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Abstract

Objectives. Our objectives were to: 1) assess the ability of MRI phase-contrast (MRI-PC) to detect sub-clinical age-related variations of left ventricular (LV) diastolic parameters and thus to provide age-related reference ranges currently available for echocardiography but not for MRI-PC, and 2) identify independent associates of such variations. **Methods.** We studied 100 healthy volunteers (age=42±15years, 50 females) who had MRI with simultaneous blood pressure measurements. LV mass and volumes were assessed. Semi-automated analysis of MRI-PC data provided: 1) early transmitral (Ef) and atrial (Af) peak filling flow-rates (ml/s) and filling volume (FV), 2) deceleration time (DT), isovolumic relaxation time (IVRT), and 3) early myocardial longitudinal (E') peak velocity. **Results.** MRI-PC diastolic parameters were reproducible as reflected by low coefficients of variations (ranged between 0.31 to 6.26%). Peak myocardial velocity E' ($r=-0.63$, $p<0.0001$) and flow-rate parameters were strongly and independently associated to age (Ef/Af:$r=-0.63$, DT:$r=0.46$, IVRT:$r=0.44$, Ef/FV:$r=-0.55$, Af/FV:$r=0.56$, $p<0.0001$). Furthermore, LV relaxation parameters (E', DT, IVRT), were independently associated to LV remodeling (LV mass/end-diastolic volume) and myocardial wall thickness ($p<0.01$). **Conclusions.** MRI-PC age-related reference ranges of diastolic parameters are provided. Such parameters might be useful for a fast, reproducible and reliable characterization of diastolic function in patients referred for clinical MRI exam.

Key Words: Diastole, Aging, MRI, Reference Values, Left Ventricle

Key Points

- MRI age-related reference values of left ventricular diastolic parameters are provided
- MRI diastolic parameters can characterise sub-clinical age-related variations in healthy individuals
- Addition of diastolic function to cardiac MRI exams will provide complementary data that are currently neglected
- Addition of diastolic function to patients undergoing cardiac MRI could enhance its diagnostic value in cardiomyopathy and heart-failure

Abbreviations and Acronyms

LV: Left ventricular

PC: Phase contrast

MRI: Magnetic resonance imaging

E: early filling peak velocity

Ef: early filling peak flow-rate

A: atrial peak velocity

Af: atrial peak flow rate

FV: filling volume

DT: deceleration time

IVRT: isovolumic relaxation time

E': myocardial longitudinal peak velocity

BMI: Body mass index

BSA: body surface area

LVM: Left ventricular mass

ESV: end systolic volume

EDV: end-diastolic volume

WT: wall thickness

SBP: systolic blood pressure

DBP: diastolic blood pressure

Introduction

Age-related alterations of the heart include concentric left ventricular (LV) remodeling [1] along with altered diastolic function [2; 3], although ejection fraction remains frequently preserved. Indeed, previous studies indicated that an apparently preserved systolic function, as assessed by a normal ejection fraction, was found in 30 to 50% of elderly subjects with heart failure [4; 5]. Furthermore, diastolic dysfunction contributes substantially to heart failure in the elderly [6; 7]. Accordingly, an accurate longitudinal assessment of LV diastolic function could be of major usefulness in predicting heart failure onset [8]. However, distinguishing physiological from pathological variations in LV diastolic filling requires a priori knowledge on expected physiological age-related subclinical changes in asymptomatic individuals.

Doppler echocardiography is the modality of choice for the non-invasive evaluation of LV diastolic dysfunction in clinical routine, based on transmitral blood flow maximal velocities and mitral annulus longitudinal velocities. Previous echocardiographic studies demonstrated that healthy aging is associated with altered LV diastolic function as reflected by a decrease in transmitral early filling peak velocity (E) along with an increase in atrial peak velocity (A), resulting in a decrease in E/A ratio [9-13] . A decrease in mitral annular early peak velocity (E'), associated with an overall increase in filling pressures (E/E') [10; 11; 14; 15], and prolonged deceleration [11] and isovolumic relaxation [10; 16] times have also been found to be associated to healthy aging.

Recent studies demonstrated the ability of phase-contrast cardiovascular magnetic resonance (MRI-PC) to assess diastolic dysfunction[17-23], resulting in relevant findings as confirmed by a head-to-head comparison with echocardiography as a clinical reference [17; 20-22; 24]. Although MRI is an accurate non-invasive modality for the evaluation of global LV systolic function [25], as well as myocardial viability [26; 27], its routine usefulness for the

assessment of diastolic function is not established. To date, MRI-PC studies have evaluated diastolic function in small groups of healthy controls and patients with known diastolic dysfunction [20-23]. However, to the best of our knowledge, no systematic study has reported age-related variations of MRI-PC diastolic function indices and provided normal values. Accordingly, we analyzed MRI-PC data of 100 healthy volunteers, with equal distribution of males and females, to characterize age-related variations in diastolic function and to report MRI age-associated normal values.

