Impact of Multi-parametric Analyses on Normal Left Atrial Strain by Cardiovascular Magnetic Resonance Feature Tracking

Jan Eckstein  
Heart and Diabetes Center North-Rhine Westphalia, Ruhr-University of Bochum, Bad Oeynhausen

Hermann Körperich (hkoerperich@hdz-nrw.de)  
Heart and Diabetes Center North-Rhine Westphalia, Ruhr-University of Bochum, Bad Oeynhausen

Lech Paluszkiewicz  
Heart and Diabetes Center North-Rhine Westphalia, Ruhr-University of Bochum, Bad Oeynhausen

Wolfgang Burchert  
Heart and Diabetes Center North-Rhine Westphalia, Ruhr-University of Bochum, Bad Oeynhausen

Misagh Piran  
Heart and Diabetes Center North-Rhine Westphalia, Ruhr-University of Bochum, Bad Oeynhausen

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Abstract

Left-atrial (LA) strain is the result of complex hemodynamics, increasingly assessed by feature-tracking cardiovascular magnetic resonance (CMR). We investigate the value of multi-parametric regression (MPR) analyses and the influence of the heart rate on LA-strain. As LA-strain data remains limited, CMR-quantified sex- and age-dependent normal values were derived. After following a health assessment questionnaire, 183 healthy volunteers (11-70 years, 97 females, median 32.9±28.3 years) were recruited for LA-strain assessment. LA volumetric data, left ventricular strain, transmitral and pulmonary venous blood flow parameters were utilized to create clusters for MPR analyses for all subjects and heart rate-specific subgroups (range: 60–75 beats-per-minute, N=106).

In comparison to the total cohort, subgroups showed no gender differences (p>0.05) for LA reservoir, conduit and booster strains (all: 47.3±12.7%; 29.0±15.5%; 17.6±5.4%) and strain rates (all: 2.1±1.0 s$^{-1}$; -2.9±1.5 s$^{-1}$; -2.3±1.0 s$^{-1}$). MPR analyses identified parameter clusters with large effect size ($|R^2|\geq 0.26$) for reservoir-, conduit- and booster strain and corresponding active and passive cardiac functional parameters. Increased correlations for the subgroup were found.

In contrast to previous studies, heart rate selected subgroups showed no gender differences in LA-strain. MPR analyses improve characterization of LA-strain at selected heart rates.

Introduction

Myocardial strain studies the deformation between the contractile and relaxed state of the heart. Similar to the ejection fraction (EF), strain represents a load-dependent estimation of cardiac function. However, strain additionally acknowledges the spatial dimensions of contractile function in the form of longitudinal strain, radial strain and circumferential strain [1]. In particular, left atrial strain is a valuable diagnostic measure for the diagnosis and progression of cardiovascular diseases such as hypertension, atrial fibrillation and heart failure [2–5]. It represents the shortening between the superior left atrial wall and the annular ring of the mitral valve and can be divided into three physiological phases. The reservoir phase occurs during ventricular systole until the opening of the mitral valve, when blood from pulmonary venous return accumulates in the left atrium. The subsequent conduit phase continues after mitral valve opening until the onset of left atrial contraction. The final booster phase begins with the contraction of the left atrium until the end of ventricular diastole and leads to active filling of the left ventricle [6, 7].

Speckle tracking and tissue doppler imaging are useful and widely available clinical tools for quantifying left atrial strain[8, 9]. However, notable limitations of echocardiography include dependence on operator experience, reduced reproducibility, through-plane motion, as well as its patient echogenicity. Furthermore, the left atrium is characterized by complex geometric aspects with its thin interatrial septum, the pulmonary veins and the left atrial appendage. To overcome the geometric obstacles and limitations of echocardiography, cardiac chamber quantification by cardiovascular magnetic resonance (CMR) imaging has set the gold standard[10–12].

Until today, CMR-quantified sex- and age-dependent left atrial strain of healthy individuals remain data limited[12, 13]. In addition, the influence of heart rate on left atrial strain has not been studied so far. This study contributes CMR-attained normal left atrial strain values and investigates the effect of heart rate on left atrial strain using a large cohort of healthy participants. Moreover, we aimed to provide novel insights utilizing multiparametric analyses of the left atrial strain to better characterize the complexity of strain mechanics.

Results

Baseline characteristics of study cohort

This study entailed 183 healthy subjects of ages 11 - 70 years (97 females and 86 males, median ± interquartile range 32.9 ± 28.3 years of age). There was no gender difference for median age. The mean left ventricular ejection fraction (LV-EF) of all
subjects was 65% ± 5%. BSA-indexed muscle mass (MM) and BSA-indexed volumetric parameters were greater in males compared to females (p <0.001). The baseline characteristics are summarized in Table 1.

| Table 1 | Baseline characteristics of healthy participants |
|---------|-----------------------------------------------|
|         | All (n=183) | Women (n=97) | Men (n=86) | p† |
| All heart rates | | | | |
| Age [years] | 32.9±28.3a (11-70) | 33.8±25.9a (11-68) | 32.7±30.0a (13-70) | 0.629 |
| HR [bpm] | 67±14a (47-111) | 70±13a (47-111) | 65±14a (47-100) | 0.026 |
| Weight [kg] | 69±21a (38-120) | 61±11a (38-93) | 81±14 (50-120) | <0.001 |
| Height [cm] | 173±11 (140-200) | 166±11a (140-180) | 182±8 (161-200) | <0.001 |
| BSA [m²] | 1.8±0.2 (1.2-2.6) | 1.7±0.2 (1.2-2.0) | 2.0±0.2 (1.5-2.6) | <0.001 |
| BMI [kg/m²] | 23.2±4.9a (17-35) | 22.3±4.0a (16.7-34.6) | 24.6±3.5 (17.2-33.2) | <0.001 |
| LV-EDVi [ml/m²] | 76±10 (48-103) | 72±9 (48-97) | 80±9 (55-103) | <0.001 |
| LV-ESVi [ml/m²] | 26±5 (14-43) | 24±5 (14-40) | 29±5 (18-43) | <0.001 |
| LV-SVi [ml/m²] | 49±7 (31-66) | 48±6 (31-64) | 51±6 (37-66) | <0.001 |
| LV-EF [%] | 65±5 (54-77) | 66±5 (57-76) | 64±5 (54-77) | 0.003 |
| MMi [g/m²] | 56±15a (37-81) | 50±11a (37-73) | 64±7 (50-81) | <0.001 |

Normally distributed values were expressed as mean±standard deviation, otherwise as median (a) with interquartile range. Ranges in parentheses. † p-value related to gender. Normally distributed data were tested by the unpaired t-test, otherwise with the Mann-Whitney-U-test. BSA, body surface area; BMI, body mass index; LV-EDVi, BSA-indexed end-diastolic volume; LV-ESVi, BSA-indexed end-systolic volume; LV-SVi, BSA-indexed stroke volume; LV-EF, left ventricular ejection fraction; MMi, BSA-indexed muscle-mass; HR, heart rate.
Left atrial volumes and strains of the total cohort and heart rate specific subgroup

