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Termination of dobutamine infusion causes transient rebound left heart diastolic dysfunction in healthy elderly women but not in men: a cardiac magnetic resonance study

Kiril A. Ahtarovski, Kasper K. Iversen, Jacob T. Lønborg, Per L. Madsen, Thomas Engstrøm, and Niels G. Vejlstrup

Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen University Hospital and Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

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Ahtarovski KA, Iversen KK, Lønborg JT, Madsen PL, Engstrøm T, Vejlstrup NG. Termination of dobutamine infusion causes transient rebound left heart diastolic dysfunction in healthy elderly women but not in men: a cardiac magnetic resonance study. *Am J Physiol Heart Circ Physiol* 305: H1098–H1103, 2013. First published June 25, 2013; doi:10.1152/ajpheart.00324.2013.—Men and women are known to react differently to stress. Thus, stress cardiomyopathy almost solely strikes women. Stress cardiomyopathy is suggested to relate to sex differences in catecholamine reaction. Left heart function during dobutamine stress is well described, but sex-specific inotropic and lusitropic response to abrupt termination of dobutamine stress is not. We aimed to investigate sex differences in left ventricular (LV) and atrial (LA) function during and after dobutamine stress. We enrolled 20 healthy elderly subjects (60–70 yr, 10 females) and measured their LV and LA volumes throughout the cardiac cycle by cardiac magnetic resonance imaging at rest, during dobutamine stress (15 $\mu g \cdot kg^{-1} \cdot min^{-1}$), 15 min after termination (T_{15}), and 30 min after termination (T_{30}) of dobutamine stress. We calculated LV ejection fractions, LV stroke volumes, LV peak filling rates, and LA passive, active, and conduit volumes. Sex differences were not observed at rest or during dobutamine stress. Compared with prestress values, at T_{15} a rebound decrease in LV peak filling rate was observed in women ($-22 \pm 3\%$, $P < 0.001$) but not in men. This was reflected in reduced LA passive emptying volume ($-40 \pm 3\%$, $P < 0.001$) and a corresponding increase in LA active emptying volume ($36 \pm 2\%$, $P < 0.001$). At T_{30} there were no differences between the sexes. We conclude that dobutamine causes greater stress to the female heart. This is revealed after termination of dobutamine stress where the left heart recovers in men, whereas women experience rebound LV stiffening with reduced diastolic relaxation. This is the first report of a sex-specific transient rebound phenomenon in cardiovascular response to catecholamines.

dobutamine stress; rebound effect; diastolic function; stress cMRI

A NUMBER OF SEX DIFFERENCES are noted with respect to the cardiovascular system. Women are more susceptible to developing heart failure with preserved ejection fraction (22) and suffer from greater morbidity and mortality after myocardial infarction (18). Stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy, is a syndrome characterized by severe transient systolic and diastolic impairment of the left ventricle (LV) and is seen almost exclusively in postmenopausal women (6, 11, 12, 20, 25, 26). The condition is seen after a surge of catecholamines as a result of psychological, physical, or pharmacological stress. Even though several theories behind the condition have been suggested, the mechanisms that result in Takotsubo cardiomyopathy remains to be explained.

Dobutamine is a synthetic analog of dopamine developed as an inotropic agent that is widely used for support of patients with low output states of cardiogenic decompensation (14). Dobutamine increases cardiac perfomance through a combined chronotropic, inotropic, and lusitropic action. In critical care this is supportive, however, at the expense of increased oxygen consumption. Dobutamine is also widely used in stress testing in patients with suspected coronary artery disease (19). We (3) have previously documented altered left heart diastolic function during dobutamine stress in healthy elderly vs. healthy young subjects, but no data exist about sex difference in the response to catecholaminergic stress.

Takotsubo cardiomyopathy primarily affects postmenopausal women. We aimed to investigate whether there is a sex difference in the response to catecholaminergic stress with dobutamine in healthy elderly subjects and thereby partly elucidate potential mechanisms precipitating Takotsubo cardiomyopathy.

METHODS

Subjects

Twenty elderly (60–70 yr; 10 females) were enrolled in the study (Fig. 1). All subjects were unmedicated (including hormone therapy) and free of cardiovascular, pulmonary, metabolic, or any other disease including arterial hypertension. This was ensured through screening, in the Danish national patient registries, a brief clinical examination including measurement of blood pressure and a questionnaire including questions about exercise and lifestyle. Subjects gave informed oral and written consent, and the study protocol was approved by The Danish National Committee on Biomedical Research Ethics.

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 SSFP 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, slice thickness 8 mm without gap) in the two-, three-, and four-chamber views followed by contiguous short-axis plane slices covering the entire LV (10–12 slices) and transaxial plane covering the LA (6–8 slices). cMRI was performed at rest, during dobutamine stress, 15 min after termination of dobutamine infusion, and finally 30 min after termination of dobutamine infusion.