Materials and methods

Study population

We studied 100 healthy volunteers (age=42±15years, 50 females) who underwent an MRI exam for the evaluation of LV systolic and diastolic function. Subjects were prospectively recruited by advertisement from the community to complete 5 age groups with an equal distribution of females and males. Group 1: 20 to 29 years, group 2: 30 to 39 years, group 3: 40 to 49 years, group 4: 50 to 59 years, and group 5 ≥ 60 years. The resulting population had a mixed racial background with a majority of Caucasians. All subjects were asymptomatic and had no history of cardiovascular disease, and no diabetes. Body mass index (BMI) was <30kg/m² and all subjects had a normal electrocardiogram. Subjects with cardiovascular risk factors such as hypertension, hypercholesterolemia, and smoking were excluded from this study. The study protocol was approved by the institutional review board and informed consent was obtained from all participants.

Cardiac magnetic resonance imaging

MRI was performed using a 1.5T magnet (Signa HDx, GEMS, Waukesha, WI, USA) with an 8-channel cardiac-phased array surface coil. Retrospective ECG-gated PC pulse sequences were used to acquire two series of images during two consecutive breath-holds, at the tips of

the mitral leaflets perpendicular to the transmitral inflow: 1) transmitral through-plane flow velocity (slice thickness= 8 mm, Field of view was 400-480 mm, acquisition matrix was 256x128, interpolated to 256x256 resulting in a spatial resolution of 1.56 to 1.88 mm , encoding velocity Venc=180cm/s, echo time TE=2.5-3.1ms, repetition time TR=5-7.6ms, views per segment=2; temporal resolution=10 to 15 ms after applying view sharing technique[28]), and 2) longitudinal myocardial velocity (slice thickness= 8 mm, field of view was 400-480 mm, acquisition matrix 256x128, interpolated to 256x256 resulting in a spatial resolution of 1.56 to 1.88 mm,, TE=4-5ms, TR=6.5-9.5ms, views per segment=2; temporal resolution=15 to 20ms after applying view sharing technique. The acquisition was first performed using Venc=20 cm/s, and was repeated with Venc=15 cm/s in case of noisy images). A 50% rectangular field of view centred on the mitral annulus was used to avoid wrap-around artefacts.

Prior to PC data, cine standard steady-state free precession (SSFP) sequences were acquired in long and short axis views during breath-holdings to cover the whole left heart using the following averaged scan parameters: acquisition matrix = 260×192, TR = 3.7 ms, TE = 1.5 ms, flip angle = 50°, pixel size = 0.74 mm × 0.74 mm, slice thickness = 8 mm, views per segment=12, temporal resolution was 15ms after applying a view sharing technique. SSFP cine acquisitions were analyzed using QMASS ® software (Medis, version 6, Leiden, the Netherlands), resulting in LV end-diastolic (EDV) and end-systolic (ESV) volumes, LV mass, left atrial end-diastolic and end-systolic volumes. Moreover mid-LV myocardial wall thickness was calculated on the anterior, lateral, inferior, and septal segments.

Brachial systolic (SBP) and diastolic (DBP) blood pressures were measured simultaneously to the MRI-PC acquisitions.

Automated analysis of MRI-PC data (Fig. 1)

Transmitral blood flow and myocardial MRI-PC images were analyzed by an operator blinded to clinical data using custom software [17], which was previously described and tested on controls and patients with severe aortic valve stenosis in comparison to Doppler echocardiography. Briefly, this software enables: 1) a colour-coded display of PC velocity images designed to distinguish through-plane velocities in both directions, 2) a semi-automated delineation of transmitral and aortic flows, resulting in mean velocity, maximal velocity and flow-rate curves throughout the cardiac cycle, 3) a semi-automated delineation of the myocardium, resulting in maximal myocardial longitudinal velocity curve throughout the cardiac cycle, and 4) an automated peak velocities and flow-rates detection as well as semi-automated down-slopes and up-slopes linear fitting on flow-rate curves to estimate temporal parameters (Fig. 2). For linear fitting of slopes, a manual interaction which consists in delimiting an appropriate portion of the filling flow-rate curve remained possible in case of erroneous automated fitting.

This software was used to estimate the following diastolic parameters: 1) conventional transmitral early (E) and atrial (A) peak velocities as well as transmitral early (Ef) and atrial (Af) peak flow-rates and filling volume (FV), which was estimated as the area under the transmitral flow-rate curve between the automatically detected beginning and end of filling period, 2) deceleration time (DT), isovolumic relaxation time (IVRT), and 3) myocardial longitudinal (E') peak velocity on basal lateral and septal wall. Of note, the same dataset used for transmitral flow analysis was used to extract aortic ejection flow-rate curves and thus end of ejection time, which was used for IVRT estimation.

A second operator blinded to clinical data and to measurements of the first operator also performed the analysis of MRI-PC data on a sub-group of 30 subjects, including 6 subjects randomly selected in each age group.

Statistical Analysis

Normality of continuous variables distribution was tested using Shapiro-Wilk's test. Differences across age groups were tested using a one-way ANOVA test, and a Tukey's range test was used to assess the significance of differences between all age groups (2 to 5) as compared to group 1. For all tests, p value<0.05 was considered as statistically significant.

Independent associations between age and LV diastolic parameters were performed using multivariate linear regression with adjustment for basic characteristics (gender, BMI, heart rate, SBP and DBP) as well as LV remodeling parameters and myocardial wall thickness.

The inter-observer variability was studied using the coefficient of variation defined as the standard deviation of the differences between the two series of measurements performed by the two operators, divided by the mean of the measurements. Analyses were performed using STATA 12, Statacorp LP.