In all subjects, females had higher left atrial strain rates, reservoir strain and conduit strain compared to males (Table 2). No gender difference was observed for left atrial booster strain (p=0.058). Interestingly, for the subgroup with a selected heart rate between 60 – 75 beats per minute (bpm), the left atrial strain and strain rate were comparable for both genders (Table 3). Furthermore, heart rate selection diminished gender differences of left atrial chamber volume indices and ejection fraction phases. Thereby gender differences for indexed minimum left atrial volume (LA-Volmin_i) and passive left atrial ejection fraction (LA-EF_{con}) became statistically insignificant after heart rate selection.
### Table 2
Left atrial strain and volumes of the total cohort

|                          | All (n=183) | Women (n=97) | Men (n=86) | p† |
|--------------------------|-------------|--------------|------------|----|
| **Left atrial function** |             |              |            |    |
| LA-Vol\(_{\text{max,}i}\) [ml/m²] | 46.6±12.4\(^a\) | 45.4±12.0\(^a\) | 50.3±9.6 | 0.002 |
|                           | (27.3-77.6) | (30.6-74.0)  | (27.3-77.6) |    |
| LA-Vol\(_{\text{min,}i}\) [ml/m²] | 20.7±6.7\(^a\) | 20.0±5.8\(^a\) | 21.8±8.0\(^a\) | 0.003 |
|                           | (10.3-39.8) | (10.5-39.3) | (10.3-39.8) |    |
| LA-Vol\(_{\text{boo,}i}\) [ml/m²] | 32.5±11.9\(^a\) | 29.4±9.8\(^a\) | 36.0±9.1 | <0.001 |
|                           | (15.0-58.1) | (17.4-52.3) | (15.0-58.1) |    |
| LA-EF\(_{\text{total}}\) [%] | 55±5 | 56±5 | 55±6 | 0.127 |
|                           | (40-67) | (40-67) | (41-65) |    |
| LA-EF\(_{\text{con}}\) [%] | 31±8 | 33±8 | 29±7 | 0.001 |
|                           | (13-54) | (13-54) | (15-48) |    |
| LA-EF\(_{\text{boo}}\) [%] | 35±9\(^a\) | 34±9\(^a\) | 35±6 | 0.065 |
|                           | (5-49) | (5-46) | (19-49) |    |
| **Left atrial strain**   |             |              |            |    |
| LA-S\(_{\text{res}}\) [%] | 44.7±16.7\(^a\) | 49.7±12.9 | 42.9±11.4 | <0.001 |
|                           | (19.3-81.1) | (24.1-81.1) | (19.3-75.7) |    |
| LA-S\(_{\text{con}}\) [%] | 28.6±14.7\(^a\) | 32.0±11.0 | 26.1±10.5\(^a\) | 0.001 |
|                           | (8.3-61.8) | (8.3-61.8) | (10.7-59.2) |    |
| LA-S\(_{\text{boo}}\) [%] | 16.9±6.9\(^a\) | 17.7±5.4 | 16.1±5.3 | 0.058 |
|                           | (4.2-35.0) | (4.7-35.0) | (4.2-33.0) |    |
| LA-SR\(_{\text{res}}\) [s\(^{-1}\)] | 2.1±1.0\(^a\) | 2.2±1.1\(^a\) | 2.0±0.8\(^a\) | 0.028 |
|                           | (0.6-5.0) | (0.6-5.0) | (0.9-4.1) |    |
| LA-SR\(_{\text{con}}\) [s\(^{-1}\)] | -2.9±1.6\(^a\) | -3.2±1.9\(^a\) | -2.8±1.2\(^a\) | 0.019 |
|                           | (-8.9 to 3.9) | (-8.9 to 3.9) | (-6.2 to 2.6) |    |

Normally distributed values were expressed as mean±standard deviation, otherwise as median (\(^a\)) with interquartile range. Ranges in parentheses. † p-value related to gender. Normally distributed data were tested by the unpaired t-test, otherwise with the Mann-Whitney-U-test. LA-Vol\(_{\text{max,}i}\), indexed maximum left atrial volume; LA-Vol\(_{\text{min,}i}\), indexed minimum left atrial volume; LA-Vol\(_{\text{boo,}i}\), indexed booster left atrial volume; LA-EF\(_{\text{total}}\), total left atrial ejection fraction; LA-EF\(_{\text{con}}\), passive left atrial ejection fraction; LA-EF\(_{\text{boo}}\), booster left atrial ejection fraction; LA-S\(_{\text{res}}\), reservoir left atrial strain; LA-S\(_{\text{con}}\), conduit left atrial strain; LA-S\(_{\text{boo}}\), booster left atrial strain; LA-SR\(_{\text{res}}\), reservoir left atrial strain rate; LA-SR\(_{\text{con}}\), conduit left atrial strain rate; LA-SR\(_{\text{boo}}\), booster left atrial strain rate.
|                      | All (n=183) | Women (n=97) | Men (n=86) | p† |
|----------------------|-------------|--------------|------------|----|
| LA-SR$_{boo}$ [s$^{-1}$] | -2.2±1.1$^a$ | -2.4±1.0$^a$ | -2.0±1.1$^a$ | 0.032 |
|                      | (-5.5 to 0.0) | (-5.5 to -0.9) | (-4.5 to 0.0) |    |

Normally distributed values were expressed as mean±standard deviation, otherwise as median ($^a$) with interquartile range. Ranges in parentheses. † p-value related to gender. Normally distributed data were tested by the unpaired t-test, otherwise with the Mann-Whitney-U-test. LA-Vol$_{max,i}$ indexed maximum left atrial volume; LA-Vol$_{min,i}$ indexed minimum left atrial volume; LA-Vol$_{boo,i}$ indexed booster left atrial volume; LA-EF$_{total}$ total left atrial ejection fraction; LA-EF$_{con}$ passive left atrial ejection fraction; LA-EF$_{boo}$ booster left atrial ejection fraction; LA-S$_{res}$ reservoir left atrial strain; LA-S$_{con}$ conduit left atrial strain; LA-S$_{boo}$ booster left atrial strain; LA-SR$_{res}$ reservoir left atrial strain rate; LA-SR$_{con}$ conduit left atrial strain rate; LA-SR$_{boo}$ booster left atrial strain rate.
Table 3
Left atrial strain and volumes of the subgroup with heart rates between 60 to 75 beats-per-minute

