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Left atrial and ventricular function during dobutamine and glycopyrrolate stress in healthy young and elderly as evaluated by cardiac magnetic resonance

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Ahtarovski KA, Iversen KK, Lønborg JT, Madsen PL, Engstrøm T, Vejlstrup N. Left atrial and ventricular function during dobutamine and glycopyrrolate stress in healthy young and elderly as evaluated by cardiac magnetic resonance. *Am J Physiol Heart Circ Physiol* 303: H1469–H1473, 2012. First published October 19, 2012; doi:10.1152/ajpheart.00365.2012.—The aim of this study is to describe phasic volume changes of the left atrium (LA) in healthy young and elderly subjects at rest and during pharmacological stress (PS). LA maximum size is related to cardiovascular mortality. LA has passive, active, and conduit function for left ventricular (LV) filling. We hypothesized that changes in LV compliance from normal aging are reflected in LA volume changes and that PS will augment these differences. We enrolled twenty young (20–30 yr) and twenty elderly (60–70 yr) healthy subjects and measured their LV and LA volumes by cardiac magnetic resonance imaging at rest and during dobutamine and glycopyrrolate stress. We identified LA minimum, maximum, and middiastolic volumes and the volume before atrial contraction. LA emptying volumes were calculated as LA passive and active emptying volumes and LA conduit volume. We also calculated LV peak filling rates (LVPFRs). Both at rest and during PS, LA maximum and minimum volumes were similar in the groups, whereas middiastolic volume was higher in the elderly. During PS, a marked decrease in LA passive emptying function and a corresponding increase in LA active emptying function were seen in the elderly but not in the young. At rest, LVPFR was lower in the elderly, and during PS this difference was augmented. The aging heart has reduced LVPFR, which is reflected in reduced LA passive and compensatory increased LA active volumetric contribution to LV stroke volume. These age-related differences are evident at rest and highly augmented during both dobutamine and glycopyrrolate stress.

inotropic stress; chronotropic stress; left atrium function; left ventricular diastolic function

THE MAXIMUM VOLUME AND FUNCTION of the left atrium (LA) is correlated with cardiovascular morbidity and mortality (2, 3, 12, 22). The LA connects the pulmonary vascular bed to the left ventricle (LV), and in LV systole it serves as a reservoir of pulmonary venous blood. In early LV diastole, the LA empties passively and serves as a conduit for blood to the LV; and in late LV diastole, during atrial systole, the LA contracts and thereby augments LV filling (5, 8). An amount of blood passes through the LA to the LV without affecting the size of the LA. This volume is known as the LA conduit volume. The LA reflects venous inflow, intrinsic atrial properties, mitral valve properties, as well as LV function. When the mitral valve opens, the diastolic pressure gradient from LA to LV rapidly equalizes, and, accordingly, increased LV diastolic pressure will over time result in an increased LA size (18, 22).

Boyd and colleagues (7, 21) showed that LA volume does not increase with normal aging, and hence LA enlargement before the eighth decade is the result of heart disease; however, a trend in the diastolic filling pattern of the LV suggested that the LV becomes less compliant with age. Age-related ultrastructural changes as well as energetic shift in the myocardium has been reported (10, 14), and the metabolic response to dobutamine has been shown to change with age (19). As suggested by mathematical models of LV relaxation, a small difference in LV relaxation can be amplified by increasing heart rate (16). The aims of this study were to determine *1*) the normal range of LA size and function in healthy young and healthy elderly subjects at rest and during pharmacological stress *2*) to determine whether LA time-volume curves could detect age related changes in LV diastolic function, and *3*) to evaluate whether chronotropic and inotropic pharmacological stress would augment differences.

METHODS

Subjects. Twenty young (20–30 yr; 10 females) and twenty elderly (60–70 yr; 10 females) were enrolled (Fig. 1). All subjects were unmedicated and free of cardiovascular, pulmonary, metabolic, or any other disease including arterial hypertension. Subjects with resting heart rate < 50 or > 75 beats/min were excluded to minimize effects of heart rate variability. Subjects gave informed oral and written consent, and the study protocol was approved by The Danish National Committee on Biomedical Research Ethics (HS: H1-2009-078).