Results

Baseline characteristics, pressures, as well as MRI parameters of LV function, myocardial wall thickness and left atrial volumes are summarized in table 1, for the five age groups. Pressures were significantly higher with increasing age. LV volumes were slightly lower in older subjects resulting in a moderate increase in LV ejection fraction with age. While there were no significant differences in LV mass indexed to body surface area between age groups, LV mass indexed to end-diastolic volume increased significantly with age. A mild increase in myocardial wall thickness with age was also observed. A slight increase in left atrial end-diastolic volumes with age was noted; however such trend was no longer significant when volumes were indexed to body surface area. Indeed, a significant difference was found only for comparison between group1 <30 years and group 5 ≥ 60 years.

Reproducibility of diastolic parameters measurement

For each subject, the processing time for MRI-PC data was less than 5 minutes. Diastolic indices estimation was reproducible as reflected by overall low variability averaged over the

sub-group of 30 volunteers: 0.31% for E, 0.80% for A, 0.70% for Ef, 2.70% for Af, 2.15% for FV, 3.25% for DT, 3.73% for IVRT, and 6.26% for E'.

Associations of Diastolic Function with Age

Diastolic parameters averaged for the five age groups, representing the distribution of normal LV filling MRI-PC indices over age, along with SSFP left atrial end-systolic volumes are summarized in table 2. Differences across age groups were statistically significant for all parameters and the expected trends were found. For comparisons against the group 1, differences were statistically significant for groups 3, 4 and 5 for E', E/A, Ef/Af and Af/FV. Temporal parameters (DT, IVRT) and E/E' increased with age, with a significant increase only in elderly groups, as compared to group1. Linear regression analysis of age-related variations in LV diastolic parameters is summarized in Fig. 3, while highlighting males and females. Again, the strongest correlations were obtained for E' and for the flow-rate-related Ef/Af, Ef/FV, and Af/FV ratios. Conversely to MRI-PC diastolic parameters, left atrial end-systolic volumes increased only slightly with age and when indexed to body surface area significant differences were found only between group1 < 30 years and group5 ≥60 years.

Associations with age were adjusted for basic characteristics such as gender, BMI, heart rate, SBP and DBP (Table 3-Model 2). Resulting multivariate analysis showed that all diastolic parameters were independently associated with age. In addition, gender was an independent correlate of Ef/Af, DT, Ef/FV and IVRT; and heart rate was an independent correlate of E' and Ef/Af.

Associations of Diastolic Function with LV Remodeling

MRI-PC parameters of LV relaxation such as E', DT, IVRT were significantly associated with LV remodeling index (respectively r=-0.51, r=0.49, r=0.48, all $p<0.0001$) and global mid-LV wall thickness (respectively r=-0.42, r=0.53, r=0.55, all $p<0.0001$). Multivariate

analysis (Table 3-model 3 and 4) revealed that such associations were independent of age, gender, body size and blood pressure.

Discussion

This study demonstrates that a quantitative MRI-PC method can provide consistent diastolic function parameters able to independently characterize subclinical age-related variations of diastolic function in healthy volunteers. Consequently, age-related reference ranges were provided and were shown to vary significantly across age groups, highlighting the importance of using age-adapted values as standard of reference when evaluating MRI studies. In addition, LV remodeling as well as myocardial wall thickness were found to be strong independent correlates of MRI-PC diastolic parameters related to LV and myocardial relaxation, such as E', DT, and IVRT.

First, MRI measurements of LV mass and systolic function, myocardial wall thickness and left atrial volumes obtained in our healthy volunteers were reliable, as reflected by the expected trends observed with age. Indeed, the decrease in LV volumes along with the moderate increase in LV ejection fraction with age were previously described in a large population [2]. Also, as expected, we observed a significant increase in both LV mass indexed to end-diastolic volume [2] and myocardial wall thickness [1] with age. Finally, in line with those previously presented [29] left atrial volumes indexed to body surface area did not vary with age.

Only few MRI studies, based on cine SSFP [30] or tagging [1; 16; 31; 32] data, evaluated age-related variations of diastolic function parameters. Indeed, Hollingsworth et al.[30] estimated LV early filling volume in relation to stroke volume from cine SSFP MRI data of 49 healthy subjects and showed its significant decrease with age. Moreover, studies based on MRI tagging showed a significant decrease with age in mean early diastolic strain and strain

rate [2], as well as an increase in the torsion to shortening ratio [30]. However, our study is the first to report a comprehensive evaluation of age-related variations of diastolic function parameters with corresponding reference ranges estimated by MRI-PC. MRI-PC -specific values measured with a standardized semi-automated method can be considered as a first step toward robust clinical evaluation of diastolic function using MRI. This a priori knowledge is crucial since the variety of reference ranges available in echocardiography cannot directly be transposed and used in MRI-PC studies. Indeed, differences between MRI-PC and echocardiographic diastolic parameters are expected, and previously shown in various studies [23; 33]. Such differences are mainly due to technical differences between the two modalities such as: 1) differences in temporal resolution which is lower in MRI-PC despite recent and continuing developments, 2) differences in measurement site for E', since echocardiography measurements are performed at the level of the mitral annulus while MRI-PC measurements are performed on a basal short axis slice. Also, in our study, MRI-PC data were acquired during breath-hold while echocardiography was commonly performed during free breathing, which could induce differences in heart rate and thus in the transmitral flow pattern.