|                      | All (106) | Women (60) | Men (46) | \( p^\dagger \) |
|----------------------|-----------|------------|-----------|-----------------|
| HR [bpm]             | 68±8\(^a\) | 69±8\(^a\) | 68±9\(^a\) | 0.202           |
| **Left atrial function** |           |            |           |                 |
| LA-Vol\(_{\text{max,ij}}\) [ml/m²] | 47.3±8.4 (27.3-77.6) | 45.9±8.0 (32.1-67.4) | 49.2±8.7 (27.3-77.6) | 0.049 |
| LA-Vol\(_{\text{min,ij}}\) [ml/m²] | 20.7±6.6\(^a\) (10.3-39.3) | 20.2±6.3\(^a\) (13.3-39.3) | 21.9±5.2 (10.3-37.7) | 0.207 |
| LA-Vol\(_{\text{boo,ij}}\) [ml/m²] | 33.2±7.6 (15.0-55.7) | 30.7±11.7\(^a\) (22.0-52.3) | 34.8±7.8 (15.0-55.7) | 0.047 |
| LA-EF\(_{\text{total}}\) [%] | 56±7\(^a\) (40-65) | 55±6\(^a\) (40-62) | 56±5 (41-65) | 0.489 |
| LA-EF\(_{\text{con}}\) [%] | 30±7 (13-48) | 31±7 (13-46) | 30±7 (19-48) | 0.442 |
| LA-EF\(_{\text{boo}}\) [%] | 36±6 (22-49) | 35±5 (23-46) | 37±6 (22-49) | 0.060 |
| **Left atrial strain** |           |            |           |                 |
| LA-S\(_{\text{res}}\) [%] | 47.3±12.7 (19.3-81.1) | 49.2±13.2 (24.1-81.1) | 44.9±11.8 (19.3-75.7) | 0.079 |
| LA-S\(_{\text{con}}\) [%] | 29.0±15.5\(^a\) (8.3-59.2) | 31.1±11.3 (8.3-58.4) | 27.0±13.0\(^a\) (10.7-59.2) | 0.109 |
| LA-S\(_{\text{boo}}\) [%] | 17.6±5.4 (4.8-35.0) | 18.1±6.0 (4.8-35.0) | 17.0±4.6 (7.2-29.3) | 0.297 |
| LA-SR\(_{\text{res}}\) [s\(^{-1}\)] | 2.1±1.0\(^a\) (0.6-5.0) | 2.2±1.0\(^a\) (0.6-5.0) | 1.9±0.9\(^a\) (0.9-3.4) | 0.278 |
| LA-SR\(_{\text{con}}\) [s\(^{-1}\)] | -2.9±1.5\(^a\) (-7.2 to 3.9) | -3.0±1.7\(^a\) (-7.2 to 3.9) | -2.8±1.0\(^a\) (-6.2 to -1.6) | 0.389 |

Normally distributed values were expressed as mean±standard deviation, otherwise as median (\(^a\)) with interquartile range. Ranges in parentheses. \( p^\dagger \) p-value related to gender. Normally distributed data were tested by the unpaired t-test, otherwise with the Mann-Whitney-U-test. LA-Vol\(_{\text{max,ij}}\) indexed maximum left atrial volume; LA-Vol\(_{\text{min,ij}}\) indexed minimum left atrial volume; LA-Vol\(_{\text{boo,ij}}\) indexed booster left atrial volume; LA-EF\(_{\text{total}}\) total left atrial ejection fraction; LA-EF\(_{\text{con}}\) passive left atrial ejection fraction; LA-EF\(_{\text{boo}}\) booster left atrial ejection fraction; LA-S\(_{\text{res}}\) reservoir left atrial strain; LA-S\(_{\text{con}}\) conduit left atrial strain; LA-S\(_{\text{boo}}\) booster left atrial strain; LA-SR\(_{\text{res}}\) reservoir left atrial strain rate; LA-SR\(_{\text{con}}\) conduit left atrial strain rate; LA-SR\(_{\text{boo}}\) booster left atrial strain rate.
|                          | All       | Women     | Men       | \(p^\dagger\) |
|--------------------------|-----------|-----------|-----------|---------------|
|                          | (106)     | (60)      | (46)      |               |
| LA-SR_{boo} [s\(^{-1}\)]| -2.3±1.0\(^a\) | -2.4±1.0\(^a\) | -2.2±1.0\(^a\) | 0.483         |
|                          | (-4.9 to -0.1) | (-4.9 to -0.9) | (-4.5 to -0.1) |               |

Normally distributed values were expressed as mean±standard deviation, otherwise as median (\(^a\)) with interquartile range. Ranges in parentheses. \(\dagger\) \(p\)-value related to gender. Normally distributed data were tested by the unpaired \(t\)-test, otherwise with the Mann-Whitney-U-test. LA-Vol\(_{\text{max,i}}\), indexed maximum left atrial volume; LA-Vol\(_{\text{min,i}}\), indexed minimum left atrial volume; LA-Vol\(_{\text{boo,i}}\), indexed booster left atrial volume; LA-EF\(_{\text{total}}\), total left atrial ejection fraction; LA-EF\(_{\text{con}}\), passive left atrial ejection fraction; LA-EF\(_{\text{boo}}\), booster left atrial ejection fraction; LA-S\(_{\text{res}}\), reservoir left atrial strain; LA-S\(_{\text{con}}\), conduit left atrial strain; LA-S\(_{\text{boo}}\), booster left atrial strain; LA-SR\(_{\text{res}}\), reservoir left atrial strain rate; LA-SR\(_{\text{con}}\), conduit left atrial strain rate; LA-SR\(_{\text{boo}}\), booster left atrial strain rate.

**Cardiovascular functional parameters**

All mean global left ventricular strain values were higher in females than in males (\(p<0.001\), Table 4). Statistical significance did not change when heart rate was limited to 60 - 75 bpm (\(p<0.001\), Table 5). There were no gender differences in the other parameters when all subjects were considered, except for the E-wave (E), which was greater in females. Heart rate selection was associated with a greater E/e' ratio in females and a greater systolic excursion of the mitral annulus (MAPSE) in males. All other parameters remained comparable between both genders after heart rate selection.
Table 4
Cardiovascular functional parameter of the total cohort

|                         | All       | Women     | Men       | p†      |
|-------------------------|-----------|-----------|-----------|---------|
| **All heart rates**     |           |           |           |         |
| LV-GLS [%]              | -16.9±1.7 | -17.6±1.6 | -16.1±1.5 | <0.001  |
|                         | (-22.3 to-12.9) | (-22.3 to-14.2) | (-20.8 to-12.9) |         |
| LV-GCS [%]              | -19.2±2.0 | -20.1±1.8 | -18.2±1.8 | <0.001  |
|                         | (-24.8 to-14.1) | (-24.8 to-15.6) | (-21.8 to-14.1) |         |
| LV-GRS [%]              | 33.6±8.0a | 36.5±6.9a | 31.3±4.9  | <0.001  |
|                         | (21.4-53.9) | (24.0-53.9) | (21.4-42.1) |         |
| S/D []                  | 1.12±0.57a | 1.09±0.54a | 1.14±0.63a | 0.847   |
|                         | (0.43-2.61) | (0.53-2.61) | (0.43-2.47) |         |
| E/A []                  | 1.86±0.85a | 1.86±0.84a | 1.91±0.62  | 0.352   |
|                         | (0.81-5.14) | (0.81-5.14) | (0.82-3.74) |         |
| E [cm/s]                | 52.9±9.1  | 54.5±8.8  | 51.0±9.0  | 0.010   |
|                         | (25.4-76.2) | (25.4-76.2) | (31.9-72.6) |         |
| A [cm/s]                | 28.3±11.0a | 28.5±9.9a | 27.5±11.7a | 0.824   |
|                         | (14.8-57.5) | (14.8-54.0) | (15.0-57.5) |         |
| é [ cm/s]               | 13.3±4.0  | 13.3±3.8  | 13.3±4.2  | 0.988   |
|                         | (4.2-23.2) | (4.2-23.2) | (4.8-23.0) |         |
| E/é []                  | 4.16±1.56a | 4.22±1.42a | 3.99±1.47a | 0.137   |
|                         | (1.73-13.28) | (1.73-13.28) | (2.00-9.26) |         |
| MAPSE [cm]              | 1.7±0.3   | 1.6±0.3   | 1.7±0.3   | 0.196   |
|                         | (0.9-2.5)  | (1.0-2.5)  | (0.9-2.4)  |         |
| SI []                   | 1.26±0.51a | 1.28±0.50a | 1.26±0.54a | 0.669   |
|                         | (0.49-3.46) | (0.49-3.46) | (0.72-2.72) |         |