Cardiac magnetic resonance imaging. Cardiac magnetic resonance imaging (CMRi) was performed with subjects lying supine on the back with a 1.5 Tesla magnetic resonance scanner with chest and back surface coils (MAGNETOM Avanto 1.5T, Siemens, Erlangen, Germany). Images were acquired with retrospective ECG triggering. Following piloting scans, balanced steady-state free precession end-expiratory breath hold cine images were acquired (echo time, 1.5 ms; resolution matrix, 192 × 162; field of view, 300–360 mm; phases 25; and slice thickness, 7 mm without gap) in the two-, three-, and four-chamber views followed by contiguous short-axis slices covering the entire heart (18–22 slices for full coverage). CMRi was performed at rest and then during pharmacological inotropic and lastly during pharmacological chronotropic stress.

Stress protocol. Inotropic stress was induced by intravenous infusion of dobutamine (15 $\mu g \cdot kg^{-1} \cdot min^{-1}$; Dobutrex, PharmaCoDane, Herlev, Denmark). Dobutamine infusion (10 min) ensured constant heart rate. Image acquisition was then performed with continued infusion. After termination of dobutamine infusion, the subjects rested for 20 min to ensure that the heart rate had returned to rest value and that there was no residual effect of dobutamine. Chronotropic stress was induced by an intravenous bolus injection of glycopyrrolate (4 μg/kg; Robinul, Meda, Allerød, Denmark), a quaternary atropine analog that does not pass the blood-brain barrier. As with dobutamine

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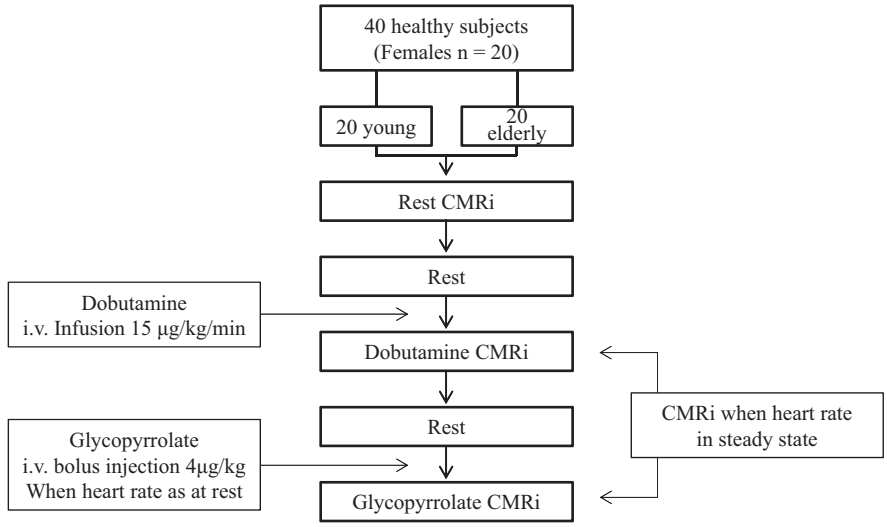

Fig. 1. Enrolled subjects' characteristics and cardiac magnetic resonance imaging protocol. CMRi, cardiac magnetic resonance imaging.

stress, image acquisition during glycopyrrolate stress was performed 10 min after administration of a bolus to ensure constant heart rate.

Image analysis. For volume measurements of the data sets, we used semiautomated dedicated software (Argus 2004, Siemens). The LV and LA volumes were measured in 25 phases covering the cardiac cycle. All measurements were performed by manually tracing endocardial borders in the short-axis view images. When measuring LA volumes, the pulmonary veins (PVs) were excluded but the atrial appendage was included (Fig. 2), and by convention the inferior LA border was defined as the plane of the mitral annulus (1, 11). We carefully distinguished the LA from the LV in three ways. First, we used long-axis view images to identify the atrioventricular plane. Second, from short-axis images we defined thin wall myocardium as LA and thick wall myocardium as LV. Finally, we distinguished LA from LV by the volume changes through the cardiac cycle, i.e., diastolic expansion of the LV and corresponding volume reduction of the LA.

