Improvement in Right Ventricular Strain with Ambrisentan and Tadalafil Upfront Therapy in Scleroderma-associated Pulmonary Arterial Hypertension

To the Editor:

Scleroderma-associated pulmonary arterial hypertension (SSc-PAH) is characterized by poor survival, mainly related to the development of right ventricular (RV) failure (1). Although recent advances in PAH-specific treatment have improved survival, patients with SSc-PAH have a modest response to therapy and higher mortality compared with those with PAH due to other etiologies (1, 2). Initial upfront PAH combination therapy is a novel approach aimed at improving outcomes (3).

In a recent prospective, multicenter, open-label study of treatment-naive patients with SSc-PAH (the ATPAHSS [Ambrisentan and Tadalafil in Pulmonary Arterial Hypertension Associated with Systemic Sclerosis] trial; clinicaltrial.gov NCT01042158), initial upfront therapy with a phosphodiesterase-5 inhibitor (tadalafil 40 mg oral once daily) and an endothelin receptor antagonist (ambrisentan 10 mg oral once daily) demonstrated improvement in invasive hemodynamics and functional status (4). Because survival is predominantly dependent on RV function (5), we evaluated the effects of such treatment on RV morphology and function using conventional and novel speckle tracking–derived echocardiography in the ATPAHSS trial cohort. Some of the results of this study have been previously reported in abstract form (6).

Full details regarding the methods used are provided in Reference 4 and its online supplement. Two-dimensional and M-mode echocardiography was performed locally at each site according to the American Society of Echocardiography guidelines (7, 8). The results were stored on CDs and sent to the core laboratory at Johns Hopkins University (Baltimore, MD).

Two echocardiographers (V.M. and M.M.) blinded to patient information, clinical variables, and timing of study acquisition performed echocardiographic analysis offline using Synapse cardiovascular software (V4.0.8; Fujifilm Medical Systems U.S.A., Inc.) for the conventional analysis, and a commercially available vendor-independent strain software (Epsilon) for the RV longitudinal systolic strain (RVLSS) analysis.

Twenty-three of the 24 patients enrolled in the ATPAHSS trial had adequate echocardiographic image quality for measurements. The baseline characteristics of the cohort and all main study findings are summarized in Table 1.

At baseline, patients had normal left ventricular (LV) size and function, borderline left atrial enlargement, and mild LV diastolic dysfunction (as demonstrated by mean values of the E/A ratio [ratio of early (E) to late (A for atrial) ventricular filling velocities], and E deceleration time). Right heart chambers were significantly dilated (8). RV hypertrophy was present. RV systolic pressure, estimated by measuring the tricuspid regurgitation pressure gradient, was severely elevated (8). Conventional RV function parameters (i.e., tricuspid annular systolic plane excursion [TAPSE] and fractional area change) were pathologically impaired.

After 36 weeks of treatment, there was a significant reduction in right heart chamber sizes and a decrease in RV free wall thickness. Both TAPSE and fractional area change improved significantly, whereas RV systolic pressure decreased significantly.

Baseline strain analysis demonstrated a marked reduction of global RVLSS in comparison with normal values (9), mainly due to a reduction in midventricular and apical RVLSS, with relative hyperkinesis of the basal RVLSS. After 36 weeks of treatment, there was a significant improvement in global RVLSS, mainly related to an improvement of the basal and midventricular RVLSS without a significant change in apical RVLSS (Figure 1). In addition, both LV end-diastolic and end-systolic diameters and volumes increased significantly. A positive correlation between an improvement in basal RVLSS and a reduction in RV mass on cardiac magnetic resonance imaging (4) was observed (correlation coefficient 0.504, $P < 0.05$).

Intra- and interobserver agreement of RVLSS was excellent, as assessed by the intraclass correlation coefficient (ICC) (intraobserver ICC = 0.98, 0.99, 0.97, and 0.98; and interobserver ICC = 0.925, 0.859, 0.928, and 0.958 for basal, midventricular, apical, and global RVLSS, respectively).

To our knowledge, this is the first study to demonstrate an improvement in regional and global RV myocardial contractility in patients with SSc-PAH after initial upfront combination therapy. The beneficial effects of upfront treatment in connective tissue disease–related PAH were recently described in a subanalysis of the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial, which revealed that ambrisentan and tadalafil combination therapy reduced the risk of clinical failure in comparison with pooled monotherapy (10), similar to what was observed in the parent study (3). However, there was no echocardiographic assessment in that trial.