Normally distributed values were expressed as mean±standard deviation, otherwise as median (a) with interquartile range. Ranges in parentheses. † p-value related to gender. Normally distributed data were tested by the unpaired t-test, otherwise with the Mann-Whitney-U-test. LV-GLS, left ventricular global longitudinal strain; LV-GCS, left ventricular global circumferential strain; LV-GRS, left ventricular global radial strain; S/D, ratio S-wave to D-wave by quantitative right upper pulmonary vein blood flow measurements; E/A, ratio E-wave to A-wave by quantitative transmitral blood flow measurements; E, E-wave by quantitative transmitral blood flow measurements; A, A-wave by quantitative transmitral blood flow measurements; é, mean lateral and septal cine CMR velocities; E/é, ratio E-wave to é; MAPSE, Mitral annulus plain systolic excursion; SI, Sphericity index.
Table 5  
Cardiovascular functional parameter of the subgroup with heart rates between 60 to 75 beats-per-minute

|                         | All (LV-GLS [%]) | Women (LV-GLS [%]) | Men (LV-GLS [%]) | p†  |
|-------------------------|------------------|--------------------|------------------|-----|
| All heart rates         |                  |                    |                  |     |
| LV-GLS [%]              | -17.1±1.7        | -17.8±1.6          | -16.1±1.2        | <0.001 |
|                         | (-22.3 to -12.9) | (-22.3 to -14.4)   | (-18.3 to -12.9) |     |
| LV-GCS [%]              | -19.5±1.9        | -20.2±1.8          | -18.6±1.6        | <0.001 |
|                         | (-24.2 to -15.3) | (-24.2 to -15.6)   | (-21.8 to -15.3) |     |
| LV-GRS [%]              | 34.4±6.9a        | 37.1±5.6           | 32.2±4.5         | <0.001 |
|                         | (24.0-52.1)      | (24.0-52.1)        | (24.2-41.5)      |     |
| S/D []                  | 1.12±0.59a       | 1.11±0.58a         | 1.13±0.61a       | 0.811 |
|                         | (0.58-2.48)      | (0.58-2.48)        | (0.59-2.33)      |     |
| E/A []                  | 1.84±0.87a       | 1.84±0.86a         | 1.93±0.59        | 0.985 |
|                         | (0.81-5.14)      | (0.81-5.14)        | (0.86-3.33)      |     |
| E [cm/s]                | 52.6±9.3         | 53.3±9.6           | 51.8±8.9         | 0.409 |
|                         | (25.4-76.2)      | (25.4-76.2)        | (31.9-70.6)      |     |
| A [cm/s]                | 28.2±12.8a       | 29.2±8.1           | 26.6±13.3a       | 0.562 |
|                         | (14.8-54.0)      | (14.8-54.0)        | (18.0-49.8)      |     |
| é [cm/s]                | 13.3±3.7         | 12.8±3.6           | 14.1±3.9         | 0.096 |
|                         | (5.0-23.0)       | (5.0-21.9)         | (6.4-23.0)       |     |
| E/é []                  | 4.14±1.41a       | 4.18±1.32a         | 3.92±1.04        | 0.045 |
|                         | (2.13-7.61)      | (2.54-7.61)        | (2.13-6.11)      |     |
| MAPSE [cm]              | 1.6±0.3          | 1.6±0.3            | 1.7±0.3          | 0.038 |
|                         | (0.93-2.43)      | (0.95-2.34)        | (0.93-2.43)      |     |
| SI [cm]                 | 1.23±0.47a       | 1.21±0.44a         | 1.26±0.72a       | 0.761 |
|                         | (0.72-3.46)      | (0.72-3.46)        | (0.72-2.45)      |     |

Normally distributed values were expressed as mean±standard deviation, otherwise as median (a) with interquartile range. Ranges in parentheses. † p-value related to gender. Normally distributed data were tested by the unpaired t-test, otherwise with the Mann-Whitney-U-test. LV-GLS, left ventricular global longitudinal strain; LV-GCS, left ventricular global circumferential strain; LV-GRS, left ventricular global radial strain; S/D, ratio S-wave to D-wave by quantitative right upper pulmonary vein blood flow measurements; E/A, ratio E-wave to A-wave by quantitative transmitral blood flow measurements; E, E-wave by quantitative transmitral blood flow measurements; A, A-wave by quantitative transmitral blood flow measurements; é, mean lateral and septal cine CMR velocities; E/é, ratio E-wave to é; MAPSE, Mitral annulus plain systolic excursion; SI, Sphericity index.

Bivariate strain correlation
Correlation analyses of strain with a wide range of cardiac parameters were performed and are listed in the Supplementary Table S1 online. Several parameters correlate moderately but statistically significant with strain. As an example, the E wave correlates with the passive measures of reservoir- (LA-S$_{res}$) and conduit strain (LA-S$_{con}$) but not with the active measure of booster strain (LA-S$_{boo}$). In contrast, the A-wave only correlates moderately with LA-S$_{boo}$ (Supplementary Table S1, Table I).

**Correlation between age and strain**

The correlations between strain and age are shown as percentiles in Figure 1 and are summarized in Supplementary Table S1 (Tables III, IV) online. The female conduit strain correlates negatively with age, while the female booster strain correlates positively with age, both at a 0.01 significance level. The male booster strain correlates positively with age at a 0.05 significance level. Although not all strain correlate significantly, the trend dynamics imply a point of inflection at age 40 - 45 for both sexes.

**Correlation between age and strain rate**

Similarly to strain percentiles, strain rate percentiles show an inflection point at 40 to 45 years of age (Figure 2). Female reservoir and booster strain rates correlate negatively with age, while a positive correlation is observed for female conduit strain rate and age. For males, the conduit strain rate correlates positively with age. The correlations are summarized in Supplementary Table 1 (Tables V, VI) online.