LV end-systolic and -diastolic volumes were measured from short-axis view images. We measured the LV volumes in 25 phases and calculated the corresponding LV peak filling rates (LVPFRs; Δvolume/Δtime). From LV end-systolic and -diastolic volumes, we calculated LV ejection fraction (LVEF) and stroke volume (LVSV). Cardiac output (CO) was calculated as the product of heart rate and LVSV.

Assessment of size and function. From measurements of LA volumes in short-axis plane images, time-volume curves were constructed consisting of 25 volumes covering the entire heart cycle (Fig. 3). All volumes were indexed to body surface area. On the individual LA time-volume curves, specific LA volumes were determined: the minimum (LA_{min}), maximum (LA_{max}), and middiastolic (LA_{mdv}, volume after passive emptying but before middiastolic expansion) volumes, as well as the volume immediately before atrial contraction (LA_{bac}) (9). The analysis of the LA time-volume curve was also used to decipher the three volumetric contributions to LVSV; i.e., the passive, active, and conduit contribution of the LA. The following volumes were calculated: LA passive emptying volume = $LA_{max} - LA_{mdv}$; LA active emptying volume = $LA_{bac} - LA_{min}$; LA conduit volume = LVSV − (LA passive emptying volume + LA active emptying volume). From calculated volumes, the LA emptying fractions were calculated as follows: LA total emptying fraction = (LA passive emptying volume + LA active emptying volume)/LA_{max}; LA passive emptying fraction = LA passive emptying volume/LA_{max}; and LA ejection fraction (LAEF) = LA active emptying volume/LA_{bac}.

Statistical analysis. Continuous data were tested for normality using the Kolmogorov-Smirnov test and are listed as means ± SD. Data were tested using ANOVA, and a P value < 0.05 was considered statistically significant. Interobserver variability was analyzed using the Bland and Altman's method (6). For all analyses, we used SPSS software version 18 (SPSS, Chicago, IL).

RESULTS

All data are presented in Table 1, and all time-volume curves from mean values are shown in Fig. 4, *A–C*.

LA emptying volumes. Both in young and elderly LA_{max} and LA_{min} volumes decreased as heart rate increased, but there were no differences between the groups at rest or during stress. At rest, the elderly had lower LA passive emptying volume and LA conduit volume than the young, whereas the LA active emptying volume was higher. Pharmacological stress amplified these differences between the groups by lowering the passive emptying volume (dobutamine, $P < 0.001$; and glycopyrrolate, $P < 0.001$) and increasing the active emptying volume (dobutamine, $P < 0.001$; and glycopyrrolate, $P < 0.001$) in the elderly. The passive and active emptying volumes were not affected during stress in the young subjects. At rest the LA conduit volume was higher in the young. During dobutamine stress, the LA conduit volume increased in both groups but more substantially in the young. During glycopyrrolate, there was a tendency for the LA conduit volume to decrease in both groups.

LA emptying fractions. At rest, the LA_{mdv} and also the LA_{bac} were lower in the young, and hence the LA passive fraction was lower and the LAEF was higher in the elderly. Both at rest and during stress LA total emptying fraction was similar in the two groups. Pharmacological stress reduced the LA passive emptying fraction in the elderly (dobutamine, $P < 0.001$; and glycopyrrolate, $P < 0.001$), but in the young it was unchanged (dobutamine, $P = 0.15$; and glycopyrrolate, $P = 0.80$). During dobutamine stress, LAEF increased in both groups ($P < 0.001$), but glycopyrrolate stress did not change LAEF in the young group, whereas glycopyrrolate stress increased LAEF in the elderly ($P < 0.001$).

LV parameters. At rest and during stress, LVEF was higher and LVSV smaller in the elderly. At rest, LVPFRs were lower in the elderly group. During dobutamine stress, LVPFRs increased in both groups, however, much more substantially in the young (elderly, 20 ± 9%; and young, 72 ± 24%). During glycopyrrolate stress, LVPFRs increased in the young (22 ± 10%), whereas LVPFRs decreased in the elderly (−13 ± 9%).

