RESEARCH ARTICLE

Determinants of left ventricular structure, filling and long axis function in systemic sclerosis

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Abstract

Background

Abnormalities of left ventricular (LV) structure, filling and long-axis function have all been reported in subjects with systemic sclerosis (SSc) and a normal LV ejection fraction (EF), but previous study findings have not been consistent. The aim of this study was to identify factors which could have confounded the analyses in previous studies of SSc, and in particular to consider the variables of body surface area (BSA), sex, age, heart rate, blood pressure (BP), disease duration (DD), disease type (limited versus diffuse) and interstitial lung disease (ILD).

Methods

Echocardiography was performed on 100 subjects with SSc (79 women; age 56 ± 15 years) with a LVEF ≥ 50% and free of pulmonary arterial hypertension, coronary artery disease, more than mild valvular heart disease and atrial fibrillation. Measurements were performed of the LV end-diastolic dimension (LVEDD) and septal wall thickness (SWT), the transmitral Doppler E, A and deceleration time (DT), and the peak systolic (s’) and early diastolic (e’) LV long-axis velocities. Multivariate analyses were performed to investigate correlations of the above LV variables with BSA, sex, age, heart rate, BP, DD, disease type, and the presence of ILD.

Results

DD varied between 0.1 and 41.2 years, 25% had diffuse and 75% had limited disease, and 37% had ILD. SWT and LVEDD were positively correlated with BSA, SWT was also positively correlated with age and larger in males, and LVEDD was larger in diffuse disease. Age was positively correlated with A and DT, and inversely correlated with E and E/A, and heart rate was inversely correlated with E and E/A. None of E, A, E/A, or DT were independently associated with DD or disease type. Septal and lateral LV wall s’ and e’ were all inversely correlated with age, and there was a small independent contribution to the prediction of
lateral s’ from DD, but no association of either s’ or e’ with disease type. The presence of ILD was not a predictor of any of the LV variables.

Conclusion
In SSc there are associations of sex, body size, age and disease type with LV structural variables, of age and heart rate with E/A, and of age with both systolic and early diastolic LV long-axis velocities. Appropriate adjustment for these variables could help to resolve current uncertainties regarding SSc effects on the left ventricle.

Introduction
Systemic sclerosis (SSc) is a chronic, multi-system disease characterized by fibrosis and vascular damage [1], for which clinical involvement of the heart is associated with a worse prognosis [2]. Left ventricular (LV) ejection fraction (EF) is generally normal in SSc [3–5], but there have been reports that SSc can affect LV structure and function in the presence of a normal LVEF. Reported LV abnormalities include increases in septal wall thickness (SWT), relative wall thickness (RWT), LV mass (LVM) index [5–7], decreases in the transmitral E [8] and E/A ratio [8–13], and increases in A [7, 8, 10, 13–15], and the deceleration time (DT) [8, 12, 16], and reductions in peak pulse wave tissue Doppler imaging (TDI) velocities of long-axis motion in both systole (s’) [15, 17] and early diastole (e’) [11, 17–20]. However, there have also been a number of negative studies with regard to all of the above LV abnormalities [6–24], and there have been few attempts to provide explanations for the divergences in findings.

The aim of this study was to identify possible determinants of LV structure, transmitral flow and LV long-axis function which could have confounded previous studies in SSc, but may not have been taken into account. Body surface area (BSA), sex, age, heart rate and blood pressure (BP) have all been considered based on data from healthy populations indicating associations with LV echocardiographic variables. For example, in healthy subjects increasing age is associated with increases in wall thickness and RWT [25, 26] and accompanied by lower transmitral E, E/A, s’ and e’, a higher A, and a longer DT [27]. Sex and body size also have recognized effects on LV structure, filling and long-axis velocities in healthy subjects [26, 28–36], and transmitral Doppler and LV long-axis peak velocities have associations with heart rate [28, 35, 37], and BP [28, 34, 36, 38, 39]. The possibility of LV effects of the SSc-specific features of interstitial lung disease (ILD), disease type (limited versus diffuse) and disease duration (DD) has also been investigated.

Methods
Subjects
Subjects were identified from a dedicated SSc clinic at a tertiary hospital (Monash Medical Centre, Monash Health) between February 2010 and February 2014. Subjects were over 18 years of age and satisfied the ACR/EULAR 2013 Classification Criteria for diagnosis of SSc [40]. The LeRoy and Medsger criteria were used for classification into limited and diffuse types [41]. At this clinic the subjects undergo annual screening for cardiac disease and pulmonary arterial hypertension (PAH) with a transthoracic echocardiogram, and for ILD with respiratory function testing and selective performance of high resolution computed tomography of the chest. ILD has been defined for this study as the presence of interstitial...
abnormalities on high-resolution computed tomography of the chest. Patients suspected of having PAH (estimated systolic pulmonary artery pressure \([\text{PAP}] \geq 40 \text{ mmHg}\) at echocardiography, diffusing capacity of the lung for carbon monoxide \([\text{DLCO}] \leq 50\%\) with forced vital capacity > 85\%, or with \(\text{DLCO} \geq 20\%\) and/or unexplained dyspnoea) are considered for right heart catheterisation (RHC) \([42]\). PAH was defined as a mean \(\text{PAP} \geq 25 \text{ mmHg}\) in association with a pulmonary arterial wedge pressure < 15 mmHg and subjects found to have PAH were not included in this study. Exclusion criteria for the current study were clinical evidence of coronary artery disease (based on past history, symptoms, or electrocardiographic or echocardiographic changes suggesting ischemia or myocardial infarction), a LVEF < 50\% \([43]\), reduction of right ventricular ejection fraction, more than mild valvular stenosis or regurgitation, atrial fibrillation or flutter, diabetes, stroke, symptomatic peripheral vascular disease or an estimated glomerular filtration rate \((\text{eGFR}) < 30 \text{ mL/min/1.73 m}^2\). Patients were defined as having chronic kidney disease \((\text{CKD})\) if they had an \(\text{eGFR} \leq 30 \text{ mL/min/1.73 m}^2\). The study was approved by the Monash Health Human Research and Ethics Committee, the need for written consent was waived, and analysis was performed on anonymized data.