**Multiple linear regression analyses**

Multiple linear regression analyses derived from the bivariate correlation analyses are summarized in the Supplementary Tables S2a-S2d online. Individual parameters were selected for clustering based on their correlative value and presumed associations with cardiac function. Due to the multifactorial influences of left atrial strain, clusters of selected parameters may better characterize strain function. Multiple linear regression analyses were performed for strain and strain rate of all subjects and subgroups with heart rates between 60 – 75 bpm.

**All subjects**

A sub-selection of multiple linear regression analyses of all subjects are summarized in Table 6. Interestingly, left atrial reservoir- and conduit strain correlate moderately with the E-wave and corresponding left ventricular strain, among others (e.g. Clusters 2 and 4). In contrast, contractile parameters such as left atrial booster ejection fraction (LA-EF$_{boo}$) and the A wave (e.g. Cluster 8) show moderate (males) to large (females) correlation with left atrial booster strain (LA-S$_{boo}$). A comprehensive collection of the multiple linear regression analyses is given in the Supplementary Tables S2a and S2b online.
Table 6
Multilinear regression analysis to study multifactorial influences of left atrial strain. Analysis was done on the total study group. A sub-selection is shown. Note: A comprehensive summary of all testings is provided in the supplement online.

| Validity* | Parameter | Sex | $R^2$ | corr $R^2$ | ANOVA significance | Sample size$^+$ | Goodness-of-fit | Function |
|-----------|-----------|-----|-------|-------------|---------------------|----------------|----------------|----------|
| reservoir 2 | LA-S$_{res}$ | E, f | 0.158 | 0.131 | 0.001 | 80 | medium | $\text{LA-S}_{\text{res}} = 0.659^{*}\text{LA-EF}_{\text{tot}} + 1.946^{*}\text{LV-GCS} + 0.152^{*}\text{E} + 44.010$ |
| conduit 4 | LA-S$_{con}$ | LA-V$_{boo,j}$, LA-EF$_{tot}$, LV-GRS, E | 0.265 | 0.233 | $< 0.001$ | 48 | large | $\text{LA-S}_{\text{con}} = -0.144^{*}\text{LA-V}_{\text{boo,j}} + 0.463^{*}\text{LA-EF}_{\text{tot}} - 0.613^{*}\text{LV-GRS} + 0.270^{*}\text{E} + 18.627$ |
| conduit 4 | LA-S$_{con}$ | LA-V$_{boo,j}$, LA-EF$_{tot}$, LV-GRS, E | 0.225 | 0.181 | 0.001 | 59 | medium | $\text{LA-S}_{\text{con}} = -0.124^{*}\text{LA-V}_{\text{boo,j}} + 0.418^{*}\text{LA-EF}_{\text{tot}} + 0.064^{*}\text{LV-GRS} + 0.175^{*}\text{E} - 2.450$ |

* green = valid; orange = valid, but with fewer concerns due to the prerequisites; red = not valid due to violation of prerequisites.

number of females = 97; number of males = 86.

Interpretation of $|R^2|$ according to Cohen. [Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, N.J.: L. Erlbaum Associates. Page 412 ff].

small effect size: $|R^2| = .02$; medium effect size $|R^2| = .13$; large effect size $|R^2| = .26$.

$^+$ Sample size calculation see reference [Calculation according to Hemmerich, W. (2019). StatistikGuru: Poweranalyse und Stichprobenberechnung für Regression. Retrieved from https://statistikguru.de/rechner/poweranalyse-regression.html].

LA-S$_{res}$ reservoir left atrial strain; LA-S$_{con}$ conduit left atrial strain; LA-S$_{boo}$ booster left atrial strain; LA-V$_{boo,j}$ indexed booster left atrial volume; LA-EF$_{tot}$ total left atrial ejection fraction; LA-EF$_{boo}$ booster left atrial ejection fraction; LV-GCS, global left ventricular circumferential strain; LV-GRS, global left ventricular radial strain; E, E-wave by quantitative transmitral blood flow measurements; A, A-wave by quantitative transmitral blood flow measurements; LV-ESV$_i$ indexed left ventricular end systolic volume.
Subgroup with HR 60 – 75 bpm

Identical clustering was used for subgroups with selected heart rates between 60 – 75 bpm. A sub-selection of multiple linear regression analyses are summarized in Table 7. In contrast to all subjects, the subgroups with a heart rate of 60 – 75 bpm showed higher correlation between the selected cardiac parameters and left atrial strain or left atrial strain rate. With greater correlation, an overall reduction in sample size was achieved for most clusters of subgroups compared to all subjects. This becomes evident when comparing the R² correlation values and sample sizes (ss) of all subjects and subgroups with heart rates between 60 – 75 for cluster 2 (all subjects: R² female: 0.158, ss: 80, male: 0.205, ss: 60/ subgroup: R² female: 0.278, ss: 41, male: 0.320, ss: 35). Overall the clusters show increased correlative value for the subgroup. A comprehensive summary of the multiple linear regression analyses performed in the subgroups is given in the Supplementary Tables S2c and S2d online.
Table 7
Multilinear regression analysis to study multifactorial influences of left atrial strain. Analysis was done on subjects with heart rates between 60 – 75 bpm. A sub-selection is shown in this table. Note: A comprehensive summary of all testings is provided in the supplement online.

| Validity* | Parameter | Sex | R²  | corr | ANOVA significance | Sample size† | Goodness-of-fit | Function |
|-----------|-----------|-----|-----|------|--------------------|--------------|-----------------|----------|
| reservoir | LA-S<sub>res</sub> | E,  | f   | 0.278| 0.238              | < 0.001      | 41              | large    |
|           |           |     |     |      |                    |              |                 | LA-S<sub>res</sub> = 0.825*LA-EF<sub>tot</sub> + 2.633*LV-GCS + 0.250*E + 44.270 |
|           |           |     |     |      |                    |              |                 |          |
| conduit   | LA-S<sub>con</sub> | E,  | f   | 0.320| 0.267              | 0.002        | 35              | large    |
|           |           |     |     |      |                    |              |                 | LA-S<sub>con</sub> = 0.897*LA-EF<sub>tot</sub> + 1.114*LV-GCS + 0.212*E – 36.764 |
|           |           |     |     |      |                    |              |                 |          |
| conduit   | LA-S<sub>con</sub> | LA-Vol<sub>boo</sub>, | m   | 0.437| 0.395              | < 0.001      | 26              | large    |
|           |           |     |     |      |                    |              |                 | LA-S<sub>con</sub> = 0.185*LA-Vol<sub>boo</sub> + 0.931*LA-EF<sub>tot</sub> – 1.056*LV-GRS + 0.351*E - 5.403 |
|           |           |     |     |      |                    |              |                 |          |
| conduit   | LA-S<sub>con</sub> | LA-Vol<sub>boo</sub>, | m   | 0.405| 0.341              | 0.001        | 28              | large    |
|           |           |     |     |      |                    |              |                 | LA-S<sub>con</sub> = -0.004*LA-Vol<sub>boo</sub> + 0.458*LA-EF<sub>tot</sub> + 0.030*LV-GRS + 0.437*E - 21.650 |

* green = valid; orange = valid, but with fewer concerns due to the prerequisites; red = not valid due to violation of prerequisites.

number of females = 60; number of males = 46.