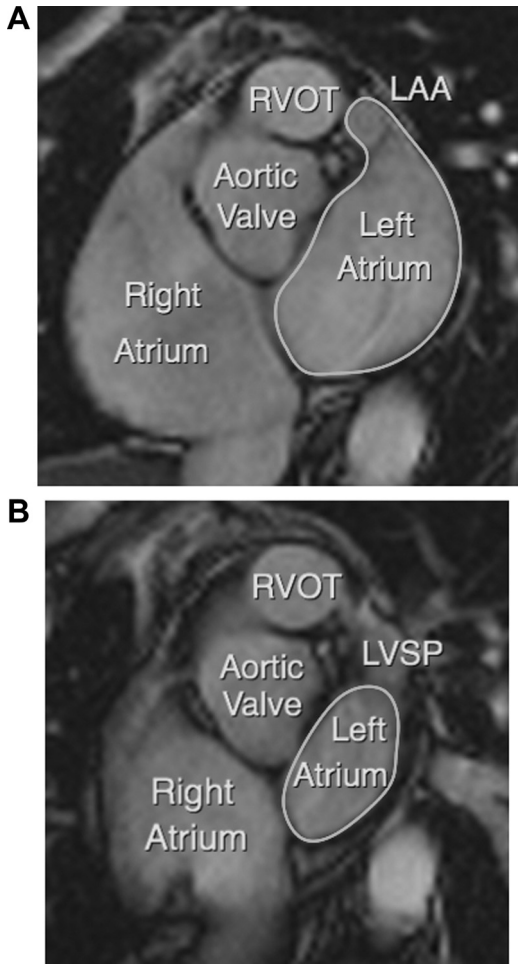

Fig. 2. Representative short-axis slices of the heart showing left atrium (LA) at left ventricular end-diastolic and end-systolic volumes. *A*: LA at left ventricular end-systolic volume. *B*: LA at left ventricular end-diastolic volume. RVOT, Right ventricle outflow tract; LAA, left atrial appendage; LSPV, left superior pulmonary vein.

Cardiac parameters. The elderly responded to pharmacological stress with lower CO during dobutamine stress (7.6 ± 1.4 vs. 6.3 ± 0.9 l/m^2, $P < 0.001$) and higher heart rate during glycopyrrolate stress (89 ± 12 vs. 99 ± 10 beats/min, $P < 0.01$) compared with the young (Table 1).

Interobserver variability. Bland-Altman plots showed no systematic bias. Bland-Altman analysis of interobserver variability for LA_{min}, LA_{max}, LA_{mdv}, and LA_{bac} demonstrated a bias (±95% limits of agreement) of 0.3 ± 3.0, 0.8 ± 5.1, 0.4 ± 1.8, and 0.9 ± 5.3 ml/m^2, respectively.

DISCUSSION

In this study, we present normal values for left atrial (LA) phasic volume changes and LVPFRs measured with CMRi for healthy young and elderly at rest and during inotropic (dobutamine) and chronotropic (glycopyrrolate) pharmacological stress. We have found that the aging heart has reduced LVPFR, which is reflected in a reduced LA passive and a compensatory increased LA active volumetric contribution to LVSV. These age-related differences are evident at rest and highly augmented during both dobutamine and glycopyrrolate stress.

The physiology of aging. Normal aging results in ultrastructural changes in the myocardium. The number of cardiac myocytes decreases and the remaining myocytes undergo a degree of hypertrophy and stretching (14). Furthermore, with aging there is an energetic shift toward a greater reliance on glucose use (10). These age-related adaptations result in reduced LV relaxation. Previous studies have demonstrated age-related deterioration in indexes representing LV diastolic properties (4, 17, 20).

The left atrium. We have found that in normal young subjects, the LA empties to a level very close to LA_{min} by passive mechanisms, but this is not the case in the elderly. Hence the LA_{mdv} is a very sensitive marker for changes in diastolic filling of the LV. Our data support previous echocardiographic findings that LA_{max} and LA_{min} are not increased with normal aging (7), but CMRi can detect discrete differences in diastolic filling of the LV between young and elderly. While the difference in LA_{mdv} was already apparent and prominent at rest, we have shown how pharmacological stress evokes very different responses in healthy elderly subjects compared with the young. With increased heart rates and COs, the elderly have compensatory changes in the LA emptying dynamics to maintain LVSV. Unlike the elderly, the young subjects had a preserved LA time-volume curve during stress. During stress, the elderly had a relatively higher LA_{mdv}, a lower passive emptying function, and therefore a compensatory higher active emptying function. LA_{max} and LA_{min} volumes were similar between young and elderly at rest and during stress, the volumes that differed in the two groups were LA_{mdv} and LA_{bac}, and both were higher in the elderly group.