Mukherjee and colleagues recently described regional RVLSS abnormalities in SSc patients free from PAH or clinical RV failure that were not appreciable by standard echocardiography alone (11), consisting of basal RVLSS hyperkinesis, with midventricular and apical hypokinesis, and a reduction in global RVLSS (11). In the ATPAHSS cohort, we demonstrated a similar regional heterogeneity with relative basal hyperkinesis, and hypokinesis of the midventricular and apical segments, but the RVLSS gradient along the RV free wall was diminished compared with prior reports, and there was a worse global RVLSS in patients with SSc-PAH. It is conceivable that a heterogeneous RVLSS pattern exists in patients

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Author Contributions: P.M.H., R.E.G., and S.C.M.: study design; P.M.H., R.T.Z., S.C.M., R.D., T.M.K., R.J.T., O.A.M., F.T., T.S., and K.C.: patient recruitment, care, and follow-up; R.D., R.M.K., and P.M.H.: data collection, maintenance, and analysis; V.M. and M.M.: echocardiographic interpretation of conventional and strain analysis; P.M.H., S.C.M., R.D., V.M., and R.M.K.: statistical analyses; V.M.: drafting of the manuscript; M.M. and P.M.H.: critical revision of the manuscript for important intellectual content. P.M.H. was the principal investigator, had access to all the data in the study, and takes full responsibility for the integrity and accuracy of the data analysis.

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Table 1. Demographics, Functional Class, 6-Minute-Walk Distance, Serum NTproBNP, and Hemodynamic and Echocardiographic Findings in Patients with SSc-PAH at Baseline and after 36 Weeks of Initial Upfront Combination Treatment with Ambrisentan and Tadalafil

Parameters (*N = 23* patients)	Baseline	36 Weeks	*P* Value	Reference Values (Healthy Adults)
Demographics				
Age, yr	59.9 ± 10.2			
Female sex, *n* (%)	21 (91.3)			
Race: white/black/other, *n*	20/2/1			
Limited scleroderma, *n* (%)*	18 (78.3)			
WHO functional class I/II/III/IV, *n*	0/7/15/0	1/13/9/0	<0.05	
6-minute-walk distance, m	341 ± 134	401 ± 101	<0.001	
NTproBNP, pg/ml	1,630 ± 2,698	739 ± 1227	<0.05	
Right heart catheterization				
Right atrial pressure, mm Hg	7 ± 5	5 ± 3	<0.05	
Mean PAP, mm Hg	42 ± 12	31 ± 7	<0.01	
PAWP, mm Hg	9 ± 4	11 ± 4	n.s.	
Cardiac index, L/min/m^2	2.6 ± 0.7	3.2 ± 1.6	<0.01	
PVR, WU	8.6 ± 5.1	3.8 ± 3.3	<0.01	
Pulmonary arterial O_2 saturation, %	65 ± 6	72 ± 4	<0.001	
Conventional echocardiography				
LVED diameter, mm	42.9 ± 7.3	45.7 ± 5.9	<0.01	
LVES diameter, mm	27.3 ± 7.1	30.1 ± 5.6	<0.01	
IVS thickness, mm	9.2 ± 1.6	9.02 ± 1.5	n.s.	
LVPW thickness, mm	8.1 ± 1.2	8.1 ± 1.2	n.s.	
LA volume, ml	50.1 ± 15.1	54.2 ± 18.2	n.s.	
E deceleration time, ms	238.9 ± 52.0	243.3 ± 36.4	n.s.	
E/A	0.88 ± 0.3	0.94 ± 0.3	n.s.	
LVED volume, ml	75.1 ± 28.1	86.4 ± 22.1	<0.01	
LVES volume, ml	28.3 ± 14.0	32.9 ± 10.3	<0.05	
LV ejection fraction, %	63.3 ± 6.8	62.2 ± 4.6	n.s.	
RA area, cm^2	22.6 ± 5.3	19.3 ± 4.6	0.001	⩽ 18 (8)
RV basal diameter, mm	45.9 ± 4.3	42.4 ± 4.4	<0.0001	⩽ 42 (8)
RV midventricular diameter, mm	32.6 ± 4.3	30.3 ± 5.3	n.s.	⩽ 35 (8)
RV base-to-apex diameter, mm	72.3 ± 4.9	74.0 ± 5.9	n.s.	⩽ 86 (8)
RV end-diastolic area, cm^2	25.1 ± 4.6	22.4 ± 5.1	<0.01	⩽ 25 (8)
RV end-systolic area, cm^2	18.6 ± 5.1	14.1 ± 5.2	<0.0001	⩽ 14 (8)
RV FAC, %	26.6 ± 9.9	38.4 ± 7.9	<0.0001	⩾ 35 (8)
TAPSE, mm (*N* = 19)	16.1 ± 3.5	22.5 ± 3.2	<0.0001	⩾ 16 (8)
RV free wall thickness, mm	7.3 ± 1.1	6.5 ± 0.9	<0.01	⩽ 5 (8)
TR gradient, mm Hg	57.2 ± 18.8	37.4 ± 9.8	0.001	⩽ 30 (8)
RV strain analysis				
Basal RVLLS, %	−18.05 ± 8.2	−25.7 ± 9.0	0.01	−25 ± 6 (9)
Midventricular RVLLS, %	−13.5 ± 6.6	−18.8 ± 6.8	0.001	−27 ± 5 (9)
Apical RVLLS, %	−10.1 ± 5.9	−11.6 ± 6.0	n.s.	−24 ± 6 (9)
Global RVLLS, %	−13.9 ± 5.2	−18.7 ± 4.9	0.001	−26 ± 4 (9)

