Supplementary material

Methods

Echocardiography and speckle tracking study

All subjects underwent a comprehensive conventional 2D and Doppler echocardiography study, by the same certified operator. An ultrasound system (Vivid 7 pro, General Electric Medical Systems, Horten, Norway) with a 2.5 MHz transducer was used. All the data were stored for off-line analysis (EchoPAC 113.05 version, GE Healthcare, Horten, Norway). All images were obtained with a frame rate >50 frames/sec.

The study protocol included a complete conventional and Doppler assessment of ventricles, atriums, pericardium and valves according to recent recommendations (1-6). Left ventricle (LV) volumes and ejection fraction (EF) were calculated using Simpson's biplane method (2). Left atrium (LA) volumes were derived from four and two chamber apical view with biplane method of disk (2). LV mass was estimated with area-length method (2). LV diastolic function and filling pressures were assessed according the new recommended algorithm (1). The early (Emv) and late mitral valve (Amv) inflow peak velocity were taken by pulse wave Doppler, placing the sample volume at the tips of mitral leaflets. Averaged (lateral and septal side of mitral annulus) systolic (S) and diastolic early (e') and late (a') peak velocities were obtained using pulse-wave tissue Doppler imaging techniques (1).

In modified apical four chamber view, right ventricle (RV) areas and right atrium volume were estimated (2). RV diastolic function was assessed by the ratio (E/A, tv) of early (Etv) and late (Atv) tricuspid inflow waves velocities and by the ratio of early diastolic velocities by pulse wave and tissue Doppler (E/e', tv) (7). Fractional area changing (FAC), tricuspid annular longitudinal excursion by M-mode (Tapse) and peak systolic velocity (Stv) at tricuspid annulus by pulsed-wave tissue Doppler imaging were used for evaluating the systolic performance of right ventricle (2). Systolic pulmonary arterial pres-