After glycopyrrolate injection, heart rate increased, but there was only a modest increase in CO, the LA passive emptying volume in the young was unaffected by the tachycardia, but in the elderly the LA passive emptying volume decreased significantly. During chronotropic stress, the LA active emptying volume was unchanged in the young and, interestingly, also unchanged in the elderly, which plausibly was so due to

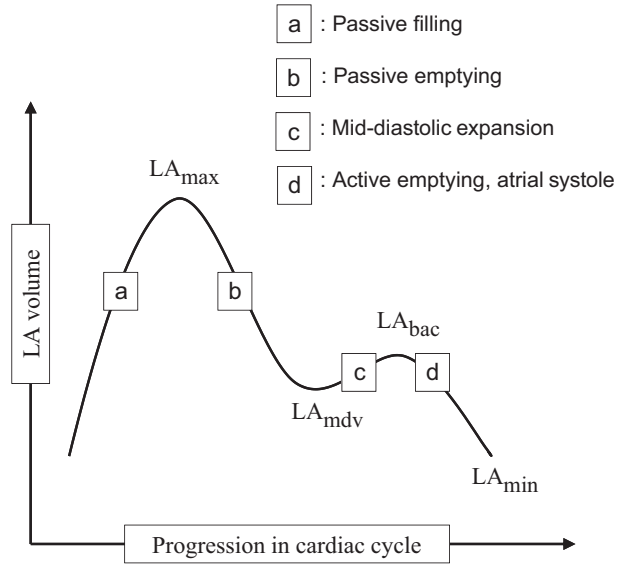

Fig. 3. The normal left atrial time-volume curve at rest. LA_{max}, LA maximum volume; LA_{mdv}, LA middiastolic volume; LA_{bac}, LA volume before atrial contraction; LA_{min}, LA minimum volume.

Table 1. *Left ventricular and left atrial parameters at rest and during dobutamine and glycopyrrolate stress*

	Rest			Dobutamine			Glycopyrrolate		
	Young	Elderly	*P*	Young	Elderly	*P*	Young	Elderly	*P*
Heart rate, beats/min	66 ± 11	71 ± 8	0.12	111 ± 20*	118 ± 13*	0.25	89 ± 12*	99 ± 10*	0.01
CI, $l \cdot min^{-1} \cdot m^{-2}$	4.0 ± 1	3.7 ± 0.8	0.22	7.6 ± 1.4*	6.3 ± 0.9*	0.001	4.7 ± 0.6*	4.3 ± 0.7*	0.05
LA volume, ml/m^2									
LA_{min}	19 ± 8	19 ± 4	0.77	12 ± 7*	13 ± 4*	0.73	15 ± 6*	17 ± 4*	0.37
LA_{max}	44 ± 9	47 ± 7	0.25	40 ± 9*	39 ± 6*	0.79	40 ± 8*	41 ± 7*	0.69
LA_{mdv}	26 ± 10	33 ± 6	0.01	22 ± 7*	31 ± 6*	<0.001	24 ± 7*	34 ± 6	<0.001
LA_{bac}	29 ± 10	34 ± 6	0.11	24 ± 9*	30 ± 6*	0.01	24 ± 8*	33 ± 6	<0.001
LA emptying volume, ml/m^2									
LA passive volume	18 ± 4	14 ± 4	0.004	18 ± 5	9 ± 4*	<0.001	16 ± 5	7 ± 4*	<0.001
LA active volume	11 ± 3	14 ± 3	0.001	11 ± 3	17 ± 5*	<0.001	9 ± 3	16 ± 5	<0.001
LA conduit volume	31 ± 11	22 ± 5	0.002	40 ± 9*	28 ± 6*	<0.001	29 ± 8*	21 ± 5	<0.001
LA emptying fractions, %									
LA total emptying fraction	59 ± 10	59 ± 5	0.85	70 ± 7*	67 ± 7*	0.21	63 ± 8*	60 ± 6	0.14
LA passive emptying fraction	42 ± 11	30 ± 7	<0.001	45 ± 8	22 ± 9*	<0.001	41 ± 11	16 ± 9*	<0.001
LA active emptying fraction	37 ± 8	43 ± 6	0.02	49 ± 9*	57 ± 9*	0.01	38 ± 11*	49 ± 11*	0.001
Left ventricular parameters									
LVSV, ml/m^2	60 ± 10	51 ± 8	0.004	69 ± 12*	55 ± 8*	<0.001	54 ± 9*	44 ± 5*	<0.001
LVEF, %	64 ± 5	68 ± 6	0.04	78 ± 6*	85 ± 3*	<0.001	60 ± 6*	68 ± 6	<0.001
LVPFR, ml/s	585 ± 62	493 ± 55	<0.001	998 ± 144*	591 ± 76*	<0.001	714 ± 138*	426 ± 56*	<0.001
ΔLVPFR, %	—	—	—	72 ± 24	20 ± 9	<0.001	22 ± 10	−13 ± 9	<0.001