Definition of abbreviations: CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; E = early deceleration time; E/A = early (E) to late (A) ventricular filling velocities; FAC = fractional area change; IVS = interventricular septum; LA = left atrial; LV = left ventricular; LVED = left ventricular end-diastolic; LVES = left ventricular end-systolic; LVPW = left ventricular posterior wall; n.s. = not significant; NTproBNP = N-terminal pro-brain natriuretic peptide; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RA = right atrial; RV = right ventricular; RVLLS = right ventricular longitudinal systolic strain; SSc-PAH = scleroderma-associated pulmonary arterial hypertension; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; WHO = World Health Organization; WU = Wood unit. Data are expressed as mean ± standard deviation, absolute numbers, or percentage. Paired *t* test, Wilcoxon's signed-rank test, and chi-square test were performed as appropriate, between baseline and 36 weeks. $P < 0.05$ was considered significant. Statistical analysis was performed using SPSS (version 22.0; IBM Corp.). WHO functional class data were not available for one subject at baseline.
*One patient had diffuse scleroderma, and four patients had CREST syndrome.

with SSc, with the longitudinal hyperkinetic basal segment being the predominant vector of contraction early in the disease course. As PAH develops, the ability of the basal segment to compensate decreases and RV failure ensues, suggesting a "two-hit" hypothesis: a preexisting RV contractile dysfunction may predispose to further RV impairment when a second insult (PAH development) occurs.

TAPSE, a standard echocardiographic parameter of RV function, improved significantly with upfront therapy (4). However, TAPSE utilizes movement of the lateral tricuspid annulus as an estimate of global RV function, whereas RV strain offers a quantitative measure of both regional and global contractility, providing additive information about the regional nature of contractile improvement.

We also observed a reduction in RV wall thickness coinciding with a significant reduction in RV mass on cardiac magnetic resonance imaging, as reported in the ATPAHSS trial (4). This finding, in association with improvements in RV dimensions and function, may represent a