**Echocardiography**

Two-dimensional echocardiography was performed by an experienced ultrasonographer using a Vivid 7 ultrasound machine \((\text{Vingmed, General Electric, Milwaukee, WI, USA})\) and studies were stored digitally for measurement off-line using Xcelera V1.2 LA SP2 \((\text{Philips, Amsterdam, The Netherlands})\). Brachial blood pressure \((\text{BP})\) was measured at the time of echocardiogram. M-mode recordings of the left ventricle were made from the parasternal long-axis view according to the American Society of Echocardiography guidelines \([44]\). Standard LV M-mode measurements were made of LV end-diastolic diameter \((\text{LVEDD})\), SWT and posterior wall thickness \((\text{PWT})\). Relative wall thickness was calculated as 2 x \(\text{PWT}/\text{LVEDD}\). LV mass has not been reported in this study due to concern about the effects of older age on the accuracy of the M-mode formula, and also on the recognized discrepancy between echocardiographic and cardiac magnetic resonance findings \([33, 45, 46]\). 2D loops from the 4-chamber, 2-chamber and apical long-axis views were recorded for assessment of LV regional contraction and for measurement of LVEF using the biplane method of discs. 4- and 2-chamber loops were recorded after optimisation on the atria and used for measurement of left atrial \((\text{LA})\) area and length, with calculation of LA volume performed by the biplane area-length method \([47]\). LA volume was indexed to BSA \((\text{LA volume index; LAVI})\), and categorized as increased if \(>34 \text{ mL/m}^2\).

LV inflow velocities were recorded using pulsed-wave Doppler in the apical 4-chamber view with the sample volume at the level of the mitral leaflet tips, and the peak transmitral E and A wave velocities were measured off-line. If there was onset of the atrial flow signal during the deceleration phase of the early diastolic flow signal \((\text{i.e. partial fusion of the signals})\) then the A has been calculated as the peak velocity of the atrial signal minus the velocity at the time of the onset of the atrial signal. Pulsed wave TDI was recorded at the mitral annular level during end-expiration apnoea with particular attention made to orientation of the cursor parallel to the long-axes of the septal and lateral walls. Off-line measurements of 3 consecutive cardiac cycles of \(s'\) and \(e'\) were performed as previously described \([34, 36]\). Continuous wave Doppler of the tricuspid regurgitation \((\text{TR})\) jet was performed in all available imaging planes to enable identification of the peak velocity. Systolic PA pressure was calculated as estimated RV pressure \((4 \times \text{the square of the peak velocity of the TR jet} + \text{the right atrial pressure})\) \([48]\). Diastolic function was assessed as recommended by the American Society of Echocardiography \((\text{ASE})/\)
European Association of Cardiovascular Imaging (EACVI) in their 2016 guidelines using the following variables: septal and lateral e’, E/e’ (average e’ from septal and lateral walls), LAVI, and the TR peak velocity [27]. Abnormal findings were a septal e’ < 7 cm/s or lateral e’ < 10 cm/s, an E/e’ > 14, a LAVI > 34 mL/m2, and a TR velocity > 2.8 m/s.

Statistics
Statistical analysis was performed using Systat V13 (Systat Software, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation (SD) or median [range] and compared with an unpaired t test, or a non-parametric test if the variable was not normally distributed. Independent variables which were not normally distributed were log transformed before inclusion in regression analyses. For univariate linear regression analysis the correlation coefficient (r) is provided and for multivariate analyses, the partial standardized correlation coefficient (β) is provided. The coefficient of determination has been adjusted for the number of terms in multivariate models (adjusted r²) and used to estimate the percentage of the variance of a dependent variable explained by that model. The decisions regarding testing of independent variables in multivariate models were based on the aims of the study, variables were added step-wise, and variables which did not contribute to an increase in the adjusted r² for a model were removed. Dummy variables were used for sex (female = 1, male = 0), type of disease (diffuse = 1, limited = 0) and ILD (present = 1, absent = 0). Multiple logistic regression was performed for selected bivariate LV variables and the area under the curve (AUC) for the receiver operating characteristic curve is provided. A p value of <0.05 was considered significant.

Results
The relevant characteristics of the study group are shown in Table 1. The range of ages in the cohort was 22–83 years and the range of DD was 0.1–41.2 years, 79% were females, 25% had diffuse and 75% had limited disease, 37% had ILD and 31% had a history of hypertension. The group with diffuse disease were younger than those with limited disease (48 ±16 v 59±13 years, p = 0.003), and also had a younger age at onset of symptoms (40±14 v 50±14 years, p = 0.007).

Table 1. Clinical characteristics of subjects with systemic sclerosis (n = 100).

| Characteristic                        | Value          |
|--------------------------------------|----------------|
| Female                               | 79 (79%)       |
| Age (years)                          | 56.2±14.6      |
| Hypertension                         | 31 (31%)       |
| Systolic BP at time of study (mmHg)  | 131±19         |
| Diastolic BP at time of study (mmHg) | 74±10          |
| Heart rate at time of study (beats/min) | 67±8       |
| Body surface area (m²)               | 1.70±0.17      |
| Body mass index (kg/m²)              | 25.6±5.1       |
| Chronic kidney disease (eGFR 30–60 mL/min/1.73 m²) | 4 (4%)         |
| Age at onset of symptoms (years)     | 47.4±14.5      |
| Disease duration (years)             | 6.0 [0.1–41.2] |
| Diffuse disease                      | 25 (25%)       |
| Anti-centromere Ab positive          | 42 (42%)       |
| Anti-Scl-70 Ab positive              | 22 (22%)       |
| Interstitial lung disease            | 37 (37%)       |

Results are shown as mean±SD or median [range].

https://doi.org/10.1371/journal.pone.0258593.t001
but there was no significant difference in DD between these groups (7.1 [0.4–28.5] v 5.6 [0.1–41.0] years, p = 0.82). There were no differences in age, age at onset of symptoms or DD between those with and without ILD (p = 0.35, p = 0.59 and p = 0.46, respectively). Given that DD was not normally distributed, it was natural log transformed prior to its inclusion as an independent variable in regression analyses due to colinearity between age, DD and BP was explored. Age was positively correlated with systolic BP (r = 0.56, p<0.001) and diastolic BP (r = 0.23, p = 0.024), log DD was positively correlated with age (r = 0.25, p = 0.011), but log DD was not correlated with either systolic or diastolic BP (p>0.10 for both).

### Left ventricular structural variables

The echocardiographic findings of the study group are shown in Table 2. Measurements of SWT and PWT, and calculation of RWT, were feasible in 98 subjects. A SWT or PWT >1.1 cm was only present in 3 subjects. In univariate linear regression analysis, LVEDD, SWT and PWT were all positively correlated with BSA, and smaller in females than males (p<0.05 for all), whereas RWT was not correlated with BSA or different based on sex (p>0.2 for both). Multivariate models of LV structural variables with age and log DD, after adjustment for sex and BSA (except for RWT), are shown in Table 3. Age was positively correlated with SWT, PWT and RWT, but not with LVEDD. Log DD was only positively correlated with RWT.