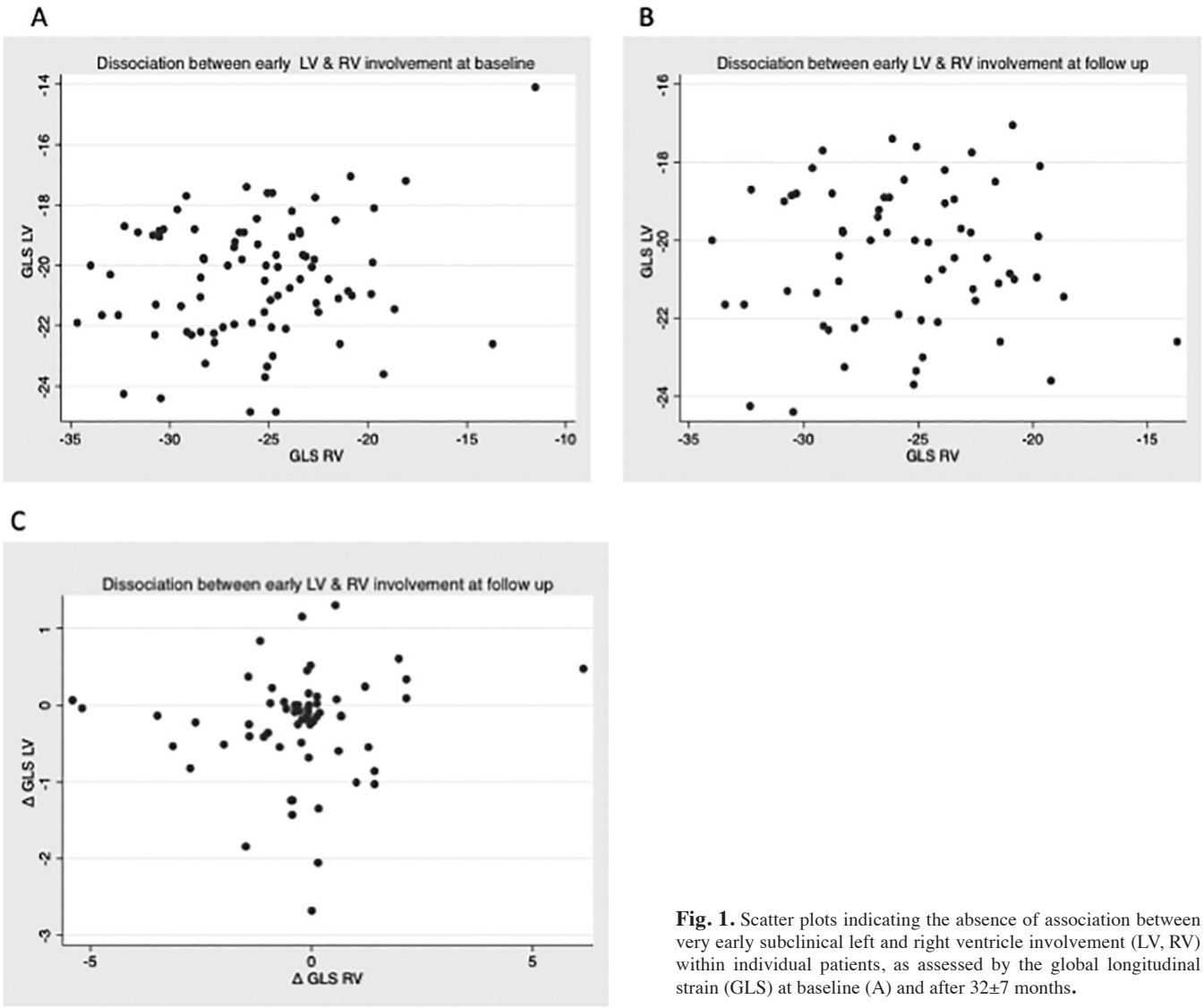

Fig. 1. Scatter plots indicating the absence of association between very early subclinical left and right ventricle involvement (LV, RV) within individual patients, as assessed by the global longitudinal strain (GLS) at baseline (A) and after 32±7 months.

Supplementary Table 1. 1a. Associations between left ventricular function/structure and arterial haemodynamic parameters in systemic sclerosis patients; 1b. Associations between left ventricular function/structure and left ventricular performance

	1a. Arterial haemodynamics				**1b. Left ventricular performance indices**			
	AP75, (mmHg)	AIx75 (%)	SVI (%)	Total arterial compliance (mL/mmHg)	LV stroke work (kg cm)	LV stroke work index (g/cm^{-2})	PVA, (kg cm)	LV energetic efficiency (%)
LV EDVi, (mL/m^2)	***0.035*** ***Rs=-0.23***	***0.018*** ***Rs=-0.25***	0.07 Rs=0.19	***<0.001*** ***Rs=0.48***	0.118	***<0.001*** ***Rs=-0.53***	***0.008*** ***Rs=0.28***	*<0.001* *Rs=-0.54*
LV ESVi, (mL/m^2)	0.33	0.16	0.262	***0.009*** ***Rs=0.29***	0.469	***<0.0001*** ***Rs=-0.52***	0.079	***<0.001*** ***Rs=-0.78***
LVMi, (g/m^2)	***<0.001*** ***Rp=0.36***	0.14	0.907	***0.02*** ***Rs=-0.26***	***0.023*** ***Rs=0.33***	0.38	***0.001*** ***Rs=0.36***	***0.03*** ***Rs=-0.24***
LV E/e'	***<0.001*** ***Rs=0.5***	***0.005*** ***Rs=0.3***	***0.03*** ***Rs=-0.23***	***<0.001*** ***Rs=-0.53***	***<0.001*** ***Rs=0.44***	***<0.001*** ***Rs=0.54***	***<0.001*** ***Rs=0.42***	***0.002*** ***Rs=0.34***
GLS LV, (%)	0.21	0.25	0.133	0.08	***0.006*** ***Rs=-0.3***	0.259	***0.038*** ***Rs=-0.23***	***0.003*** ***Rs=-0.33***
GLSR, (sec^{-1})	***<0.001*** ***Rs=-0.43***	***0.001*** ***Rs=-0.36***	0.491	***0.002*** ***Rs=0.35***	0.098	***0.028*** ***Rs=-0.25***	0.056	0.97
GCS LV, (%)	0.82	0.9	0.225	0.69	***0.012*** ***Rs=-0.29***	***0.007*** ***Rs=-0.31***	0.08	***<0.001*** ***Rs=-0.42***