Address for reprint requests and other correspondence: K. A. Ahtarovski, Dept. of Cardiology, The Heart Centre, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark (e-mail: kirilaleksov@live.dk).

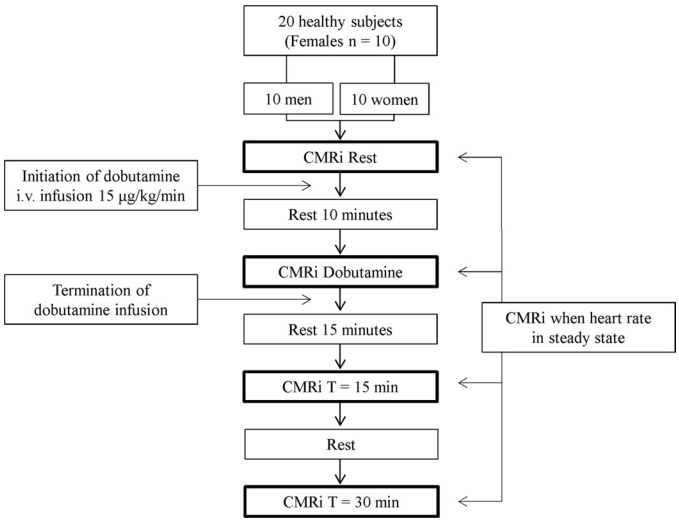

Fig. 1. Enrolled subjects and cardiac magnetic resonance imaging (cMRI) protocol. T = 15 min and T = 30 min, i.e., 15 and 30 min after termination of dobutamine infusion.

Stress Protocol

Inotropic stress was induced by intravenous infusion of dobutamine (Dobutrex; PharmaCoDane, Herlev, Denmark; 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Dobutamine dosage was determined in order to obtain an approximate doubling of cardiac output. Dobutamine infusion was infused continuously for 10 min to ensure a constant heart rate. Image acquisition was performed during continued infusion. After termination of dobutamine infusion, the subjects rested for 15 min to ensure that the heart rate had returned to rest values and that there was no residual effect of dobutamine.

Image Analysis

For volume measurements, we used dedicated semiautomated software (Argus 2004; Siemens, Erlangen, Germany). The LV and LA (left atrium) volumes were measured in 25 phases covering the cardiac cycle. All measurements were performed by manually tracing endocardial borders in the short-axis plane images for the LV and transaxial plane images for the LA. When LA volumes were measured, the pulmonary veins 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 valve annulus (1, 13). We carefully distinguished the LA from the LV in three ways. First, we used long-axis view images as references for the AV plane. Second, 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., systolic volume reduction of the LV and corresponding expansion of the LA. Measurements were made by an experienced cMRI physician blinded to the patient's sex.

Assessment of Size and Function

The left ventricle. Time-volume curves were constructed from the 25 volumes covering the entire LV in short-axis plane throughout the cardiac cycle (Fig. 3). From the LV time-volume curves, specific LV volumes were defined: LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), LV stroke volume (LVSV), and LV ejection fraction (LVEF). Furthermore, from the time volume curves, we calculated the LV diastolic peak filling rates (LVPFR; Δvolume/Δtime) and the corresponding time to peak filling rate (Fig. 3). Cardiac output (CO) was calculated as the product of heart rate and LVSV. All volumes were indexed to body surface area (BSA).

The left atrium. Time-volume curves were constructed from the 25 volumes covering the entire LA in transaxial plane throughout the cardiac cycle (Fig. 3). From the LA time-volume curves, specific LA volumes were determined: the minimum volume (LA_{min}), maximum volume (LA_{max}), mid-diastolic volume (LA_{mdv}, volume after passive emptying but before mid-diastolic expansion), and the volume immediately before atrial contraction (LA_{bac}) (10). The analysis of the LA time-volume curve was also used to decipher the three volumetric contributions to LVSV, that is, the passive, the active, and the conduit contributions to LV filling. 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