Interpretation of |R²| according to Cohen. [Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, N.J.: L. Erlbaum Associates. Page 412 ff].

small effect size:|R²| = 0.02; medium effect size |R²| = 0.13; large effect size |R²| = 0.26. † Sample size calculation see reference [Calculation according to Hemmerich, W. (2019). StatistikGuru: Poweranalyse und Stichprobenberechnung für Regression. Retrieved from https://statistikguru.de/rechner/poweranalyse-regression.html].

LA-S<sub>res</sub> reservoir left atrial strain; LA-S<sub>con</sub> conduit left atrial strain; LA-S<sub>boo</sub> booster left atrial strain; LA-Vol<sub>boo</sub> indexed booster left atrial volume; LA-EF<sub>total</sub> total left atrial ejection fraction; LA-EF<sub>boo</sub> booster left atrial ejection fraction; LV-GCS, global left ventricular circumferential strain; LV-GRS, global left ventricular radial strain; E, E-wave by quantitative transmitral blood flow measurements; A, A-wave by quantitative transmitral blood flow measurements; LV-ESVi<sub>i</sub> indexed left ventricular end systolic volume.
| Validity* | Parameter | Sex | $R^2$ | corr $R^2$ | ANOVA significance | Sample size† | Goodness-of-fit | Function |
|----------|-----------|-----|-------|------------|---------------------|--------------|-----------------|----------|
| booster 8 | LA-$S_{boo}$ | f   | 0.418 | 0.374 | <0.001 | 27 | large | LA-$S_{boo}$ = 0.430*LA-EF$_{boo}$ + 0.286*LV-ESV$_{i}$ + 0.116*age + 0.138*A− 11.988 |
| 8        | LA-$S_{boo}$ | m   | 0.217 | 0.139 | 0.040 | 61 | medium | LA-$S_{boo}$ = 0.209*LA-EF$_{boo}$ - 0.259*LV-ESV$_{i}$ - 0.008*age + 0.120*A + 13.311 |

* green = valid; orange = valid, but with fewer concerns due to the prerequisites; red = not valid due to violation of prerequisites.

Interpretation of $|R^2|$ according to Cohen. [Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, N.J.: L. Erlbaum Associates. Page 412 ff].

small effect size: $|R^2| = .02$; medium effect size $|R^2| = .13$; large effect size $|R^2| = .26$. † Sample size calculation see reference [Calculation according to Hemmerich, W. (2019). StatistikGuru: Poweranalyse und Stichprobenberechnung für Regression. Retrieved from https://statistikguru.de/rechner/poweranalyse-regression.html].

LA-$S_{res}$, reservoir left atrial strain; LA-$S_{con}$, conduit left atrial strain; LA-$S_{boo}$, booster left atrial strain; LA-$Vol_{boo,j}$, indexed booster left atrial volume; LA-EF$_{total,i}$, total left atrial ejection fraction; LA-EF$_{boo}$, booster left atrial ejection fraction; LV-GCS, global left ventricular circumferential strain; LV-GRS, global left ventricular radial strain; E, E-wave by quantitative transmitral blood flow measurements; A, A-wave by quantitative transmitral blood flow measurements; LV-ESV$_{i}$, indexed left ventricular end systolic volume.

count of females = 60; number of males = 46.
Intra- and interobserver variability

Intra- and interobserver variability was tested on 20 randomized subjects. All intra- and interobserver variability resulted in excellent intra-class-correlation coefficients (ICC > 0.9) and low coefficient of variation (CoV) for intra- and interobserver variability of <10%. The highest intra- and inter-observer resemblance was for reservoir strain (ICC 0.967 and 0.965), whereas the lowest intra- and inter-observer variations was for booster strain (ICC 0.941 and 0.936). The lowest bias and scatter by Bland-Altman statistics was found for the intra-observer reservoir strain, with a mean difference (95% confidence interval) of 2.0% (10. % to 14. %) whereas the greatest bias and scatter was found for the inter-observer conduit strain, with a mean difference of 6.3% (302 % to 428 %).

Discussion

This CMR-study yields normal left atrial strain and strain rate values based on a large cohort with a wide age range between 10 -70 years. Furthermore, this is the first study to provide profound insights into heart rate-associated normal values of left atrial strain and strain rate. We found that (I) subjects with a heart rate of 60 – 75 bpm do not show gender differences in strain and strain rate, (II) novel parameter clusters allow improved multiparametric characterization of strain and strain rate, (III) multiparametric analyses attained higher correlative value in the heart rate subgroup of 60 – 75 bpm, (IV) conduit strain increases with age in females and booster strain increases with age in both sexes, and (V) percentile plotting implies changes in cardiac remodeling at 40-45 years of age.

The availability of reference values and strain predictors is essential for effective cardiac evaluation and diagnostics. The need for further representative and reproducible datasets is emphasized by previous data- and trendline inconsistencies.

Influence of heart rate on left atrial strain

Although previous CMR-studies have provided age- and gender dependent strain values [12, 13], the influence of heart rate has not yet been investigated. Limiting the participant selection to a heart rate spectrum of 60 – 75 bpm resulted in the previously significant differences between the genders of all subjects in reservoir, conduit, booster strain and strain rates becoming insignificant. However, when regarding strain and strain rates of all participants, females had significantly increased strain and strain rates in all aspects except for booster strain. Apart from the conduit strain rate, no gender differences in strain or strain rate were also found in the study by Truong et al. Although their study did not selectively filter participants by heart rate, this observation can be explained given the narrow range of their participants' mean heart rate of 63 ± 10 bpm [12]. In contrast, Qu et al., presented females with increased longitudinal reservoir- and booster strain compared to males with a broadened heart rate spectrum of 69.2 ± 14.7 bpm [13]. Thus, in contrast to previous observations, the influence of gender may be secondary when considering heart rate-dependent changes in strain and strain rate.

Age- and gender related left atrial strain

Our CMR study found no difference in reservoir strain with age for both genders, which is consistent with results of Truong et al. [12]. Qu et al., however, found a decreasing reservoir strain with age for both genders [13]. Both Qu et al., and Truong et al. observed decreasing conduit function over age, which we observed only for females. It is important to note that these inconsistencies can be attributed to differences in modalities used [14] and/or software quantification techniques [1]. However, assuming that these attributions are only minor, it is possible that with increasing age alterations in cardiac fibrotic remodeling may occur [15]. Depending upon the level of left ventricular stiffness, left ventricular relaxation may be impaired [16], possibly reducing left atrial conduit strain. The onset of this cardiac remodeling could be around the ages 40 – 45 years, which could coincide with the inflection point of our percentile trend lines in both genders.
In our study, an increase in booster strain with age was observed in both genders, which is consistent with Truong et al. and Liao et al. [9, 12]. In contrast, other authors did not observe any age dependence of the booster strain [8, 13, 17]. Although we found an overall increase in booster strain, the percentiles for men and women show a plateau phase followed by a decline after the age of 45, which is more pronounced in men. A likely explanation for this development in the second half of life may be due to atrial dilation, which may expand the left atrial stroke volume beyond the Frank-Starling relationship [18, 19].