Overall, the strength of univariate associations with age is comparable to those previously reported in Doppler echocardiography. Indeed, we found the known age-related decrease in E/A ratio [34; 35] as well as in maximal longitudinal myocardial diastolic velocity E' [12; 14; 15]. This latter relationship with age was equivalent to those previously reported in the echocardiographic literature. Indeed, Sun et al. [15] provided reference echocardiographic values on a group of 100 healthy volunteers aged between 18 to 76 years and showed a significant decrease in early longitudinal myocardial peak diastolic velocity (E') ($r=-0.64$, $p>0.0001$). A similar trend was reported by Yamada et al. [13] on a group of 80 healthy subjects ($r=-0.61$, $p<0.0001$). This decrease in E' with age was associated with an independent increase in LV filling pressures [36; 37], as estimated by the E/E' ratio.

Moreover, consistently with the known increase in deceleration time[38] and isovolumic relaxation time [10] with age, strong associations between MRI-PC DT as well as IVRT and age were found in our study.

Furthermore, MRI-PC parameters of LV relaxation such as E', DT, IVRT were significantly associated with LV remodeling index and global myocardial wall thickness, independent of age and basic characteristics (Table 3). Such associations were in agreement with expected age-related variations in myocardial structure, as well as LV function and hemodynamics. Indeed, age-related LV concentric remodeling and stiffness as well as increase in myocardial wall thickness [3] may result from alterations in myocardial tissue secondary to changes in myocardial extracellular matrix [39] and increased arterial afterload, and may lead to an increase in end-diastolic filling pressures [3]. The association between cardiac remodeling and diastolic function in elder subjects [3], even asymptomatic, may compromise cardiac reserve.

An original feature of the present study was that in addition to conventional velocity-based diastolic parameters, flow-related parameters (Ef/Af, Ef/FV) were extracted from MRI-PC resulting in stronger associations with age (Fig. 3). The reliability of such parameters might be due to the fact that flow-rate curves are less sensitive 1) to data noise than peak velocities, since they are estimated from averaged velocities and 2) to the slight mismatch between the acquisition plane and the true perpendicular to the transmitral flow. In addition flow-rate curves provided reliable and reproducible temporal LV filling parameters (DT, IVRT). The strong and independent associations between these latter parameters (DT, IVRT) and LV concentric remodeling confirm their relevance. Of note, the ability of flow-rate parameters to accurately detect diastolic dysfunction was demonstrated in a previous study on a group of 35 controls and 18 patients with a severe aortic valve stenosis [17].

This is to the best of our knowledge the first study to provide age-related reference ranges of MRI-PC diastolic parameters while evaluating their consistency by comparisons against LV

remodeling and myocardial wall thickness. The addition of such reproducible and fast diastolic function evaluation to routine MRI exams already including systolic function and scar assessment would enable a comprehensive evaluation with diagnostic and prognostic implications of the LV at the expense of limited additional examination time (two breath-holds).

A limitation of our study is the imbalance in subjects effectives between age groups. In particular, the number of healthy volunteers aged >70years was limited. However, it was difficult to enrol subjects without cardiovascular co-morbidities in such age range. Another limitation, inherent to MRI acquisitions, included potential phase offset errors [40], which were not corrected in the present study but were minimized using a 50% rectangular field of view centred on the mitral annulus. Alternatively, such errors could be corrected using a region of interest positioned in stationary tissue. Also, the use of through-plane MRI-PC sequences might have induced a misalignment between blood flow jet orientation and the perpendicular to the acquisition plane. Indeed, absolute measurements would be more appropriate when using 3D MRI-PC acquisitions with retrospective valve tracking that account for the real direction of the flow and mitral annulus motion [24; 33], although such techniques require further improvements in terms of temporal [33] and spatial [41] resolutions, as well as acquisition duration.

As a conclusion, MRI-PC combined with a fast and robust automated technique resulted in consistent diastolic function parameters, which were able to characterize sub-clinical age-related variations in LV diastolic function in healthy individuals. Practically, diastolic function assessment could be added to clinical routine cardiac MRI as a “one-stop shop” imaging modality for the diagnostic and prognostic evaluation of patients with heart failure and suspected cardiomyopathy.

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Figures

Fig. 1. Diagrammatic plan of MRI-PC images processing. Schematic representation of the automated segmentation of the transmitral flow from MRI-PC velocity images using connectivity based algorithm in terms of through-plane velocity sign, along with the corresponding transmitral flow curve (top). Schematic representation of the automated detection of the myocardium from MRI-PC velocity images using a clustering of time through-plane velocity profiles along with the corresponding myocardial maximal longitudinal velocity (bottom).