Multivariate modeling of LV structural variables was performed with the sequential addition of sex, BSA, age, log DD, disease type, systolic BP, ILD and history of hypertension, and the models of LVEDD and SWT with independent variables with a p<0.10 are shown in Table 4. Female sex was associated with a smaller SWT and PWT, BSA was positively correlated with LVEDD, SWT and PWT, and age was positively correlated with SWT, PWT and RWT. There was a borderline significant inverse correlation of log DD with LVEDD, but not with RWT, and the presence of diffuse disease was associated with a larger LVEDD. After adjustments for the above variables, there were no contributions to any of the models from systolic BP, a history of hypertension or ILD.

### Table 2. Echocardiographic variables in subjects with systemic sclerosis.

| Variable                      | Mean ± SD or Median [Range] |
|-------------------------------|----------------------------|
| LVEDD (cm)                    | 4.7±0.4                    |
| SWT (cm)                      | 0.9±0.1                    |
| PWT (cm)                      | 0.8±0.1                    |
| RWT                           | 0.35±0.05                  |
| LVEF (%)                      | 60±5                       |
| Left atrial volume index (cm²/m²) | 35±10                   |
| E (cm/s)                      | 73±16                      |
| A (cm/s)                      | 66±20                      |
| E/A                           | 1.22±0.49                  |
| DT (ms)                       | 194 [28–462]               |
| Septal s' (cm/s)              | 6.6±1.3                    |
| Septal e' (cm/s)              | 8.0±2.5                    |
| Lateral s' (cm/s)             | 8.1±1.9                    |
| Lateral e' (cm/s)             | 10.5±3.7                   |
| E/Average e'                 | 8.5±3.0                    |

Results are shown as mean±SD or median [range].

https://doi.org/10.1371/journal.pone.0258593.t002
Correlates of Doppler and TDI variables

The univariate correlates of transmitral Doppler and TDI variables with age and log DD are shown in Table 3. DT was not normally distributed and was natural log transformed prior to the analysis. There were positive correlations of age with A and log DT, inverse correlations of age with E and E/A, and there was a weak positive correlation of log DD with A. Age alone accounted for more than 50% of the variances of septal and lateral e’. Log DD was also inversely correlated with septal s’ and lateral s’ and e’, but not with septal e’. Univariate correlations of transmitral Doppler and TDI variables with heart rate and systolic BP were also investigated. Heart rate was an inverse correlate of E (r = -0.24, p = 0.017), but was not correlated with any of the other transmitral or TDI variables. Systolic BP was a positive correlate of A (r = 0.53, p < 0.001) and E/e’ (r = 0.47, p < 0.001) and an inverse correlate of E/A (r = -0.43, p < 0.001), septal s’ (r = -0.42, p < 0.001), septal e’ (r = -0.48, p < 0.001), lateral s’ (r = -0.42, p < 0.001) and lateral e’ (r = -0.55, p < 0.001).

Multivariate modeling of transmitral Doppler and TDI variables was performed with the sequential addition of age, log DD, sex, heart rate, systolic BP, disease type, ILD, and hypertension history, and models of independent variables with more than one dependent variable with a p < 0.10 are shown in Table 5. Age was a correlate of all the transmitral Doppler and

| Dependent variable | Independent variable | Univariate coefficient | p value in multivariate model | Cumulative Adjusted r² |
|--------------------|----------------------|------------------------|-------------------------------|-----------------------|
| LVEDD              | BSA                  | 0.46                   | 0.42                          | <0.001                | 0.20                  |
|                    | Log DD               | -0.22                  | -0.17                         | 0.055                 | 0.22                  |
|                    | Diffuse disease      | 0.30                   | 0.27                          | 0.002                 | 0.29                  |
| SWT                | Female sex           | -0.28                  | -0.25                         | 0.006                 | 0.07                  |
|                    | BSA                  | 0.26                   | 0.25                          | 0.007                 | 0.10                  |
|                    | Age                  | 0.40                   | 0.45                          | <0.001                | 0.29                  |

https://doi.org/10.1371/journal.pone.0258593.t004
TDI variables, sex did not contribute to any of the models, and log DD was an inverse correlate of lateral s’. Heart rate was a correlate of E and E/A, and systolic BP was a correlate of A, lateral s’ and E/e’. A diagnosis of diffuse disease made a borderline significant contribution to the model of E/A. There were no independent contributions to any of the models from a diagnosis of ILD or hypertension.

Logistic regression analysis of abnormal diastolic variables

E/A was < 1.0 in 23% of subjects, there was a low septal or lateral e’ in 54%, E/e’ was >14 in 8%, the left atrium was dilated in 48% and the TR peak velocity was >2.8 m/s in 3%. Using the 2016 ASE/EACVI criteria, LV diastolic dysfunction was present in 8%, indeterminate diastolic dysfunction in 27% and elevation of mean LA pressure in 6%. Subjects with diastolic dysfunction were compared to the group with normal diastolic function. The diastolic dysfunction group was older at the time of the study (74 ± 5 v 50 ± 14 years, p < 0.001) and at onset of symptoms (59 ± 15 v 42 ± 13 years, p = 0.017), and had a higher DD (10.3 [6.4–36.8] v 5.2 [0.2–33.2], p = 0.02). On multivariate logistic regression analysis excluding those subjects with indeterminate diastolic function, and with independent variables of age, log DD, systolic BP, disease type, ILD and history of hypertension, older age was the only significant predictor of the presence of diastolic dysfunction (p = 0.002, AUC = 0.95). Including the same independent variables in multivariate logistic regression analyses of the total subject group, older age was also the only significant predictor of a low E/A (p < 0.001, AUC = 0.84), whereas older age (p < 0.001) and higher systolic BP (p = 0.004) were both predictors of a low e’ (AUC = 0.90).

Discussion

This study identified a number of variables with the potential to have confounded the findings of previous studies in which LV structural and filling variables and long-axis velocities have been compared in SSc and control subjects. In multivariate analyses, BSA, sex and age were each independent correlates of at least one of the LV structural variables, age was an independent correlate of all the Doppler and TDI variables, and heart rate was an independent correlate of some of the transmural Doppler variables. These findings are not unexpected as they have also been reported in healthy populations, but they are important because they could not be assumed to exist in SSc, they have not always been reported in studies comparing SSc and control subjects (See Tables 6 and 7 for a selection of relevant studies), and even when
reported, they have not always been taken into account when comparing the results of SSc and control subjects.