LV: left ventricle; EDVi: end-diastolic volume index; ESVi: end-systolic volume index; LVMi: left ventricle mass index by 2D methods; EF: ejection fraction; LV E/e': ratio E pulsed-wave Doppler velocity at mitral valve over e' averaged pulsed-wave tissue Doppler velocity at mitral annulus; GLS: global longitudinal strain; GLSR: global longitudinal strain rate; GCS: global circumferential strain; AP75: augmentation pressure at HR 75 min^{-1}; SVI: subendocardial viability index; AIx: augmentation index at HR 75 min^{-1}; PVA: pressure volume area; Rp: Pearson correlation coefficien Rs: Spearman's rank correlation coefficient.

sure was estimated from peak velocity of tricuspid regurgitation (TVR) using the Bernoulli equation and by right atrial pressure derived from diameter and collapsibility of inferior vena cava (7). Evaluation for pulmonary arterial hypertension was performed according to a new proposed algorithm (8), using the peak TVR and supplementary echocardiographic signs. For all the above measurements three cardiac cycles were averaged, indexing for body surface area as appropriate.

For 2D speckle tracking echocardiography four, two, and three apical chamber views were obtained. Multilayer strain analysis was performed by a specific software (EchoPAC PC, version 113.05, GE Healthcare) according to recommendations (9, 10). Global longitudinal strain (GLS) was derived from mid-myocardium using peak values (11, 12). GLSendo and GLSepi were measured as GLS, by using the region of interest on the endocardium and epicardium, respectively (11, 12). Global longitudinal strain rate in early diastole (GLSRed) was derived from mid-myocardium. In parasternal short axis at the level of papillary muscle, we measured the peak global circumferential strain (GCS) as well as GCSendo and GCSepi, with the same method as GLS. Radial strain and other cardiac mechanics indices were not derived due to the differences in reproducibility (13). In modified apical four chamber view, using the same software and adjusting the region of interest according to thickness of RV wall, we calculated the peak longitudinal strain of free wall (GLS) by adding the value of basal, mid and apical segment and dividing by three (2). With the same method and using the region of interest of endocardium and epicardium, we measured the GLSendo and GLSepi, respectively. When an inadequate view or two or more segments were not correctly visualised, we did not perform strain analysis (9, 10). All the measurements at baseline and at follow-up were obtained and analysed from the same operator.

Arterial haemodynamics, ventricular-arterial coupling and cardiovascular performance indices

All participants, after a 12-hour abstinence from food, caffeine, smoking, alcohol, and drugs, underwent arterial haemodynamics measurements by the same physician. Brachial blood pressure (BP) assessment was performed after a five-minute supine rest by a validated electronic sphygmomanometer (microlife WatchBP pro). The average of three measurements was used to calculate the systolic, diastolic and pulse pressure. After a 10-min resting period in the supine position, the carotid to femoral pulse wave velocity was non-invasively calculated with the available SphygmoCor system (Sphygmocor Atcor medical, Australia) (14). Using the same system and a validated transfer function, aortic pressures were obtained from the radial artery waveform, calibrated to branchial systolic and diastolic pressure (15). Further analysis of radial artery waves determined the subendocardial viability index, and the

aortic augmentation pressure (AP) and index (AIx), defined as the difference between the second and first peaks of central arterial waves and expressed as a percentage of pulse pressure (14, 16). Given the influence of heart rate on the above measurements, a correction for a steady heart rate of 75 bpm was performed. Also, aortic stiffness index was measured by echocardiography as the percentage of change of diameter of ascending aorta in systole and diastole (17). To further investigate arterial and left ventricular properties, several indices were calculated combining the above measurements (18-20). The effective arterial elastance (Ea), a measure of arterial stiffness, was calculated as central end-systolic pressure divided by stroke volume (21). The total arterial compliance estimated by the ratio of stroke volume to pulse pressure, and the total peripheral resistance calculated by the mean arterial pressure divided by cardiac output*80, were determined to further characterise the arterial loading. Moreover, end-systolic elastance (Ees, central end-systolic pressure/end-systolic volume), LV stroke work (central end systolic pressure*stroke volume) and stroke work index (stroke work/end-systolic volume) were calculated to characterise LV systolic stiffness and the performance and contractility of LV, respectively (22). Also, the ratio Ea/Ees was used as index of ventricular-arterial coupling (19, 22). Finally, the pressure-volume area [=(end-systolic pressure*stroke volume) + (end-systolic pressure*(end-systolic volume)/2)] and LV energetic efficiency (stroke work/PVA) were also determined (19).