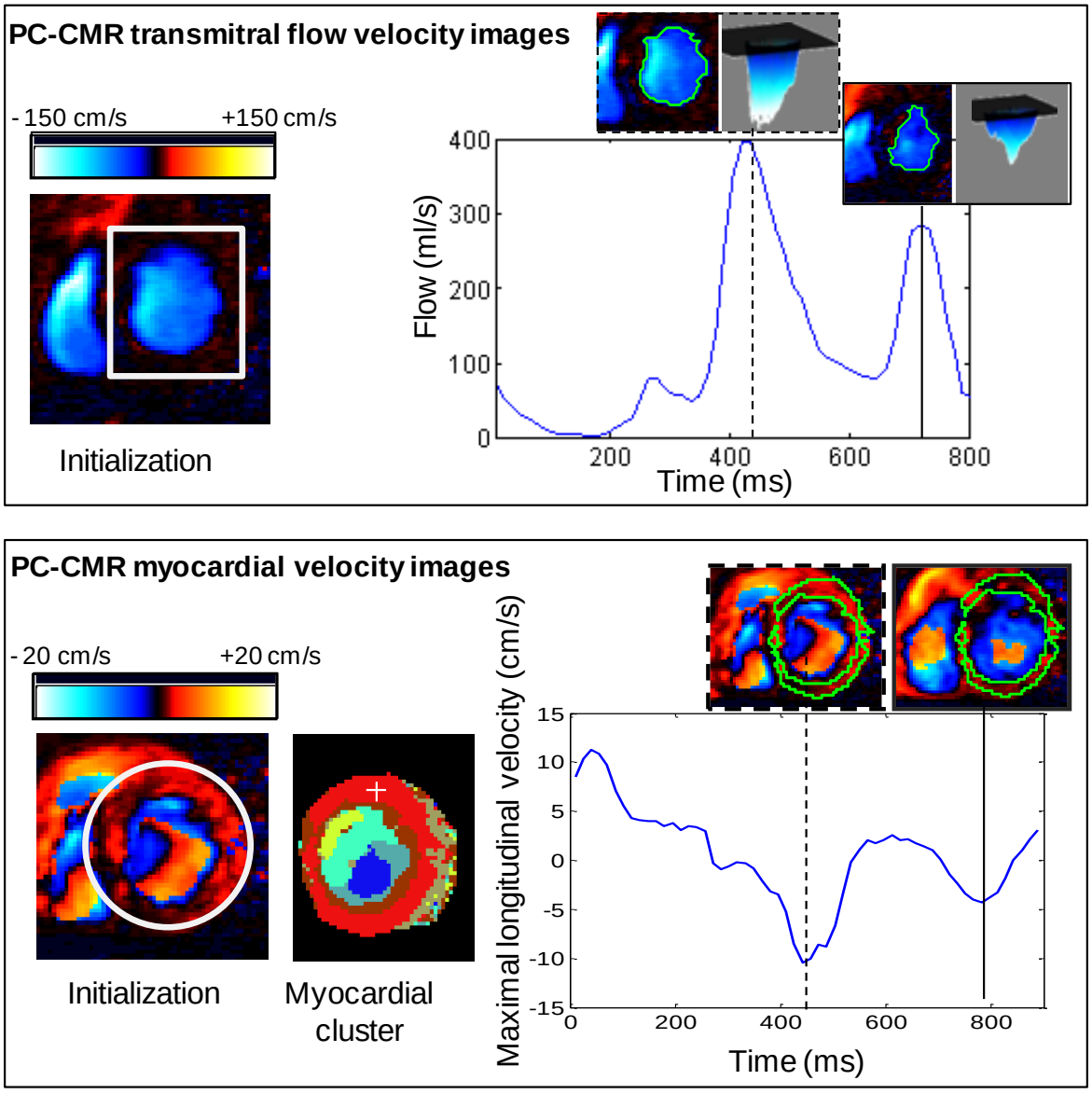


Fig. 2. MRI-PC transmitral and aortic flow-rate curves and maximal longitudinal myocardial velocities. Processes of automated peaks detection and slopes interpolations are illustrated in a young male (left) and an elderly female (right).