Body size was a determinant of LV structural variables (LVEDD, SWT and PWT) in SSc subjects in the present study, a finding consistent with data from population studies in subjects free from known cardiovascular disease [26, 32]. Male sex was a determinant of larger SWT and PWT independent of BSA in SSc subjects, and this finding is also consistent with data from healthy subjects [26, 33]. While there is no specific reason why body size and sex should not also be determinants of LV structural variables in SSc, neither could it be assumed that there would be the same relationships in SSc as in healthy subjects. Furthermore, our findings highlight the importance in considering both body size and sex in studies of LV structure in SSc. However, only 7/19 of the studies shown in Table 6 provided any data on body size in SSc.

Table 6. A summary of the subject characteristics and available demographic data in a selection of systemic sclerosis echocardiographic studies in which LV structural or filling variables or long-axis velocities have been compared to control subjects.

| Study                | SSc group (n) | SSc group (M/F) | SSc group age (years) | Limited/ Diffuse disease | Subjects with PAH | Control group (n) | Control group (M/F) | Control group age (years) | Heart rate | BSA or height & weight data | BP data | DD in years |
|----------------------|---------------|-----------------|-----------------------|--------------------------|------------------|-------------------|----------------------|--------------------------|------------|--------------------------------|---------|-------------|
| Kazam [6]            | 30            | 15/15           | 55±2 [range 25–77]    | N/A                      | N                | 48                | 26/22                | 55±2 [range 25–77]        | Y          | Y                             | Y       | 6 (0.5–23) |
| Henein [17]          | 34            | 9/25            | 49±12                 | N/A                      | N                | 21                | 14/7                 | 51±11                    | N          | N                             | N       | N           |
| Armstrong [16]       | 35            | 2/33            | 48±15                 | 21/14                    | Y                | 35                | N/A                  | 45±14                    | Y          | Y                             | Y       | 10 (0–27)  |
| Aguglia [7]          | 124           | 18/106          | 52±12                 | 67/57                    | Y                | 41                | 4/37                 | 53±14                    | Y          | N                             | Y       | 11±8        |
| Maione [8]           | 77            | 6/71            | 54±11                 | 19/17                    | N                | 45                | 4/41                 | 52±10                    | Y          | N                             | N       | 18±9        |
| D’Andrea [21]        | 23            | 3/20            | 56±8                  | 12/11                    | N                | 25                | 5/20                 | 55±9                     | Y          | Y                             | Y       | N           |
| D’Andrea [18]        | 33            | 9/24            | 56±8                  | 18/15                    | N                | 30                | 7/23                 | 55±9                     | Y          | Y                             | Y       | N           |
| Meune [9]            | 100           | 14/86           | 54±14                 | 58/42                    | N                | 26                | 5/21                 | 50±13                    | N in controls | N                             | N       | 8±8         |
| Mele [19]            | 35            | 1/34            | 55±13                 | 23/12                    | N                | 35                | 0/35                 | 53±9                     | N          | N                             | N       | 10±8        |
| Kepez [20]           | 27            | 1/26            | 46±10                 | 18/9                     | N                | 26                | 1/25                 | 44±10                    | Y          | N                             | Y       | 10 (3–18)  |
| Poanta [10]          | 20            | 2/18            | 52±10                 | 5/15                     | N                | 15                | 3/12                 | 48±13                    | Y          | N                             | N       | 47±56       |
| Lee [14]             | 35            | 9/26            | 49±13                 | N/A                      | N                | 35                | 10/25                | 52±8                     | N          | N                             | Y       | 10±2        |
| Yiu [22]             | 104           | 24/80           | 54±12                 | 51/53                    | Y                | 37                | 7/27                 | 54±10                    | N          | N                             | N       | 6±4         |
| Plazak [11]          | 46            | 3/43            | 55 [range 24–73]      | 25/21                    | N                | 30                | 0/30                 | 52 [range 38–57]         | N          | N                             | N       | 15 (2–32)  |
| Aktoz [12]           | 26            | 2/24            | 49 [range 21–71]      | N/A                      | N                | 24                | 2/22                 | 46 [range 22–56]         | Y          | N                             | Y       | 60 [range 12–276] | Mean – 12 |
| Faludi [15]          | 34            | 3/31            | 57±12                 | 27/7                     | Y                | 23                | 6/17                 | 53±10                    | N          | Y                             | N       | 9±12 (1–25) |
| Ciurzynski [13]      | 111           | 10/101          | 54±14                 | 64/47                    | N                | 21                | 3/18                 | 49±11                    | Y          | Y                             | Y       | 9±12 (1–25) |
| Karadag [23]         | 47            | 5/42            | 52±12                 | 33/14                    | N                | 36                | 3/33                 | 49±8                     | N          | Y                             | Y       | 9±6         |
| Agoston [24]         | 42            | 2/40            | 50±14                 | 35/7                     | N                | 42                | 2/40                 | 49±13                    | N          | N                             | N       | N           |

* 41 were classed as intermediate disease
$ median (25th–75th percentile)
1months; N/A—not available; N—information not provided; Y—information provided.

https://doi.org/10.1371/journal.pone.0258593.t006
and control subjects, and so differences in the body size of SSc and control subjects could not be evaluated. Moreover, sex matching of SSc and control subjects has rarely been exact in previous SSc studies, the ratio of males to females in the SSc cohort has varied between the studies, and in one study the sex of the control subjects was not even reported [16]. Importantly, even if there was exact sex matching and a similar mean BSA in SSc and control subjects in a study, this cannot exclude differences in the relationships of sex with BSA between the SSc and control groups which could confound the findings. However, knowing this possibility, the potential for such confounding can be addressed through performance of a multivariate linear regression analysis with adjustment for both BSA and sex when relevant [49].