Values are means ± SD; *P* value (between subject effect). CI, cardiac index; LA, left atrial; min, minimum volume; max, maximum volume; mdv, middiastolic volume; bac, before atrial contraction; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LVPFR, left ventricular peak filling rate. *$P < 0.05$ within subject effect.

smaller CO and hence less filling of the LA in late diastole compared with the LA filling during dobutamine stress with high CO.

The left ventricle. The measured LVPFRs in this study indicate that despite good systolic reserve in healthy elderly, the aging heart has a reduced capacity for fast relaxation. The differences in LVPFR between young and elderly were evident at rest and in accordance with previous reported values (13). However, differences in LVPFR were highly augmented during both dobutamine and glycopyrrolate stress. Dobutamine increases inotropy but also lusitropy of the heart. During dobutamine stress, LVPFRs increased as expected in both groups. However, the response in the young was much more prominent. During glycopyrrolate, we also observed an increase in LVPFR in the young, presumably because of tachycardia-induced increase in myocardial performance: the Bowditch staircase effect (15). Furthermore, cholinergic blockade results in a greater sympathetic effect on the heart, but as glycopyrrolate injection increased heart rate with only minor increase in CO, the LVEF and LVSV decreased. The increased LVPFR in the young, however, underlines increased myocardial performance despite reduction in systolic parameters. In contrast to the young, a reduction of LVPFR during anticholinergic tachycardia was observed in the elderly. This finding may indicate that despite the anticholinergically increased sympathetic effect and the Bowditch staircase phenomenon, these effects are blunted in the tachycardic aging heart.

Despite the nonphysiological response to pharmacological stress, it is widely used in assessment of various cardiac conditions. Our observation that the LA time-volume curve and LVPFR respond differently to increased heart rate and CO in elderly subjects is predicted in the mathematical model by Remme et al. (16), but to our knowledge this prediction has not been previously verified experimentally.

The results from this study could have potential clinical implications. Pathological LA emptying function and LV peak filling rates can be discriminated from normal physiology using the presented data. In the context of heart failure with preserved LVEF, assessment of LA function and LVPFR during