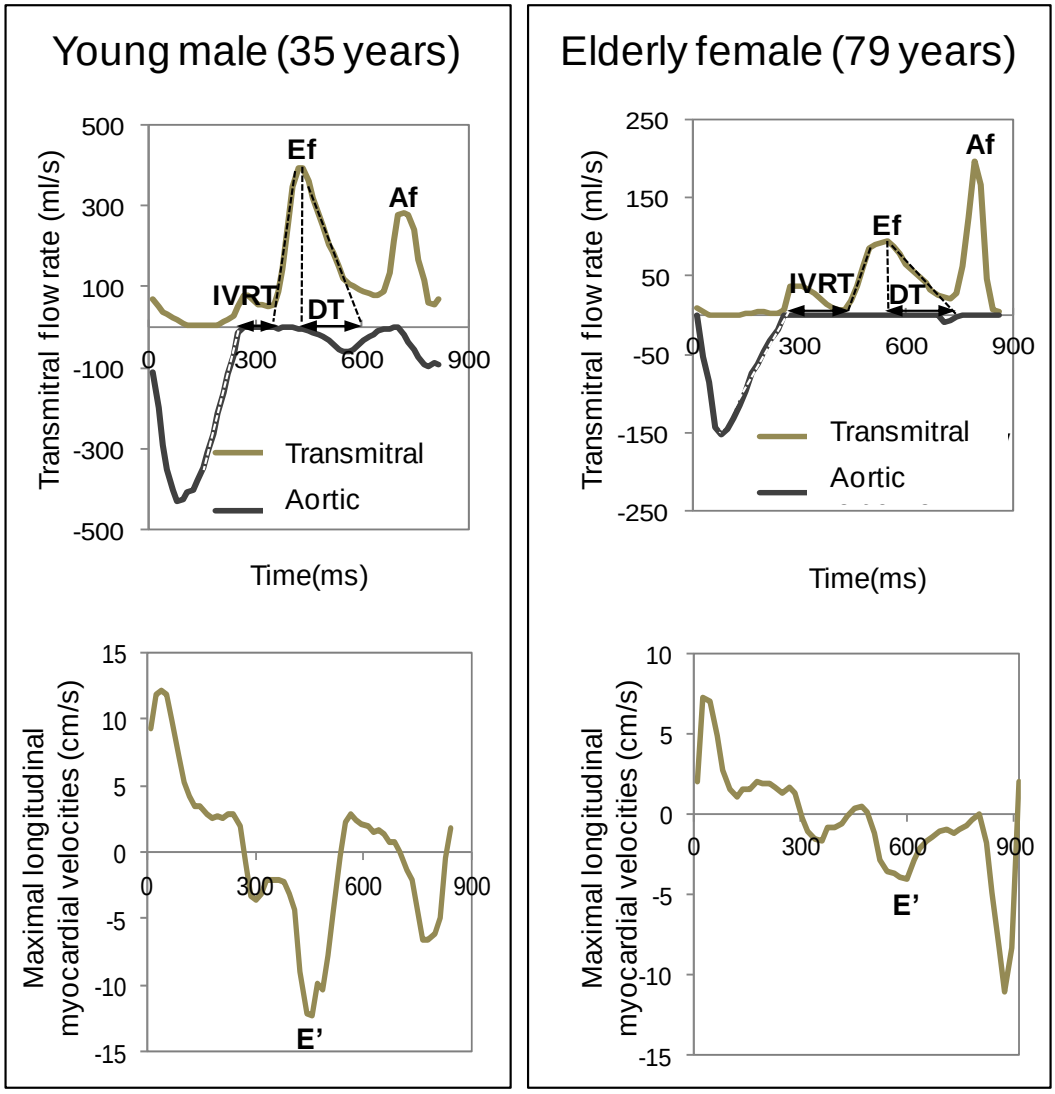
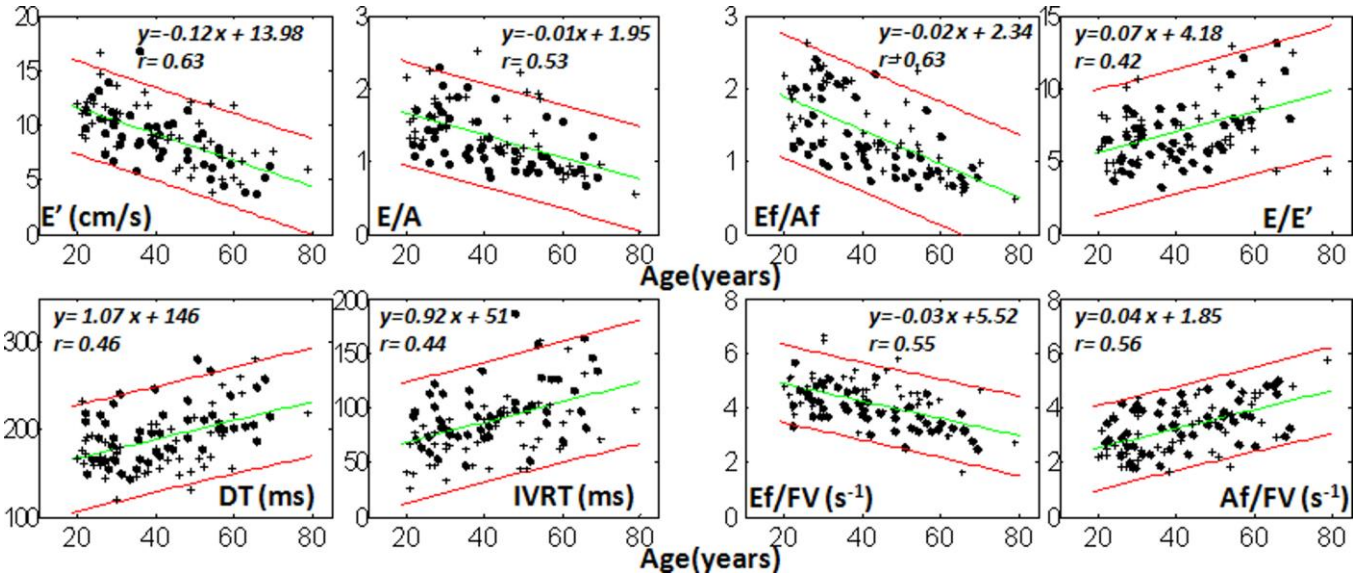


Fig. 3. Linear regressions of age-related variation of MRI-PC diastolic parameters with men represented by ● and women by +. Red lines show 95% prediction intervals.