Age was an independent predictor of SWT, PWT and RWT in the present study, findings which are consistent with previous reports in healthy subjects [25, 26, 33], and which are particularly relevant in the study of the left ventricle in SSc given that the ages of affected subjects can range from young adults to those >80 years. A lack of correlation of LVEDD with age in SSc subjects after adjustment for sex and BSA in the present study is also consistent with previous studies in healthy subjects where adjustment for BSA was performed [26, 50]. Although echocardiographic data in healthy subjects has suggested that LVM index increases with age [33], this finding has not been confirmed in cardiac magnetic resonance studies [45, 46]. This discrepancy may be because of an intrinsic limitation of the echocardiographic cubed M-mode formula [51], and may be of particular importance in older age groups in which there is a change in shape of the left ventricle [52]. In view of this, determinants of LVM were not considered in the present study and LVM findings in previous echocardiographic SSc studies will be of less certain significance than the measurements of LVEDD, SWT and RWT which do not rely on complex geometric assumptions. Although the mean ages of SSc and control

| LVEF | LVEDD | Wall thickness | RWT | LVM index | E | A | E/A | DT | Septal s' | Septal e' | Lateral s' | Lateral e' | E/e' |
|------|-------|----------------|-----|-----------|---|---|-----|----|---------|---------|-----------|----------|------|
| Kazzam [6] | N | † | † | † |  |  |  |  |  |  |  |  |  |
| Henein [17] | N | N | N | N |  |  |  |  |  |  |  |  |  |
| Armstrong [16] | N | N | N | N | N |  |  |  |  |  |  |  |  |
| Aguglia [7] | N | † | † | N | † | N | N | N |  |  |  |  |  |
| Maione [8] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| D'Andrea [21] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| D'Andrea [18] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Meune [9] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Mele [19] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Kepez [20] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Poanta [10] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Lee [14] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Yiu [22] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Plazak [11] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Aktoz [12] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Faludi [15] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Ciurzynski [13] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Karadag [23] | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Agoston [24] | N | N | N | N | N | N | N | N | N | N | N | N | N |

* Average of septal and lateral TDI velocities presented

** p = 0.05.

https://doi.org/10.1371/journal.pone.0258593.t007

Table 7. A summary of the findings of a selection of systemic sclerosis echocardiographic studies in which LV structural or filling variables or long-axis velocities have been compared to control subjects.
subjects were not significantly different in any of the SSc studies listed in Table 6, standard statistical testing does not test for differences in age range or SDs, and also cannot test for grouping of variables which might affect the findings (e.g. between age, DD, sex and BSA). Indeed, an important, albeit not unexpected grouping was found in the current study, this being that subjects with diffuse disease were younger than those with limited disease.

The effects of SSc on the heart can progress over time, and while this may well not be a linear progression, it could be considered essential to take the duration of disease symptoms into account when determining SSc effects on the heart. However, DD has not always been reported in SSc studies, and even when it has been reported, it has sometimes been reported as mean and SD despite the numbers presented demonstrating DD values which are unlikely to have been normally distributed. There have been studies in which the relations of DD with LV echocardiographic variables have been evaluated, but age and disease type have generally not been considered within the same analysis. The potential importance of considering all 3 variables in the same analysis was highlighted in the present study as those with diffuse disease were younger, and there was a correlation of age with log DD (transformed because it was not normally distributed). DD had no more than a minor effect on LV structural functional variables in the present study, with a trend to a smaller LVEDD, independent of sex and BSA.

Abnormalities of LV filling variables have been reported in SSc, but there has been no consistency in the findings of the published studies (see Table 7). In studies in healthy adults, transmitral Doppler variables are well recognized to be affected by age [28, 31], and have also been reported to be affected by sex, BP and heart rate [28, 31]. That these factors also affect Doppler variables in SSc was demonstrated in the present study, as age was an independent correlate of all the transmitral variables, heart rate had an inverse association with E and E/A, and there was a positive correlation of systolic BP with A. Although adjustment for all these factors could therefore be considered essential during investigations of LV filling in SSc subjects, such adjustment has not generally been performed. Indeed, heart rate and blood pressure data have not been provided in a number of previous studies. In multivariate models in the present study, with appropriate adjustments for age, heart rate and systolic BP, there were no contributions from either DD or disease type to the prediction of LV filling variables. Furthermore, in logistic regression analysis of a low E/A, the only significant predictor was age. Therefore, there was no supporting evidence from the present study that SSc has any effect on LV filling.

There are gradual reductions in LV long-axis s’ and e’ during healthy aging [34, 36, 53, 54], with decreases in e’ becoming evident as early as the 3rd decade. The reduction in e’ with age can be substantial over the normal life span, with a decrease of >50% between an age <30 years and an age >70 years [54]. An aging effect on long-axis function therefore needs to be considered in any investigation of the effect of SSc on LV long-axis function, particularly given that SSc can be manifest in individuals over the whole span of adult ages. There have also been reports of correlations of height, BSA and heart rate with s’ [35], and of BP and BMI with e’ [34, 36]. In the present study of subjects with SSc ranging in age from 22–83 years, age was inversely correlated with septal and lateral s’ and septal and lateral e’, and age explained the
major portion of the variances in e’ for the septal and lateral walls (53% and 62%, respectively). That there was also a small additional contribution to the prediction of lateral s’ from DD after inclusion of age in the model, provides some support for the presence of a myocardial effect of SSc on long-axis function, implying an effect of both the presence and the duration of the disease. The variability in DD between studies (Table 6) could therefore be a possible contributor to previous inconsistencies in the literature regarding whether SSc results in LV long-axis dysfunction (see Table 7). However, the effect of DD on s’ was not consistent for the septal and lateral LV walls given that there was no effect of DD on septal s’. There was also a weak inverse correlation of log DD with lateral e’ in the present study, but this was no longer significant when log DD was combined in a model with age. Although this does not exclude an effect of DD on e’, it is consistent with the univariate correlation of DD with lateral e’ being due to collinearity of DD with age. Previous studies which have investigated the effect of DD on LV long-axis function had discrepant findings and did not do multivariate analyses with adjustment for age [9, 10].

We found no correlations of BSA or heart rate with s’, or of BMI with e’, in the present study, but systolic BP at the time of the study was a univariate inverse correlate of septal and lateral s’ and of septal and lateral e’. On multivariate analyses with adjustment for age, systolic BP was no longer a predictor of septal or lateral e’, or of septal s’, but was an independent inverse correlate of lateral s’ and a positive correlate of E/e’. These findings are consistent with a portion of the effect of older age on s’ and e’ being via its association with a higher BP. An association of BP at the time of the study with e’ has been previously reported in cross-sectional studies [34, 36], acute studies in healthy individuals [35], and an association of BP with e’ has also been reported in longer-term studies using BP lowering drugs [56, 57]. These findings highlight the importance of measuring BP at the time of the study, and taking BP into consideration when comparing LV function variables in SSc and control groups. There was no evidence of an effect of disease type, the presence of ILD, or a history of hypertension on any of the long-axis variables in the present study.