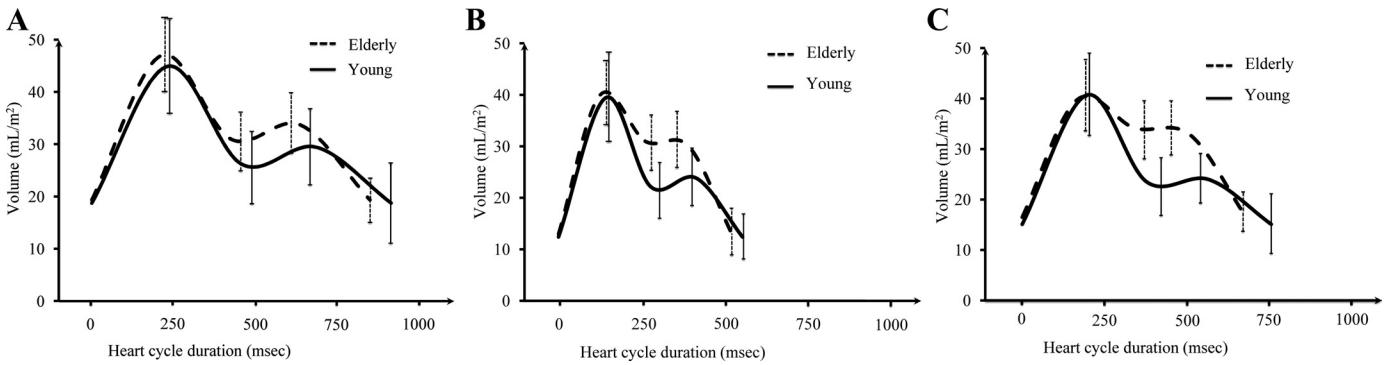

Fig. 4. Time-volume curves from mean values of the LA at rest and during dobutamine and glycopyrrolate stress. *A*: at rest. *B*: during dobutamine stress. *C*: during glycopyrrolate stress. Error bars represent SDs.

stress could importantly contribute to the evaluation of the diastolic function of the LV.

Limitations. Echocardiographic measurements of LA size and function and classic markers of LV diastolic function were not performed in the current study, and hence no comparison between the two modalities could be made. Identification of the atrioventricular plane in short-axis view images is challenging and can potentially lead to errors in measurements. Pharmacological stress is a nonphysiological stress intervention, and hence care needs to be taken when extrapolating the current results to physiological changes. Pharmacological stress is, however, a recognized method of increasing cardiac oxygen consumption and thereby revealing changes in cardiac mechanics not clearly evident at rest. In this study, we believe that both types of stress achieve this. Glycopyrrolate was used to obtain tachycardia with minimal increment in CO. However, the authors also acknowledge that anticholinergic approach to induce tachycardia in itself may alter cardiac function beyond what relates to increased heart rate and oxygen consumption. Furthermore, one could speculate that the findings in this study could be affected by differences in compliance in the LA or PVs and not merely the LV, e.g., if LA or PV is less compliant during filling, the reduced recoil of the LA or PV could partly explain the reduced passive contribution to the LV. Thomas et al. (21) showed by echocardiography that the diastolic PV flow velocity was reduced in healthy elderly $>$ 50 yr compared with a group $<$ 50 yr of age, the total volume being similar though. We did not include measures of LA or PV compliance and therefore cannot elucidate these factors. Differences in PV and LA compliance may contribute to the reduced passive blood supply to the LV observed in our study. However, we believe that in healthy subjects, the most important mechanism of diastolic filling of the LV is the capacity of the LV to relax. Furthermore, we observed a reduction in LA size during both stress interventions; hence, it is unlikely that reduced LA compliance is the cause since the LA was smaller than the putative "stretched" state at rest.

Conclusion. Cardiac MRI detects small differences in LA function and LV diastolic filling between healthy young and elderly. The differences are enhanced by increasing heart rate and CO. The LA_{mdv} is sensitive to discrete differences in LV filling unlike LA_{max} and LA_{min} volumes.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

K.A.A., K.K.I., T.E., and N.G.V. conception and design of research; K.A.A., J.T.L., and N.G.V. performed experiments; K.A.A., K.K.I., J.T.L., P.L.M., and N.G.V. analyzed data; K.A.A., K.K.I., J.T.L., P.L.M., T.E., and N.G.V. interpreted results of experiments; K.A.A. prepared figures; K.A.A. drafted manuscript; K.A.A., K.K.I., J.T.L., P.L.M., T.E., and N.G.V. edited and revised manuscript; K.A.A., K.K.I., P.L.M., T.E., and N.G.V. approved final version of manuscript.