Multiple linear regression analyses

To our knowledge, we are the first to perform a comprehensive assessment of the determinants of left atrial strain using multiple linear regression. The wealth of data attained with a single cardiovascular magnetic resonance examination requires a multiparametric approach for improved diagnostic differentiation. We provide numerous moderate to high correlations between cardiac parameters and strain, which mirror the active and passive cardiac phases. Additionally, they include extracardiac factors, such as aging, in order to consider age-dependent cardiac changes. Moreover, we found that heart rate plays an important role throughout the multiparametric approach as our subgroups with selected heart rates of 60-75 bpm generally showed higher correlations between cardiac parameters and strains than the whole study cohort. As was shown, for example, in the subgroup parameters such as E-wave, left ventricular global circumferential strain and total left atrial ejection fraction demonstrated higher correlations with reservoir strain, possibly due to increased functionality of these parameters at the selected heart rates (Tables 6 and 7). A recent CMR-study used multiparametric analyses of the left ventricle to accurately differentiate diagnostically between healthy subjects, athletes, hypertensive heart disease, hypertrophic cardiomyopathy and cardiac amyloidosis [20]. We present reference clusters and their correlative value for healthy left atrial strain with subsequent heart rate-adjusted reference values. These bear promising clinical implications and remain to be assessed under disease state.

Intra- and inter-observer variation

High resemblance in intra- and inter-observer assessment reflect the reliability for left atrial strain quantification using CMR, particularly for reservoir strain. Conduit strain has been shown to be the most difficult to determine, possibly due to variations in downward sloping. These resemblances however, can be expected to improve further, as CMR and its associated software quantifications and automatic contouring continue to progress. Although comparable intra- and inter-observer variations have been presented by a recent speckle tracking echocardiographic study (STE), the far field location of the left atrium and its thin wall remain a challenge of the STE modality [8]. A further CMR study observed superior reproducibility of CMR in contrast to echocardiographic examination [12].

Limitations

This study is a single-center study. Population studies or multi-center studies are required in order to consolidate our observations and normal strain values. Furthermore, no intermodal comparison, for example comparison between echocardiographic and CMR attained values, was carried out. Furthermore, the maximum heart rate (HR) of 111 beats per minute (bpm) of a child aged 15 remained included, considering it was nervous throughout its first CMR examination, even if this value lies slightly outside the 99th percentile age corresponding heart rate [21]. Lastly, the angulation of the 2- and 4-chamber views represent a further limitation, in which variations in the maximum longitudinal axis at end-systole occur due to the convulsive movement of the heart, even after careful planning at end-diastole.

Conclusion

This CMR-study yields normal left atrial strain and strain rate values for a wide age range of healthy subjects and is the first to demonstrate the impact of the heart rate on left atrial strain. In contrast to previous observations, no strain differences
were found between the genders when limiting heart rates to 60 – 75 bpm. This indicates that the influence of gender is secondary when considering the influence of heart rate. Moreover, heart rate adapted multiparametric analyses allow for improved characterization of the complex hemodynamics that determine left atrial strain and thus offer great diagnostic potential.

**Methods**

For the purpose of this study 208 subjects were initially recruited. The local ethics committee approved the study conditions (Ethikkommission der Medizinischen Fakultät der Ruhr-Universität Bochum, Sitz Bad Oeynhausen, registration number: 2017-238). All examinations were done in accordance with the 1964 declaration of Helsinki. Prior to inclusion in the study, a written informed consent was obtained from all participants or their legal guardians in the case of participants <18 years of age.

In order to limit the study to healthy participants only, a health assessment questionnaire was carried out beforehand. Exclusion criteria entailed clinical history of cardiovascular disease and surgery, medication for cardiovascular or metabolic disorders, associated risk factors and contraindications for CMR. After all inclusion criteria were met, the CMR assessment was performed. If CMR imaging demonstrated myocardial abnormalities, aortic ectasia, pulmonary trunk dilation, valvular heart disease, ischemic heart disease, signs of cardiomyopathy the individuals would be excluded. Based on these criteria 22 volunteers were excluded. Furthermore, three subjects were rejected from the strain analysis because of insufficient image quality. The final study group thus comprised 183 healthy individuals that participated in a CMR study.

**Cardiovascular magnetic resonance imaging**

CMR Imaging was performed using a multi-transmit 3.0 Tesla magnetic resonance imaging system (Achieva, Philips Healthcare, Best, The Netherlands; Release 5.3.1 and 5.6.1, respectively) with dStream technology. All volunteers were examined in supine position. In order to enable cardiac-triggering acquisitions, a vector electrocardiogram was applied. The maximum gradient performance was 40 mT/m, slew rate = 200 mT/m/ms and signal reception was achieved using a cardiac phased-array coil. The standard examination protocol included 2-chamber and 4-chamber long-axis views, a stack of an axially acquired stack covering the whole heart as well as a short-axis stack covering the entire left and right ventricles (12-16 slices, no gap) utilizing cine steady-state free-precession acquisitions (TR/TEflip angle = 2.7 ms/1.35 ms/42°) to assess cardiac function, morphology and strain. Twenty-eight or 45 cardiac phases were collected per cardiac cycle. Assuming an averaged heart rate of 67 bpm, temporal resolution was 32 or 20 ms per cardiac phase, respectively. Spatial resolution was 1.5 x 1.5 x 8 mm³.

A conventional flow-sensitive, retrospectively triggered gradient-echo pulse sequence (TR/TEflip angle = 10ms/4.2ms/30°) was applied to quantify transmitral and right upper pulmonary venous blood flow. Through-plane blood flow measurements were performed with velocity-encoded values of 70 to 100 cm/s. A SENSE-reduction factor of 2 was applied. In order to resolve the fine structure of the pulmonary venous flow profiles in particular, a temporal resolution of 10 msecs was chosen. Therefore, the number of phases was always adjusted to the subject’s individual heart rate. Quantitative blood flow evaluation was performed offline on a computer workstation using the homemade “HDZ MR-Tools” software package (HDZ, Bad Oeynhausen, Germany).