Tables

Table 1. Baseline characteristics, LV function parameters and left atrial end-diastolic volumes for the five age groups

	20 - 29 years	30 - 39 years	40 - 49 years	50 - 59 years	≥ 60 years	Across groups p value
Subjects number	28	20	20	18	14	
Age (years)	25 ± 3	34 ± 3	44 ± 3	55 ± 3	65 ± 5	< 0.0001
Gender (Women/Men)	14/14	10/10	10/10	9/9	7/7	
Height (cm)	171 ± 7	173 ± 10	171 ± 11	172 ± 9	170 ± 10	0.95
Weight (kg)	66 ± 12	66 ± 15	72 ± 14	77 ± 16	73 ± 14	0.07
BMI (kg/m²)	23 ± 3	22 ± 3	25 ± 3	26 ± 4*	25 ± 3	0.001
Brachial SBP (mmHg)	105 ± 6	107 ± 12	110 ± 10	118 ± 13*	119 ± 15*	0.0008
Brachial DBP (mmHg)	62 ± 6	65 ± 7	71 ± 8*	75 ± 10*	74 ± 10*	< 0.0001
MRI functional parameters						
End-diastolic LV volume (ml)	141 ± 29	136 ± 23	130 ± 31	135 ± 39	130 ± 43	0.70
End-systolic LV volume (ml)	54 ± 14	51 ± 12	45 ± 12	45 ± 14	45 ± 17	0.05
Ejection fraction (%)	62 ± 5	63 ± 6	65 ± 5	67 ± 5*	66 ± 6	0.02
LV mass/ BSA (g/m²)	64 ± 11	60 ± 12	60 ± 12	68 ± 14	64 ± 12	0.21
LV mass/ End-diastolic volume (g/ml)	0.82 ± 0.13	0.80 ± 0.21	0.85 ± 0.16	0.99 ± 0.24*	0.95 ± 0.21*	0.003
Heart rate (bpm)	71 ± 11	69 ± 9	69 ± 11	67 ± 10	66 ± 13	0.54
Cardiac output (l/min)	6.2 ± 1.5	5.7 ± 1.0	5.9 ± 1.2	5.7 ± 1.4	5.6 ± 1.9	0.61
Mid-LV anterior wall thickness (mm)	6.0 ± 1.1	6.1 ± 1.1	6.7 ± 1.4	7.0 ± 1.4	6.6 ± 1.1	0.03
Mid-LV lateral wall thickness (mm)	6.8 ± 1.1	6.6 ± 1.3	6.8 ± 1.1	7.4 ± 1.3	6.9 ± 1.2	0.32
Mid-LV inferior wall thickness (mm)	6.9 ± 1.2	6.7 ± 1.1	7.3 ± 1.4	7.7 ± 1.6	7.6 ± 1.5	0.06
Mid-LV septal wall thickness (mm)	7.0 ± 1.1	7.1 ± 1.2	7.9 ± 1.6	8.2 ± 1.8*	7.8 ± 1.4	0.02
Left atrium end-diastolic volume (ml)	21 ± 6	24 ± 6	26 ± 9	26 ± 9	29 ± 10*	0.03
Left atrium end-diastolic volume/BSA (ml/m²)	12 ± 3	14 ± 4	14 ± 4	14 ± 4	16 ± 5*	0.05

Differences across groups were tested using a one-way ANOVA test and p values are provided. * means p <0.05 for comparisons against first group (20 - 29 yrs)
LV is left ventricular, BMI is body mass index, SBP and DBP are systolic and diastolic blood pressures, and BSA is body surface area

Table 2. MRI-PC diastolic function parameters and left atrial systolic volumes according to age group. Mean values along with ranges defined as mean ± 2 standard deviations are provided.

	20 - 29 years	30 - 39 years	40 - 49 years	50 - 59 years	≥ 60 years	Across groups p value
$E'_{Lateral}$ (cm/s)	11. 0 (10.1, 11.8)	10.2 (9.1, 11.4)	8.5 (7.6, 9.3)*	7.2 (6.2, 8.2)*	6.2 (4.7, 7.7)*	<0.0001
E'_{Septal} (cm/s)	9. 0 (8.1, 9.6)	8.2 (7.5, 9.0)	7.5 (6.4, 8.5)	6.6 (5.4, 7.7)*	5.9 (4.2, 7.5)*	0.0003
E (cm/s)	64 (59, 69)	64 (58, 69)	55 (50, 60)	56 (49, 63)	55 (44, 67)	0.06
A(cm/s)	42 (38, 45)	43 (39, 47)	46 (43, 50)	49 (44, 54)	62 (52, 73)*	<0.0001
E/A	1.6 (1.4, 1.7)	1.5 (1.3, 1.7)	1.2 (1.1, 1.4)*	1.2 (1.0, 1.4)*	0.92 (0.76, 1.1)*	<0.0001
Ef(ml/s)	337 (298, 376)	343 (306, 381)	292 (259, 326)	299 (246, 351)	253 (184, 322)	0.04
Ef/FV (s^{-1})	4.5 (4.3, 4.7)	4.7 (4.3, 5.1)	4.3 (3.9, 4.7)	3.9 (3.6, 4.2)*	3.1 (2.8, 3.5)*	<0.0001
Af(ml/s)	198 (171, 224)	211 (186, 236)	248 (215, 280)	279 (224,335)*	323 (241, 406)*	0.0002
Af/FV (s^{-1})	2.7 (2.4, 2.9)	2.9 (2.6, 3.3)	3.6 (3.3, 4.0)*	3.6 (3.2, 4.0)*	4.2 (3.6, 4.7)*	<0.0001
Ef/Af	1.8 (1.6, 1.9)	1.7 (1.4, 2.0)	1.2 (1.0, 1.5)*	1.1 (0.93, 1.4)*	0.78(0.66, 0.99)*	<0.0001
$E/E'_{Lateral}$	6.1 (5.5, 7.0)	6.4 (5.7, 7.2)	6.7 (5.9, 7.5)	8.1 (7.1, 9.2)*	9.5 (6.9, 12.2)*	0.0003
DT (ms)	181 (172, 191)	170 (157, 182)	185 (161, 198)	208 (190, 226)*	227 (209, 244)*	<0.0001
IVRT (ms)	75 (66, 84)	77 (66, 88)	94 (80, 108)	99 (82, 116)	108 (89, 127)*	0.002
Left atrium end-systolic volume (ml)	50 (45, 54)	54 (49, 58)	59 (52, 66)	62 (52, 71)	64 (50, 78)*	0.02
Left atrium end-systolic volume/BSA (ml/m²)	28 (26, 30)	31 (28, 34)	32 (29, 35)	32 (28, 37)	35 (28, 42)*	0.06