Using the 2016 ASE/EASCI criteria [27], we identified LV diastolic dysfunction in 8%, indeterminate diastolic dysfunction in 27% and elevation of LA pressure in 6%. Age was the only independent predictor of the presence of diastolic dysfunction, but older age and higher systolic BP were independent predictors of a low e’. There have been previous cohort studies in SSc which have evaluated diastolic function [5, 58–60], and when determinants of diastolic function have been evaluated in these studies, all have found age to be a predictor, but other predictors have also been identified [58–60]. However, there has been a wide variation in the reported frequency of diastolic dysfunction in SSc (17–44%) [5, 58–60], each study has used different diagnostic criteria, and all of the previous studies have had less strict exclusion criteria than the present study.

There were a number of limitations of the present study. Our cohort was only of moderate size and there were relatively few subjects who met the 2016 ASE/EACI criteria for diastolic dysfunction, with the result that our study had limited ability to identify determinants of diastolic dysfunction other than age. On the other hand, it is of interest that only a small proportion of our SSc cohort met the current criteria for a diagnosis of diastolic dysfunction. Moreover, the moderate group size was at least partially compensated for by having restricted inclusion criteria, as by excluding subjects with PAH, manifest coronary artery disease, atrial arrhythmias, and more than mild valvular disease, we were more able to focus on the role of a number of specific variables in the absence of these potential confounding factors. As with all studies in SSc, there was a predominance of females in this study, and the low numbers of males will have limited the ability to detect sex-related differences in LV structure and function. Although manifest coronary artery disease was an exclusion criteria, asymptomatic
coronary disease could not be excluded as testing was not performed in asymptomatic subjects. However, even if unrecognized asymptomatic coronary artery disease was present in a proportion of our cohort, given the absence of regional hypokinesis, and that this was a study of images obtained at rest, it is unlikely to have influenced the main study findings. In multivariate analyses in which DD was being considered, greater variability in DD might have improved the ability of the study to detect effects of DD which were independent of age. However, there may be intrinsic limitations to having a SSc cohort with greater DD variability and that fits our study group criteria given that complications become more likely over time. Lastly, a large control group with exact matching of SSc subjects for age, sex and body size would have contributed additional information to our understanding of SSc effects on the left ventricle, but was not available for this study, and indeed, has generally not been present in previous SSc studies. On the other hand, a control group was not necessary to address the main aim of this study, which was to identify variables which could have confounded the results of previous studies.

In this cross-sectional study of SSc, we investigated the effects of a number of disease-specific and non-disease-specific variables on echocardiographic variables of LV structure, filling and long-axis function. We demonstrated associations of sex, BSA, age and disease type with LV structural variables, associations of age, heart rate and BP with LV filling variables, and associations of age with both systolic and early diastolic LV long-axis velocities. Therefore, a number of variables have been identified which may have varied between the SSc groups in different studies and between the SSc and control groups within studies, and thus could have influenced the results of these studies. An important implication of our findings is that multivariate analyses with adjustment for these variables would provide a means for investigating and potentially resolving previous divergent findings regarding LV structure, filling and long-axis function in SSc. Such an approach should not only be considered in future studies of SSc, but there could be a role for its use in the reanalysis of data from previous studies.

Supporting information

S1 Data. Scleroderma LV function data.
(XLSX)