REFERENCES

1. **Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS.** Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol* 47: 2357–2363, 2006.
2. **Beinart R, Boyko V, Schwammenthal E, Kuperstein R, Sagie A, Hod H, Matetzky S, Behar S, Eldar M, Feinberg MS.** Long-term prognostic significance of left atrial volume in acute myocardial infarction. *J Am Coll Cardiol* 44: 327–334, 2004.
3. **Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D.** Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 92: 835–841, 1995.
4. **Benjamin EJ, Levy D, Anderson KM, Wolf PA, Plehn JF, Evans JC, Comai K, Fuller DL, Sutton MS.** Determinants of Doppler indexes of left ventricular diastolic function in normal subjects (the Framingham Heart Study). *Am J Cardiol* 70: 508–515, 1992.
5. **Bjork L, Lodin H.** Angiographic determination of left atrial and left ventricular volumes in normal children and adults. *Acta Radiol Diagn (Stockh)* 3: 577–580, 1965.
6. **Bland JM, Altman DG.** Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1: 307–310, 1986.
7. **Boyd AC, Schiller NB, Leung D, Ross DL, Thomas L.** Atrial dilation and altered function are mediated by age and diastolic function but not before the eighth decade. *JACC Cardiovasc Imaging* 4: 234–242, 2011.
8. **Hitch DC, Nolan SP.** Descriptive analysis of instantaneous left atrial volume—with special reference to left atrial function. *J Surg Res* 30: 110–120, 1981.
9. **Jarvinen V, Kupari M, Hekali P, Poutanen VP.** Assessment of left atrial volumes and phasic function using cine magnetic resonance imaging in normal subjects. *Am J Cardiol* 73: 1135–1138, 1994.
10. **Kates AM, Herrero P, Dence C, Soto P, Srinivasan M, Delano DG, Ehsani A, Gropler RJ.** Impact of aging on substrate metabolism by the human heart. *J Am Coll Cardiol* 41: 293–299, 2003.
11. **Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St. John SM, Stewart W.** Recommendations for chamber quantification. *Eur J Echocardiogr* 7: 79–108, 2006.
12. **Lonborg JT, Engstrom T, Moller JE, Ahtarovski KA, Kelbaek H, Holmvang L, Jorgensen E, Helqvist S, Saunamaki K, Soholm H, Andersen M, Mathiasen AB, Kuhl JT, Clemmensen P, Kober L, Vejlstrup N.** Left atrial volume and function in patients following ST elevation myocardial infarction and the association with clinical outcome: a cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging* 2012 Jun 12. [Epub ahead of print].
13. **Maceira AM, Prasad SK, Khan M, Pennell DJ.** Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 8: 417–426, 2006.
14. **Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR, Anversa P.** Gender differences and aging: effects on the human heart. *J Am Coll Cardiol* 26: 1068–1079, 1995.
15. **Piot C, Lemaire S, Albat B, Seguin J, Nargeot J, Richard S.** High frequency-induced upregulation of human cardiac calcium currents. *Circulation* 93: 120–128, 1996.
16. **Remme EW, Opdahl A, Smiseth OA.** Mechanics of left ventricular relaxation, early diastolic lengthening, and suction investigated in a mathematical model. *Am J Physiol Heart Circ Physiol* 300: H1678–H1687, 2011.
17. **Schulman SP, Lakatta EG, Fleg JL, Lakatta L, Becker LC, Gerstenblith G.** Age-related decline in left ventricular filling at rest and exercise. *Am J Physiol Heart Circ Physiol* 263: H1932–H1938, 1992.
18. **Simek CL, Feldman MD, Haber HL, Wu CC, Jayaweera AR, Kaul S.** Relationship between left ventricular wall thickness and left atrial size: comparison with other measures of diastolic function. *J Am Soc Echocardiogr* 8: 37–47, 1995.
19. **Soto PF, Herrero P, Kates AM, Dence CS, Ehsani AA, Davila-Roman V, Schechtman KB, Gropler RJ.** Impact of aging on myocardial metabolic response to dobutamine. *Am J Physiol Heart Circ Physiol* 285: H2158–H2164, 2003.
20. **Swinne CJ, Shapiro EP, Lima SD, Fleg JL.** Age-associated changes in left ventricular diastolic performance during isometric exercise in normal subjects. *Am J Cardiol* 69: 823–826, 1992.
21. **Thomas L, Levett K, Boyd A, Leung DY, Schiller NB, Ross DL.** Changes in regional left atrial function with aging: evaluation by Doppler tissue imaging. *Eur J Echocardiogr* 4: 92–100, 2003.
22. **Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB.** Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol* 90: 1284–1289, 2002.