Data are expressed as mean values and 95% confidence intervals. Differences across groups were tested using a one-way ANOVA test and p values are provided. * means p <0.05 for comparisons against first group (20 - 29 yrs). BSA is the body surface area, E is the early filling peak velocity, Ef is the early filling peak flow-rate, A is the atrial peak velocity, Af is the atrial peak flow rate, FV is the filling volume, DT is the deceleration time, IVRT is the isovolumic relaxation time, E' is the myocardial longitudinal peak velocity.

Table 3. Multivariate analysis: correlates of diastolic function parameters

	$E'_{Lateral}$		Ef/Af		DT		Ef/FV		IVRT		$E/E'_{Lateral}$	
	β (SD)	Overall R^2	β (SD)	Overall R^2	β (SD)	Overall R^2	β (SD)	Overall R^2	β (SD)	Overall R^2	β (SD)	Overall R^2
Model 1												
Age	– 0.12 ± 0.02*	0.40 p<0.0001	– 0.02 ± 0.003*	0.39 p<0.0001	1.07± 0.21*	0.21 p<0.0001	– 0.03 ± 0.005*	0.30 p<0.0001	0.92± 0.19	0.20 p<0.0001	0.07 ± 0.02*	0.18 p<0.0001
Model 2												
Age	– 0.13 ± 0.02*		– 0.02± 0.003*		0.98 ± 0.28*		– 0.03 ± 0.006*		1.03 ± 0.25*		0.08 ± 0.02*	
Gender	– 0.48± 0.49		– 0.22 ± 0.08*		15.0 ± 6.9*		– 0.50 ± 0.16*		16.3 ± 6.2*		0.09 ± 0.52	
BMI	– 0.07 ± 0.07	0.48	– 0.02 ± 0.01	0.53	1.05 ± 1.02	0.27	0.01 ± 0.02	0.41	1.18 ± 0.91	0.32	– 0.05 ± 0.08	0.19
HR	– 0.05 ± 0.02*	p<0.0001	– 0.01 ± 0.003*	p<0.0001	0.11 ± 0.32	p<0.0001	– 0.002 ± 0.007	p<0.0001	0.05 ± 0.28	p<0.0001	0.03 ± 0.02	p=0.005
SBP	0.02 ± 0.02		0.003 ± 0.004		– 0.09 ± 0.36		0.005 ± 0.008		–0.21 ± 0.32		0.008 ± 0.03	
DBP	– 0.004 ± 0.04		– 0.003 ± 0.007		– 0.08 ± 0.51		0.01 ± 0.01		–0.36 ± 0.46		– 0.03 ± 0.04	
Model 3: Model 2 + LVM/EDV												
LVM/EDV	–3.60 ± 1.28*	0.53 p<0.0001	– 0.47 ± 0.24*	0.55 p<0.0001	63.0 ± 18.1*	0.35 p<0.0001	– 1.4 ± 0.40*	0.48 p<0.0001	47.7 ± 16.3*	0.38 p<0.0001	– 0.15 ± 1.4	0.19 p=0.01
Model 4: Model 2 + WT												
WT	– 0.55 ± 0.20*	0.52 p<0.0001	– 0.11 ± 0.05*	0.57 p<0.0001	11.3 ± 2.8*	0.38 p<0.0001	– 0.14 ± 0.07*	0.44 p<0.0001	10.1 ± 2.5*	0.42 p<0.0001	0.32 ± 0.22	0.21 p=0.005

Gender (1 for Male), BMI is body mass index, HR is heart rate, SBP and DBP are systolic and diastolic blood pressures, LVM is LV mass, EDV is end-diastolic volume, and WT is myocardial wall thickness on a mid-LV slice, Ef is the early filling peak flow-rate, Af is the atrial peak flow rate, FV is the filling volume, DT is the deceleration time, IVRT is the isovolumic relaxation time, E' is the myocardial longitudinal peak velocity. * means statistical significance (p<0.05).