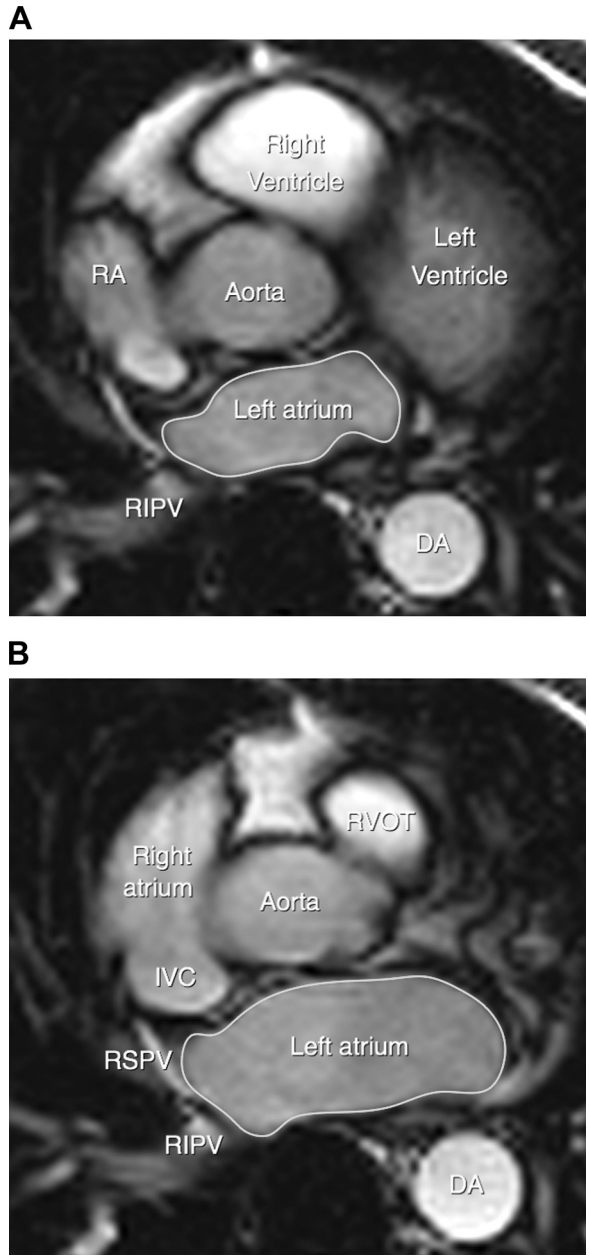

Fig. 2. Representative transaxial images of the heart showing the left atrium (LA) at LVEDV and LVESV. *A*: LA at LVEDV. *B*: LA at LVESV. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RVOT, right ventricle outflow tract; IVC, inferior vena cava; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; DA, descending aorta; RA, right atrium.

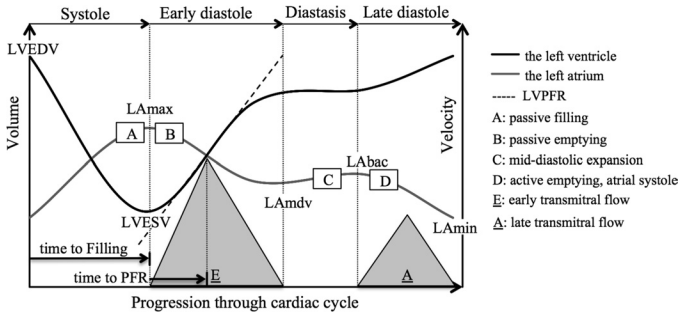

Fig. 3. Normal time-volume curve of left ventricle and left atrium at rest. LVPFR, LV peak filling rate; LA_{max}, LA maximum volume; LA_{mdv}, LA mid-diastolic volume; LA_{bac}, LA volume before atrial contraction; LA_{min}, LA minimum volume.

passive emptying volume + LA active emptying volume). All volumes were indexed to BSA.

Statistical Analysis

Continuous data were tested for normality using the Kolmogorov-Smirnov test and are listed as means ± SE. Data were tested using factorial analysis of variance (ANOVA) with Bonferroni post hoc test, and a two-sided P value < 0.05 was considered statistically significant. For all analyses we used SPSS software version 20 (SPSS, Chicago, IL).

RESULTS

All data are presented in Table 1.

The Left Ventricle

Time-volume curves with LVPFR/BSA from mean values in all states are presented in Fig. 4, *A–D*. In all states, LVEF in women tended to be larger and LVSV smaller than in men; however, the difference was not statistically significant. Furthermore, LV end-systolic wall thickness was similar between groups, and no subjects had signs of LV outflow tract obstruction. On average, LV mass was higher in men, but when normalized to BSA there was no difference between the sexes. At rest, LVPFR/BSA were equal [men, 202 ± 6 vs. women, 208 ± 6 $ml \cdot s^{-1} \cdot m^{-2}$, P = not significant (NS)], and during dobutamine stress there was a similar increase in both groups (men, 284 ± 7 *vs.* women, 285 ± 8 $ml \cdot s^{-1} \cdot m^{-2}$, P = NS). Fifteen minutes after termination of dobutamine infusion, LVPFR/BSA returned to prestress values in men, whereas a substantial rebound fall was seen in women compared with prestress values (161 ± 4 $ml \cdot s^{-1} \cdot m^{-2}$, −22 ± 3%, $P < 0.001$; men vs. women $P < 0.001$; Fig. 4*C*). Thirty minutes after termination of dobutamine infusion there were no differences in LVPFR/BSA, and both men and women had LVPFR/BSA similar to prestress values.