References

1. NAGUEH SF, SMISETH OA, APPLETON CP *et al*.: 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. *Eur Heart J Cardiovasc Imaging* 2016; 22: 107-33.
2. LANG RM, BADANO LP, MOR-AVI V *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. *Eur Heart J Cardiovasc Imaging* 2015; 16: 233-71.
3. COSYNS B, PLEIN S, NIHOYANOPOULOS P *et al*.: European Association of Cardiovascular Imaging (EACVI) position paper: *Multimodality imaging in pericardial disease* 2015 Jan; 16: 12-31.
4. ZOGHBI WA, ADAMS D, BONOW RO *et al*.: Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation. *J Am Soc Echocardiogr* 2017; 30: 303-71.
5. LANCELLOTTI P, TRIBOUILLOY C, HAGENDORFF A *et al*.: Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Hear J Cardiovasc Imaging* 2013; 14: 611-44.
6. BAUMGARTNER H, HUNG J, BERMEJO J *et al*.: OUP accepted manuscript. *Eur Hear J Cardiovasc Imaging* 2016; 18: 254-75.
7. 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. *J Am Soc Echocardiogr* 2010; 23: 685-713.
8. GALIÈ N, HUMBERT M, VACHIERY J-L *et al*.: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016; 37: 67-119.
9. MOR-AVI V, LANG RM, BADANO LP *et al*.: Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese society of echocardiography. *Eur J Echocardiogr* 201; 12: 167-205.
10. VOIGT J-U, PEDRIZZETTI G, LYSYANSKY P *et al*.: Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Hear J Cardiovasc Imaging* 2015; 16: 1-11.
11. ALCIDI GM, ESPOSITO R, EVOLA V *et al*.: Normal reference values of multilayer longitudinal strain according to age decades in a healthy population: A single-centre experience. *Eur Hear J Cardiovasc Imaging* 2018; 19: 1390-6.
12. ADAMU U, SCHMITZ F, BECKER M, KELM M, HOFFMANN R: Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters. *Eur J Echocardiogr* 2009; 10: 303-8.
13. FARSALINOS KE, DARABAN AM, ÜNLÜ S, THOMAS JD, BADANO LP, VOIGT J-U: Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *J Am Soc Echocardiogr* 2015; 28: 1171-1181.e2.
14. LAURENT S, COCKCROFT J, VAN BORTEL L *et al*.: Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27: 2588-605.
15. PAUCA AL, O'ROURKE MF, KON ND: Prospective Evaluation of a Method for Estimating Ascending Aortic Pressure From the Radial Artery Pressure Waveform. *Hypertension* 2001; 38: 932-7.
16. BARTOLONI E, PUCCI G, CANNARILE F *et al*.: Central Hemodynamics and Arterial Stiffness in Systemic SclerosisNovelty and Significance. *Hypertension* 2016; 68: 1504-11.
17. LACOMBE F, DART A, DEWAR E, JENNINGS G, CAMERON J, LAUFER E: Arterial elastic properties in man: a comparison of echo-Doppler indices of aortic stiffness. *Eur Heart J* 1992; 13: 1040-5.
18. STARLING MR: Left ventricular-arterial coupling relations in the normal human heart. *Am Heart J* 1993; 125: 1659-66.
19. LAM CSP, SHAH AM, BORLAUG BA *et al*.: Effect of antihypertensive therapy on ventricular-arterial mechanics, coupling, and efficiency. *Eur Heart J* 2013; 34: 676-83.
20. TOWNSEND RR, WILKINSON IB, SCHIFFRIN EL *et al*.: Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. *Hypertens* (Dallas, Tex 1979). 2015; 66: 698-722.
21. KELLY RP, TING CT, YANG TM *et al*.: Effective arterial elastance as index of arterial vascular load in humans. *Circulation* 1992; 86: 513-21.
22. BORLAUG BA, KASS DA: Ventricular–Vascular Interaction in Heart Failure. *Heart Fail Clin* 2008; 4: 23-36.