Author Contributions

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References

1. Gabrielli A, Avvedimento EV, Krieg T (2009) Scleroderma. N Engl J Med 360: 1989–2003. 360/19/1989 [pii]; https://doi.org/10.1056/NEJMra0806188 PMID: 19420368
2. Komocsi A, Vorobcsuk A, Faludi R, Pinter T, Lenkey Z, Kolto G, et al. (2012) The impact of cardiopulmonary manifestations on the mortality of SSc: a systematic review and meta-analysis of observational studies. Rheumatology (Oxford) 51: 1027–1036. https://doi.org/10.1093/rheumatology/ker357 PMID: 22223705
3. Champion HC (2008) The heart in scleroderma. Rheum Dis Clin North Am 34: 181–190. S0889-857 X(07)00101-9 [pii]; https://doi.org/10.1016/j.rdc.2007.12.002 PMID: 18329539
4. Allanore Y, Meune C, Vonk MC, Airo P, Hachulla E, Caramaschi P, et al. (2010) Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. Ann Rheum Dis 69: 218–221. https://doi.org/10.1136/ard.2008.103382 PMID: 22223705
5. Meune C, Avouac J, Wahbi K, Cabanes L, Wipff J, Mouthon L, et al. (2008) Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: A controlled study of 100 consecutive patients. Arthritis Rheum 58: 1803–1809. https://doi.org/10.1002/art.23463 PMID: 18512815
6. Poanta L, Dadu R, Tiboc C, Rednic S, Dumitrescu D (2009) Systolic and diastolic function in patients with systemic sclerosis. Eur J Intern Med 20: 378–382. https://doi.org/10.1016/j.ejim.2008.10.011 PMID: 19524178
7. Pizak W, Gryga K, Szajdz J, Tomkiewicz-Pajak L, Suchon E, Wilisowska J, et al. (2011) Diastolic heart dysfunction, increased pulmonary capillary wedge pressure and impaired exercise tolerance in patients with systemic sclerosis. Kardiol Pol 69: 243–249. PMID: 21432793
8. Aktoz M, Yilmaztepe M, Tatti E, Turan FN, Umit EG, Altun A (2011) Assessment of ventricular and left atrial mechanical functions, atrial electromechanical delay and P wave dispersion in patients with scleroderma. Cardiol J 18: 261–269. PMID: 21660915
9. Ciurzynski M, Bienias P, Izyk K, Kostrubiec M, Szewczyk A, Demkow U, et al. (2014) Heart diastolic dysfunction in patients with systemic sclerosis. Arch Med Sci 10: 445–454. https://doi.org/10.5114/ams.2014.43739 23011 [pii]. PMID: 25097573
10. Lee SW, Choi EY, Jung SY, Choi ST, Lee SK, Park YB (2010) E/E’ ratio is more sensitive than E/A ratio for detection of left ventricular diastolic dysfunction in patients with systemic sclerosis. Clin Exp Rheumatol 28: S12–S17. PMID: 20576210
11. Faludi R, Kolto G, Bartos B, Csima G, Czirjak L, Komocsi A (2014) Five-year follow-up of left ventricular diastolic function in systemic sclerosis patients: determinants of mortality and disease progression. Semin Arthritis Rheum 44: 220–227. S0049-0172(14)00049-3 [pii]; https://doi.org/10.1016/j.semarthrit.2014.04.001 PMID: 24830793
12. Armstrong GP, Whalley GA, Doughty RN, Gamble GD, Flett SM, Tan PL, et al. (1996) Left ventricular function in scleroderma. Br J Rheumatol 35: 983–988. https://doi.org/10.1093/rheumatology/35.10.983 PMID: 8883437
13. Henein MY, Cailes J, O’Sullivan C, du Bois RM, Gibson DG (1995) Abnormal ventricular long-axis function in systemic sclerosis. Chest 108: 1533–1540. https://doi.org/10.1378/chest.108.6.1533 PMID: 7497756
18. D’Andrea A, Stisi S, Caso P, Uccio FS, Bellissimo S, Salerno G, et al. (2007) Associations between left ventricular myocardial involvement and endothelial dysfunction in systemic sclerosis: noninvasive assessment in asymptomatic patients. Echocardiography 24: 587–597. https://doi.org/10.1111/j.1540-8175.2007.00436.x PMID: 17584198
19. Mele D, Censi S, La CR, Merli E, Lo MA, Locaputo A, et al. (2008) Abnormalities of left ventricular function in asymptomatic patients with systemic sclerosis using Doppler measures of myocardial strain. J Am Soc Echocardiogr 21: 1257–1264. https://doi.org/10.1016/j.echo.2008.08.004 PMID: 18992677
20. Kepez A, Akdogan A, Sade LE, Deniz A, Kalyoncu U, Karadag O, et al. (2008) Detection of subclinical cardiac involvement in systemic sclerosis by echocardiographic strain imaging. Echocardiography 25: 191–197. https://doi.org/10.1111/j.1540-8175.2007.00582.x PMID: 18269564
21. D’Andrea A, Stisi S, Bellissimo S, Vigorito F, Scotto di Uccio F, Tozzi N, et al. (2005) Early impairment of myocardial function in systemic sclerosis: non-invasive assessment by Doppler myocardial and strain rate imaging. Eur J Echocardiogr 6: 407–418. S1525-2167(05)00005-3 [pii]; https://doi.org/10.1016/j.euje.2005.01.002 PMID: 16293527
22. Yi KH, Schouffoer AA, Marsan NA, Ninaber MK, Stolk J, Vlieland TV, et al. (2011) Left ventricular dysfunction assessed by speckle-tracking strain analysis in patients with systemic sclerosis: relationship to functional capacity and ventricular arrhythmias. Arthritis Rheum 63: 3969–3978. https://doi.org/10.1002/art.30614 PMID: 22127711
23. Karadag DT, Sahin T, Tekeoglu S, Isik OO, Yazici A, Eraldemir FC, et al. (2020) Evaluation of left and right ventricle by two-dimensional speckle tracking echocardiography in systemic sclerosis patients without overt cardiac disease. Clin Rheumatol 39: 37–48. 10.1007/s10067-019-04604-3 https://doi.org/10.1007/s10067-019-04604-3 [pii]. PMID: 31127462
24. Agoston G, Gargani L, Miglioranza MH, Caputo M, Badano LP, Moreo A, et al. (2014) Left atrial dysfunction detected by speckle tracking in patients with systemic sclerosis. Cardiovasc Ultrasound 12: 30. 1476-7120-12-30 [pii]; https://doi.org/10.1186/1476-7120-12-30 PMID: 25090937
25. de Simone G, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinai M, et al. (2005) Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. Hypertension 45: 64–68. https://doi.org/10.1161/01.HYP.0000150108.37527.57 PMID: 15557389
26. Stoylen A, Molmen HE, Dalen H (2016) Importance of length and external diameter in left ventricular geometry. Normal values from the HUNT Study. Open Heart 3: e000465. https://doi.org/10.1113/openhrt-2016-000465 openhrt-2016-000465 [pii]. PMID: 27752332
27. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. (2016) 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 29: 277–314. S0894-7317(16)00044-4 [pii]; https://doi.org/10.1016/j.echo.2016.01.011 PMID: 27037982
28. Benjamin EJ, Levy D, Anderson KM, Wolf PA, Plehn JF, Evans JC, et al. (1992) Determinants of Doppler indexes of left ventricular diastolic function in normal subjects (the Framingham Heart Study). Am J Cardiol 70: 508–515. https://doi.org/10.1016/0002-9149(92)91199-e PMID: 1642190
29. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, et al. (1992) Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 20: 1251–1260. https://doi.org/10.1016/0735-1097(92)90385-z PMID: 1401629
30. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH (1994) Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. Hypertension 23: 600–606. https://doi.org/10.1161/01.hyp.23.5.600 PMID: 8175168
31. Mantero A, Gentile F, Gualterottci C, Zazzolini M, Barbier P, Beretta L, et al. (1995) Left ventricular diastolic parameters in 288 normal subjects from 20 to 80 years old. Eur Heart J 16: 94–105. https://doi.org/10.1093/eurheartj/16.1.94 PMID: 7737229
32. Bella JN, Devereux RB, Roman MJ, O’Grady MJ, Welty TK, Lee ET, et al. (1998) Relations of left ventricular mass to fat-free and adipose body mass: The Strong Heart Study. Circulation 98: 2538–2544. https://doi.org/10.1161/01.cir.98.23.2538 PMID: 9843460
33. Kou S, Caballero L, Dulgheru R, Voilliot D, De SC, Kacharava G, et al. (2014) Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. Eur Heart J Cardiovasc Imaging 16: 680–690. jet284 [pii]; https://doi.org/10.1093/ehjci/jet284 PMID: 24451180
34. Peverill RE, Chou B, Donelan L, Mottram PM, Gelman JS (2016) Possible mechanisms underlying aging-related changes in early diastolic filling and long axis motion—Left ventricular length and blood pressure. PLoS ONE 11: e0158302. https://doi.org/10.1371/journal.pone.0158302 PONE-D-16-02781 [pii]. PMID: 27351745
35. Peverill RE, Chou B, Donelan L (2017) Left ventricular long axis tissue Doppler systolic velocity is independently related to heart rate and body size. PLoS ONE 12: e0173383. https://doi.org/10.1371/journal.pone.0173383. PMID: 28288162

36. Peverill RE (2019) Aging and the relationships between long-axis systolic and early diastolic excursion, isovolumic relaxation time and left ventricular length—Implications for the interpretation of aging effects on e’. PLoS ONE 14: e0210277. https://doi.org/10.1371/journal.pone.0210277 PONE-D-18-21676 [pii]. PMID: 30615676

