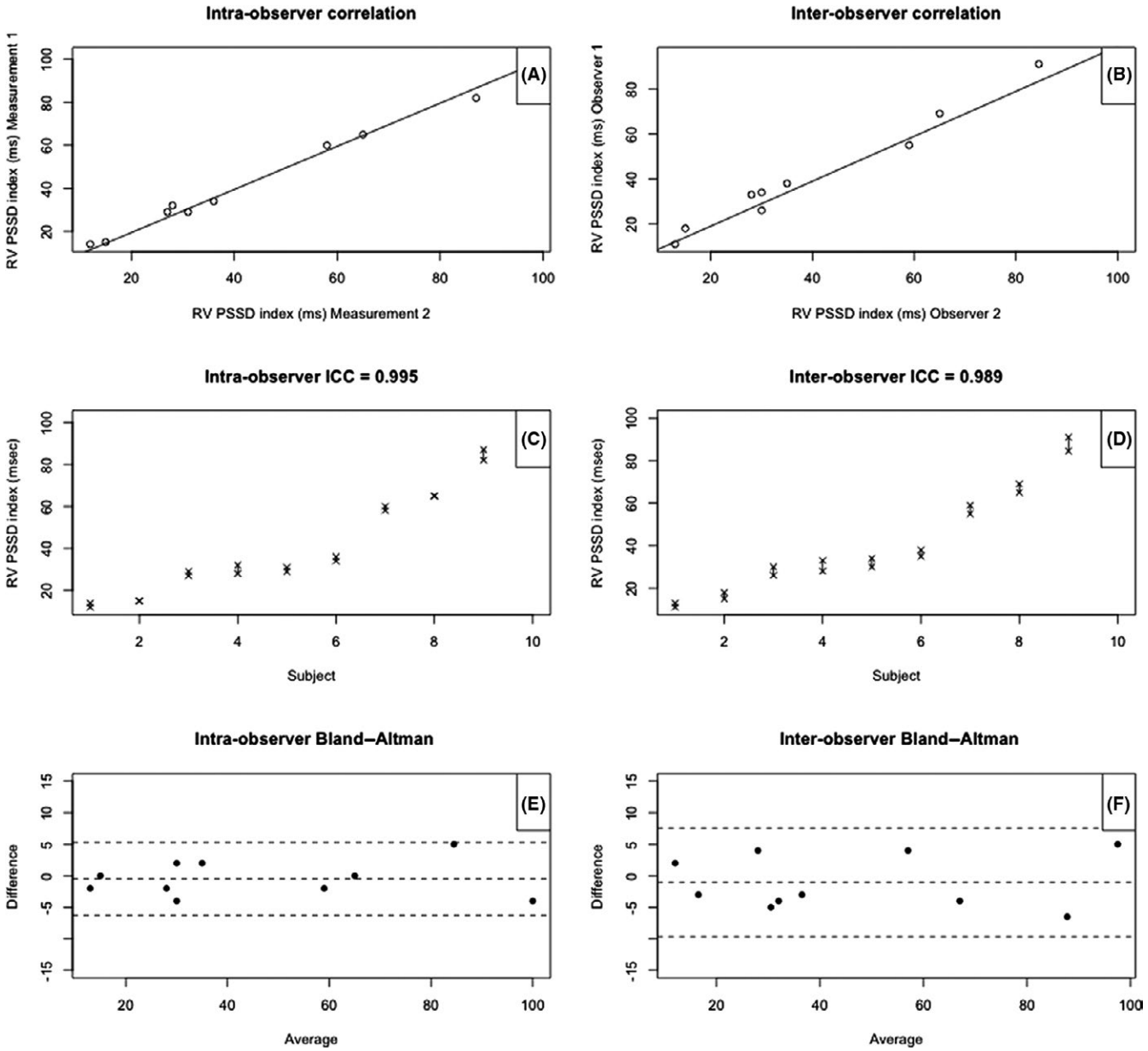

FIGURE 7 Right ventricular dyssynchrony index reproducibility study (see the text)