**Strain analysis**

Longitudinal strain was expressed in negative values. Thus, when describing an "increase" or a "higher value" an increase in negativity is meant. Strain analysis was conducted using the CVI42® software package (Circle Cardiovascular Imaging Inc., Calgary, Canada, Release 5.12.1). Endocardial and epicardial contours of the left atrium in 2-chamber and 4-chamber long-axis slices were delineated manually in the end-diastolic heart frame (Figure 3) and subsequently followed by automatic registration of the applied software. The linings excluded the ostiums of the pulmonary veins as well as the left atrial
appendage. The total global longitudinal strain (GLS) as well as individual global longitudinal strain for 4-chamber and 2-
chamber were quantified. A comprehensive set of different measures was analyzed to investigate the correlations between left atrial strain/strain rate and volumetric, hemodynamic and functional parameters (Figure 4 and Supplementary Table S1). These comprise left atrial end-diastolic volume (LA-Vol$_{\text{min, i}}$), booster volume (LA-Vol$_{\text{boo, i}}$), end-systolic volume (LA-Vol$_{\text{max, i}}$) as well as the corresponding derived ejection fractions (LA-EF$_{\text{tot, i}}$, LA-EF$_{\text{con, i}}$ and LA-EF$_{\text{boo, i}}$) which were obtained by defining the endocardial contours in the axially acquired cine stack. Global left ventricular longitudinal strain (LV-GLS), global left ventricular circumferential strain (LV-GCS) and global left ventricular radial strain (LV-GRS) as well as the BSA-indexed end-diastolic left ventricular volume (LV-EDV$_i$), BSA-indexed end-systolic left ventricular volume (LV-ESV$_i$), BSA-indexed stroke volume (LV-SV$_i$) and BSA-indexed left ventricular muscle mass (MM$_i$) were estimated based on the cine short axis steady-state free-precession acquisitions. The passive early diastolic filling of the left ventricle (E-wave), the active late diastolic filling of the left ventricle (A-wave) and the diastolic transmitral flow velocity ratio E/A were obtained by quantitative transmitral blood flow measurements. The cine 4-chamber view was used to assess the early diastolic mitral annular tissue velocity é allowing the calculation of the ratio E/é. The pulmonary venous flow ratio S/D defined as the forward flow during ventricular systole (S) to the early diastole (D) was recorded to assess diastolic function.

Statistical Analysis
Statistical analysis was carried out utilizing IBM SPSS Statistics (version 26.0.0.0, IBM Deutschland GmbH). Normal distribution was tested using Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation (SD) when normally distributed, otherwise as median with interquartile range. Differences in continuous variables between baseline parameters, cardiac function and left atrial strain of men and women were evaluated using an unpaired Student’s t-test for normal distribution and the Mann-Whitney-U test for non-normal distribution. Correlations between variables were tested by bivariate linear regression analysis. The decision to use the Pearson product-moment correlation or the Spearman’s Rho correlation was made after reviewing the prerequisites for a linear regression analysis such as linearity of the data, checking for outliers via box plots and normal distribution. The relationship between two or more independent variables and a dependent variable with previously established significant correlations was determined by multilinear regression analysis. In this study, only correlations were shown after fulfilling the prerequisites for performing multilinear regression analysis including linearity, checking for outliers, independence of residuals, multicollinearity, homoscedasticity and normal distribution according to Hemmerich [22] (version 1.96). Inter-observer and intra-observer variability was tested by Bland-Altman analysis, intra-class-correlation coefficients (ICC, two-way mixed model, absolute agreement[23] and coefficients of variation (CoV). In general, a $p$ value < 0.05 was considered statistically significant. The LMS method [24] was applied for generating age-dependent and sex-specific percentile curves of left atrial strain values, using the LMS software [25] (version 2.54) for fitting.

Declarations
Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper.

Author contributions
JE drafted the manuscript and analyzed the data. HK designed the study, conducted the CMR imaging, was responsible for the statistics and revised the manuscript, MP analyzed the data. LP assisted with interpretation of data. MP, WB and LP performed a critical revision of the manuscript. All authors read and approved the final manuscript.

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**Figures**

**Figure 1**

Gender-specific percentile curves of global longitudinal left atrial strain values by CMR feature tracking for reservoir, conduit and booster cardiac phase, respectively. LA-S<sub>res</sub>, reservoir left atrial strain; LA-S<sub>con</sub>, conduit left atrial strain; LA-S<sub>boo</sub>, booster left atrial strain.

**Figure 2**

Gender-specific percentile curves of global longitudinal left atrial strain rate values by CMR feature tracking for reservoir, conduit and booster cardiac phase, respectively. LA-SR<sub>res</sub>, reservoir left atrial strain rate; LA-SR<sub>con</sub>, conduit left atrial strain rate; LA-SR<sub>boo</sub>, booster left atrial strain rate.
Figure 3

Measurement of left atrial longitudinal strain and strain rate in a 24-year-old healthy female. Upper row: Determination of left atrial chamber volumes in the reservoir, conduit and booster cardiac phase, respectively. Note: The entire axial stack of slices was used for the volume calculations. Accordingly, endocardial (red) and epicardial (green) left atrial contours are shown in the two-chamber view (middle row) and in the four-chamber view (lower row) for strain estimation in the corresponding cardiac phases. Upper right: Left atrial strain curve. Lower right: Left atrial strain rate curve.

Figure 4

Overview of measures for investigation of the correlations between left atrial strain/strain rate and volumetric, hemodynamic and functional parameters. Left atrial and left ventricular volumetric data as well as strain/strain rate values were calculated using cine cardiovascular magnetic resonance (CMR) imaging. Systolic and diastolic functional parameters were obtained applying quantitative blood flow measurements (QFlow).

LA-S\textsubscript{res}, reservoir left atrial strain; LA-S\textsubscript{con}, conduit left atrial strain; LA-S\textsubscript{boo}, booster left atrial strain; LA-SR\textsubscript{res}, reservoir left atrial strain rate; LA-SR\textsubscript{con}, conduit left atrial strain rate; LA-SR\textsubscript{boo}, booster left atrial strain rate; LA-Vol\textsubscript{max,i}, indexed maximum left atrial volume; LA-Vol\textsubscript{min,i}, indexed minimum left atrial volume; LA-Vol\textsubscript{boo,i}, indexed booster left atrial volume; LA-EF\textsubscript{total}, total left atrial ejection fraction; LA-EF\textsubscript{con}, passive left atrial ejection fraction; LA-EF\textsubscript{boo}, booster left atrial ejection fraction; LV-EDVi, indexed left ventricular end diastolic volume; LV-ESVi, indexed left ventricular end systolic volume; LV-SVi, indexed left ventricular stroke volume; LV-EF, left ventricular ejection fraction; MMi, BSA-indexed muscle-mass; LV-GLS, global left ventricular longitudinal strain; LV-GCS, global left ventricular circumferential strain; LV-GRS, global left ventricular radial strain; MAPSE, mitral annulus plain systolic excursion; TAPSE, tricuspid annulus plain systolic excursion; S/D, ratio S-wave to D-wave by quantitative right upper pulmonary vein blood flow measurements; E/A, ratio E-wave to A-wave by quantitative transmitral blood flow measurements; E, E-wave by quantitative transmitral blood flow measurements; A, A-wave by quantitative transmitral blood flow measurements; é, mean lateral and septal cine CMR velocities; E/é, ratio E-wave to é.

Supplementary Files

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