37. Nishimura RA, Tajik AJ (1997) Evaluation of diastolic filling of left ventricle in health and disease—Doppler echocardiography is the clinician’s Rosetta stone. J Am Coll Cardiol 30: 8–18. https://doi.org/10.1016/s0735-1097(97)00144-7 PMID: 9207615

38. Graettinger WF, Weber MA, Gardin JM, Knoll ML (1987) Diastolic blood pressure as a determinant of Doppler left ventricular filling indexes in normotensive adolescents. J Am Coll Cardiol 10: 1280–1285. https://doi.org/10.1016/s0735-1097(87)80132-8 PMID: 3680798

39. Genovesi-Ebert A, Marabotti C, Palombo C, Giaconi S, Ghione S (1991) Left ventricular filling: relationship with arterial blood pressure, left ventricular mass, age, heart rate and body build. J Hypertens 9: 345–353. https://doi.org/10.1097/00004872-199104000-00006 PMID: 1646261

40. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. (2013) 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 72: 1747–1755. annrheumdis-2013-204424 [pii]; https://doi.org/10.1136/annrheumdis-2013-204424 PMID: 24092682

41. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr., et al. (1988) Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 15: 202–205. PMID: 3361530

42. Thakkar V, Stevens WM, Prior D, Moore OA, Byron J, Liew D, et al. (2012) N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study. Arthritis Res Ther 14: R143. https://doi.org/10.1186/ar3876 PMID: 22691291

43. Mahadevan G, Davis RC, Frenneaux MP, Hobbs FD, Lip GY, Sanderson JE, et al. (2008) Left ventricular ejection fraction: are the revised cut-off points for defining systolic dysfunction sufficiently evidence based? Heart 94: 426–428. https://doi.org/10.1136/hrt.2007.123877 PMID: 18947374

44. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. [Review] [26 refs]. J Am Soc Echocardiogr 2: 358–367. https://doi.org/10.1016/s0894-7317(89)80014-8 PMID: 2698218

45. Cheng S, Fernandes VR, Bluemke DA, McCielland RL, Kronmal RA, Lima JA (2009) Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging 2: 191–198. https://doi.org/10.1161/CIRCIMAGING.108.819938 PMID: 19808592

46. Eng J, McCielland RL, Gomes AS, Hundley WG, Cheng S, Wu CO, et al. (2016) Adverse left ventricular remodeling and age assessed with cardiac MR Imaging: The Multi-Ethnic Study of Atherosclerosis. Radiology 278: 714–722. https://doi.org/10.1148/radiol.2015150982 PMID: 26485617

47. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18: 1440–1463. https://doi.org/10.1016/j.echo.2005.10.005 PMID: 16376782

48. Moreno FL, Hagan AD, Holmen JR, Pryor TA, Strickland RD, Castle CH (1984) Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. Am J Cardiol 53: 579–585. 0002-9149(84)90034-1 [pii]. https://doi.org/10.1002/1514-9620(84)90034-1 PMID: 6695787

49. Slinker BK, Glantz SA (2008) Multiple linear regression: accounting for multiple simultaneous determinants of a continuous dependent variable. Circulation 117: 1732–1737. https://doi.org/10.1161/CIRCULATIONAHA.106.654376 PMID: 18378626

50. Wild PS, Sinning CR, Roth A, Wilde S, Schnabel RB, Lubos E, et al. (2010) Distribution and categorization of left ventricular measurements in the general population: results from the population-based Gutenberg Heart Study. Circ Cardiovasc Imaging 3: 604–613. https://doi.org/10.1161/CIRCIMAGING.109.911933 PMID: 20643817

51. Myerson SG, Montgomery HE, World MJ, Pennell DJ (2002) Left ventricular mass: reliability of M-mode and 2-dimensional echocardiographic formulas. Hypertension 40: 673–678. https://doi.org/10.1161/01.hyp.0000036401.99908.db PMID: 12411461
52. Hees PS, Fleg JL, Lakatta EG, Shapiro EP (2002) Left ventricular remodeling with age in normal men versus women: novel insights using three-dimensional magnetic resonance imaging. Am J Cardiol 90: 1231–1236. https://doi.org/10.1016/s0002-9149(02)02840-0 PMID: 12450604

53. Gruner Svealv B, Fritzon G, Andersson B (2006) Gender and age related differences in left ventricular function and geometry with focus on the long axis. Eur J Echocardiogr 7: 298–307. https://doi.org/10.1016/j.euje.2005.06.008 PMID: 16039910

54. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A (2010) Reference Values and Distribution of Conventional Echocardiographic Doppler Measures and Longitudinal Tissue Doppler Velocities in a Population Free From Cardiovascular Disease. Circ Cardiovasc Imaging 3: 614–622. https://doi.org/10.1161/CIRCIMAGING.109.926022 PMID: 20581050

55. Oki T, Fukuda K, Tabata T, Mishiro Y, Yamada H, Abe M, et al. (1999) Effect of an acute increase in afterload on left ventricular regional wall motion velocity in healthy subjects. J Am Soc Echocardiogr 12: 476–483. https://doi.org/10.1016/s0894-7317(99)70084-2 PMID: 10359919

56. Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, et al. (2007) Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet 369: 2079–2087. https://doi.org/10.1016/S0140-6736(07)60980-5 PMID: 17586303

57. Solomon SD, Verma A, Desai A, Hassanein A, Izzo J, Oparil S, et al. (2010) Effect of intensive versus standard blood pressure lowering on diastolic function in patients with uncontrolled hypertension and diastolic dysfunction. Hypertension 55: 241–248. https://doi.org/10.1161/HYPERTENSIONAHA.109.138529 PMID: 19996069

58. Hinchcliff M, Desai CS, Varga J, Shah SJ (2012) Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. Clin Exp Rheumatol 30: S30–S37. https://doi.org/10.1093/clinexp/2012.10.00000000000

59. Vemulapalli S, Cohen L, Hsu V (2017) Prevalence and risk factors for left ventricular diastolic dysfunction in a scleroderma cohort. Scand J Rheumatol 46: 281–287. https://doi.org/10.1080/03009742.2016.1296963 PMID: 27635465

60. Tennoe AH, Murbraeck K, Andreassen JC, Fretheim H, Garen T, Gude E, et al. (2018) Left ventricular diastolic dysfunction predicts mortality in patients with systemic sclerosis. J Am Coll Cardiol 72: 1804–1813. S0735-1097(18)36930-4 [pii]; https://doi.org/10.1016/j.jacc.2018.07.068 PMID: 30286924