RV segmental contraction and the evaluation of RV synchrony.[6] RV dyssynchrony has been associated with RV adverse remodeling and function in PAH patients;[7] moreover, global RV strain is related to important clinical outcomes in these patients.[5] Finally, RV dyssynchrony assessed by phase analysis using F-fluorodeoxyglucose positron emission tomography is also related to RV dysfunction in PAH patients, supporting the data derived from echo studies.[28] Acute response to nitric oxide, i.v. epoprostenol or adenosine during right cardiac catheterization, is recommended to identify a group of patients that could have beneficial response to chronic administration of calcium channel blockers.[27] Inhaled iloprost may be also considered for performing vasoreactivity testing as an alternative (IIb recommendation).[27] In our patients, we evaluated the acute response to inhaled iloprost using comprehensive echocardiographic evaluations. To our knowledge, this is the first study that evaluates acute changes in RV function. Iloprost inhalation induces an acute reduction in RV PSSD index and in IVD. This resynchronization response is observed together with a better RV performance with an increase in RV area change and global strain, a reduction in PVR, RV systolic area, and RV E/e′ in patients with PAH.

Right ventricular dyssynchrony is related to a segmental wall stress heterogeneity that also is related to a different RV remodeling phases.[7] An acute RV afterload reduction with inhaled iloprost could lead to a different degrees of homogenization of RV contraction, depending on the state of RV remodeling and fibrosis, and these changes are evaluable by echocardiographic deformation tools.[29]

4.2 | Right atrial function

Lately, atrial function has been related to functional capacity and prognosis in different clinical scenarios.[30] Moreover, atrial wall is particularly stressed in overload situations including sport practice[21] and could lead to atrial dysfunction in some subjects at risk.[22]

In PAH patients, strain derived from speckle tracking has shown to be a feasible technique for the evaluation of RA atrial function.[9] Sakata et al. showed good correlations between RA atrial function and right heart catheterization data in PAH patients,[9] and recently, RA strain has shown additional value to predict outcome in PAH patients.[31] Finally, RA remodeling and function are related to clinical impairment in PAH patients.[8] This evidence is closely related to our findings in terms of highlighting the potential clinical importance of acute RA atrial function changes with therapy.

Despite RA reservoir function (RASs), RA volume and compliance (time from QRS to peak strain) improved, no direct effect was observed on atrial contraction (RASa) at least in the acute setting. Further longer term follow-up studies are needed to demonstrate that the benefit on RV function also translates on an improvement in atrial contractile function.

4.3 | Limitations and strengths

The principal limitations of our study are the small cohort of patients and the assessment of RV function by echocardiography instead of magnetic resonance imaging, which is the goal standard method; however, this technique is not widely available or used in clinical evaluation of PAH patients especially for acute repeated measurements. Three-dimensional echo may be an alternative, but it has limitations for precise volume estimation of the RV.[11] Although these are interesting and promising findings, we cannot estimate the impact of them over time, neither the chronic effects on RV and RA measurements. Other important issue to consider is that right heart catheterism was not performed concomitantly with echocardiographic study, but this does not invalidate our results.

Additionally, the current speckle tracking tools applied to the right side cardiac chambers may have worse performance, especially due to a lower temporal resolution and preset algorithms for the left ventricle; nonetheless, we believe that they are based on principles which apply to both ventricle and atria.[32] Finally, we have to mention that the RV an RA remodeling and function assessment were performed from an apical four-chamber view following the recommendations for echocardiographic measurements.[20]

On the other hand, among the strengths of this study are its comprehensive echocardiographic quality, the methodology used (echo measurements were analyzed off line by blinded experts), and the consistency between changes in RV functional parameters and favorable changes in right atrial function.

In conclusion, our study shows acute changes in RV function, dyssynchrony, and RA performance after iloprost inhalation that may add relevant clinical information in the management of PAH patients. These findings deserve to be replicated in a larger cohort and long-term follow-up.

DISCLOSURE STATEMENT

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflict of interests to disclose.

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How to cite this article: Gabrielli, L., Ocaranza, M. P., Sitges, M., Kanacri, A., Saavedra, R., Sepulveda, P., Sepulveda, L., Rossel, V., Zagolin, M., Verdejo, H. E., Baraona, F., Zalaquett, R., Chiong, M., Lavandero, S. and Castro, P. F. (2017), Acute effect of iloprost inhalation on right atrial function and ventricular dyssynchrony in patients with pulmonary artery hypertension. Echocardiography, 34: 53–60. doi: 10.1111/echo.13401