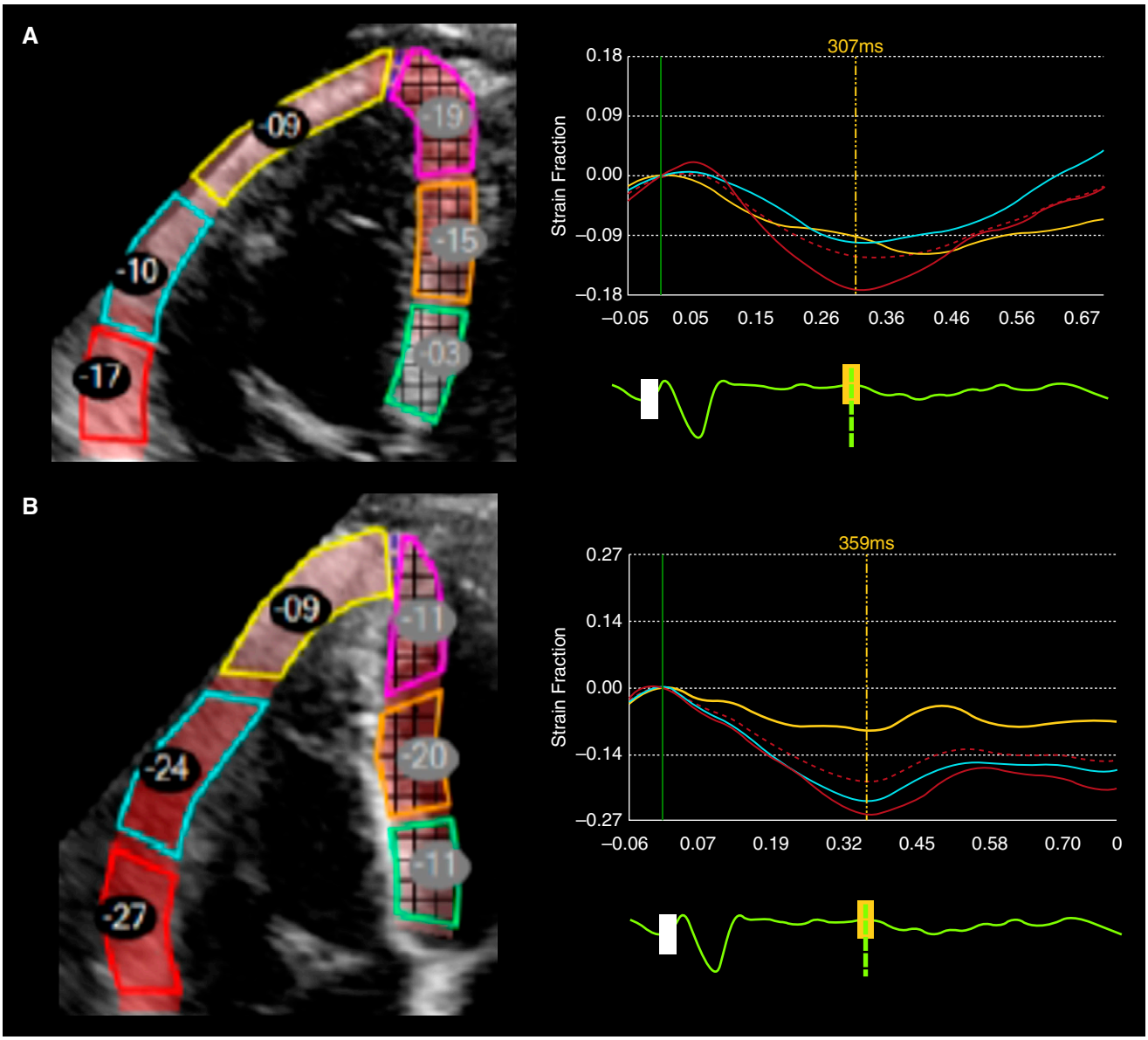

Figure 1. Right ventricular longitudinal systolic strain (RVLSS) pattern in a patient with scleroderma-associated pulmonary arterial hypertension before (*A*) and after 36 weeks (*B*) of upfront treatment with ambrisentan and tadalafil. Longitudinal strain measures the percentage systolic shortening of a specific region of interest (ROI, obtained by tracking the endocardial borders of the ventricle) relative to its original length and is expressed as a negative percentage. Global RVLSS was calculated as the average of basal, midventricular, and apical ROIs (9). Worsening strain refers to a less negative number (i.e., a lower absolute value) than expected for an ROI along the longitudinal axis, and improved strain refers to a more negative number (i.e., a higher absolute value). Focused view of the right ventricle is demonstrated in the left panels. The right ventricular free wall is divided into three color-coded wall segments that correspond to strain curves shown on the adjacent curves: basal in red, midventricular in light blue, and apical in yellow. The numbers in the black circles represent the values of regional longitudinal strain for each segment. The interventricular septum has been excluded from the analysis. The right panels demonstrate strain curves for each segment of the right ventricular free wall (basal in red, midventricular in light blue, and apical in yellow). The dashed red curve represents the average value of the three segments. The dashed yellow line indicates the time (msec) of peak systolic strain during the cardiac cycle. The *x*-axis measures the time (msec). Cardiac cycle is timed based on EKG tracings, shown in green.

transition from "maladaptive" RV remodeling (5), characterized by eccentric hypertrophy with severe chamber dilation and reduced systolic function, to a more physiological and "adaptive" RV remodeling.

There are some limitations to consider. First, the effects of treatment should be interpreted with caution, as this was an open-label study without a placebo or a single-drug control group. Furthermore, the technique of speckle-tracking echocardiography is largely dependent on two-dimensional image quality; the current analysis was performed on all but one patient. Finally, there was a vendor-specific variability in the strain measures that may affect the reproducibility of our findings.

In conclusion, these results demonstrate that ambrisentan and tadalafil upfront treatment improves regional and global RV contractility, as evaluated by strain echocardiography in patients with SSc-PAH,

strongly supporting its role in serial monitoring of RV function in response to treatments in clinical trials and clinical practice. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Rubenfire M, Huffman MD, Krishnan S, Seibold JR, Schiopu E, McLaughlin VV. Survival in systemic sclerosis with pulmonary arterial hypertension has not improved in the modern era. *Chest* 2013;144: 1282–1290.
2. Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM. Comparison of treatment response in idiopathic and connective tissue disease-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2015;192:1111–1117.
3. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, *et al*.; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373:834–844.
4. Hassoun PM, Zamanian RT, Damico R, Lechtzin N, Khair R, Kolb TM, *et al*. Ambrisentan and tadalafil up-front combination therapy in scleroderma-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2015;192:1102–1110.
5. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, *et al*. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *J Am Coll Cardiol* 2013; 62(25, Suppl)D22–D33.
6. Mercurio V, Mukherjee M, Tedford RJ, Zamanian RT, Khair R, Sato T, *et al*. Improved right ventricular chamber size and contractility after upfront combination therapy with ambrisentan and tadalfil in scleroderma-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2017;195:A1044.
7. 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.e14.
8. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, *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, quiz 786–788.
9. Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, *et al*. Reference values for right ventricular strain in patients without cardiopulmonary disease: a prospective evaluation and meta-analysis. *Echocardiography* 2015;32:787–796.
10. Coghlan JG, Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, *et al*.; AMBITION Investigators. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. *Ann Rheum Dis* 2017;76:1219–1227.
11. Mukherjee M, Chung SE, Ton VK, Tedford RJ, Hummers LK, Wigley FM, *et al*. Unique abnormalities in right ventricular longitudinal strain in systemic sclerosis patients. *Circ Cardiovasc Imaging* 2016;9:e003792.

Bronchial Provocation Testing Can Be Improved by Using Dry Powder Adenosine Instead of Nebulized Adenosine Monophosphate

To the Editor:

Airway hyperresponsiveness (AHR) to adenosine has proven to be a good marker for eosinophilic airway inflammation in asthma and can be used to monitor disease activity and the therapeutic effectiveness of inhaled corticosteroids (1–3). Adenosine is usually administered by nebulization of adenosine monophosphate (AMP), but the highest feasible concentration of AMP often fails to induce sufficient bronchoconstriction in subjects with asthma (4, 5). We studied whether this limitation could be resolved by administering adenosine as a dry powder formulation. We previously demonstrated the feasibility of this new bronchial provocation method in a small proof-of-concept study (6). The aim of the present study was to further validate the dry powder adenosine provocation test in a larger cohort of subjects with asthma.

Data were obtained from subjects recruited for the OLiVIA study (Effects of Extra-fine Particle HFA-Beclomethasone versus Coarse Particle Treatment in Smokers and Ex-smokers with Asthma; clinical trial number: NCT01741285, www.clinicaltrials.gov). Sixty current or ex-smokers with asthma (34 females, 26 males) with $FEV_1 \geqslant 50\%$ predicted, who did not use inhaled corticosteroids for at least 4 weeks, underwent provocations with both AMP and dry powder adenosine as baseline measurements on subsequent visits (1–2 weeks apart), in addition to blood sampling, spirometry, body plethysmography,

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