The Left Atrium

Time-volume curves from mean values in all states are presented in Fig. 4, *A–D*. At rest, there were no differences between the groups. During dobutamine stress, both men and women experienced a significant decrease in LA passive emptying volume ($P < 0.001$ in both groups) with a corresponding increase in the LA active emptying volume ($P < 0.001$ in both groups). During dobutamine stress, the LA conduit volume increased in both groups, however, only statistically significantly so in men ($P = 0.04$). Fifteen minutes after termination of dobutamine infusion, all LA parameters recovered to prestress values in men, but this was not the case in women. Fifteen minutes after termination of dobutamine infusion, women had a sustained decreased LA passive emptying volume (−40 ± 3%, $P < 0.001$) and an increased LA active emptying volume (36 ± 2%, $P < 0.001$) compared with

Table 1. *Left heart parameters and arterial blood pressure in all states*

	Rest			Dobutamine			15 min After Termination of Dobutamine Infusion			30 min After Termination of Dobutamine Infusion		
	Men	Women	*P*	Men	Women	*P*	Men	Women	*P*	Men	Women	*P*
Age, yr	65 ± 1	65 ± 1	NS									
BMI, kg/m^2	24.7 ± 0.4	25.3 ± 0.6	NS									
BSA, m^2	2.0 ± 0.1	1.8 ± 0.1	<0.001									
Heart rate, beats/min	68 ± 2	69 ± 2	NS	120 ± 3*	121 ± 4*	NS	75 ± 2	76 ± 2	NS	70 ± 2	72 ± 2	NS
Cardiac index, $l \cdot min^{-1} \cdot m^{-2}$	3.3 ± 0.1	3.2 ± 0.1	NS	6.6 ± 0.1*	6.5 ± 0.2*	NS	3.6 ± 0.1	3.4 ± 0.1	NS	3.4 ± 0.1	3.4 ± 0.1	NS
Systolic BP, mmHg	127 ± 3	124 ± 2	NS	159 ± 4*	158 ± 3*	NS	128 ± 2	125 ± 2	NS	127 ± 3	125 ± 2	NS
Diastolic BP, mmHg	79 ± 2	78 ± 2	NS	80 ± 1	81 ± 2	NS	80 ± 1	79 ± 1	NS	79 ± 2	80 ± 1	NS
LA emptying volumes, ml/m^2												
LA passive volume	16 ± 1	17 ± 1	NS	9 ± 1*	9 ± 1*	NS	17 ± 1	10 ± 1*	<0.001	16 ± 1	17 ± 1	NS
LA active volume	12 ± 1	12 ± 1	NS	18 ± 1*	18 ± 1*	NS	12 ± 1	18 ± 1*	<0.001	12 ± 1	12 ± 1	NS
LA conduit volume	21 ± 1	19 ± 1	NS	28 ± 1*	24 ± 1	NS	21 ± 2	19 ± 2	NS	20 ± 1	19 ± 1	NS
LV parameters												
LV mass, g/m^2	54 ± 2	50 ± 2	NS									
LV stroke volume, ml/m^2	49 ± 1	48 ± 1	NS	55 ± 2	54 ± 1	NS	50 ± 2	47 ± 1	NS	49 ± 2	47 ± 1	NS
LV ejection fraction, %	64 ± 2	68 ± 1	NS	82 ± 1*	87 ± 1*	NS	65 ± 2	68 ± 1	NS	64 ± 2	68 ± 1	NS
LVPFR/BSA, $ml \cdot s^{-1} \cdot m^{-2}$	202 ± 6	208 ± 6	NS	284 ± 7*	285 ± 8*	NS	206 ± 6	161 ± 4*	<0.001	203 ± 4	210 ± 5	NS
ΔLVPFR/BSA, %				28 ± 2*	27 ± 3*	NS	2 ± 1	−22 ± 3*	<0.001	1 ± 1	1 ± 1	NS
nLVPFR, LVEDV/s	5.4 ± 0.2	5.3 ± 0.2	NS	8.5 ± 0.3*	8.7 ± 0.4*	NS	5.4 ± 0.2*	4.3 ± 0.2*	0.01	5.3 ± 0.1	5.4 ± 0.2	NS
Time to LVPFR, ms	159 ± 4	161 ± 4	NS	101 ± 3*	105 ± 4*	NS	127 ± 4*	148 ± 5	0.004	160 ± 4	162 ± 4	NS

Values are means ± SE. *P*, between-subject effect; NS, not significant; BMI, body mass index; LA,: left atrial; LV, left ventricular; LVPFR/BSA, LV peak filling rate normalized to body surface area (BSA); nLVPFR, LV peak filling rate normalized to LV end-diastolic volume (EDV). *$P < 0.05$, within-subject effect.

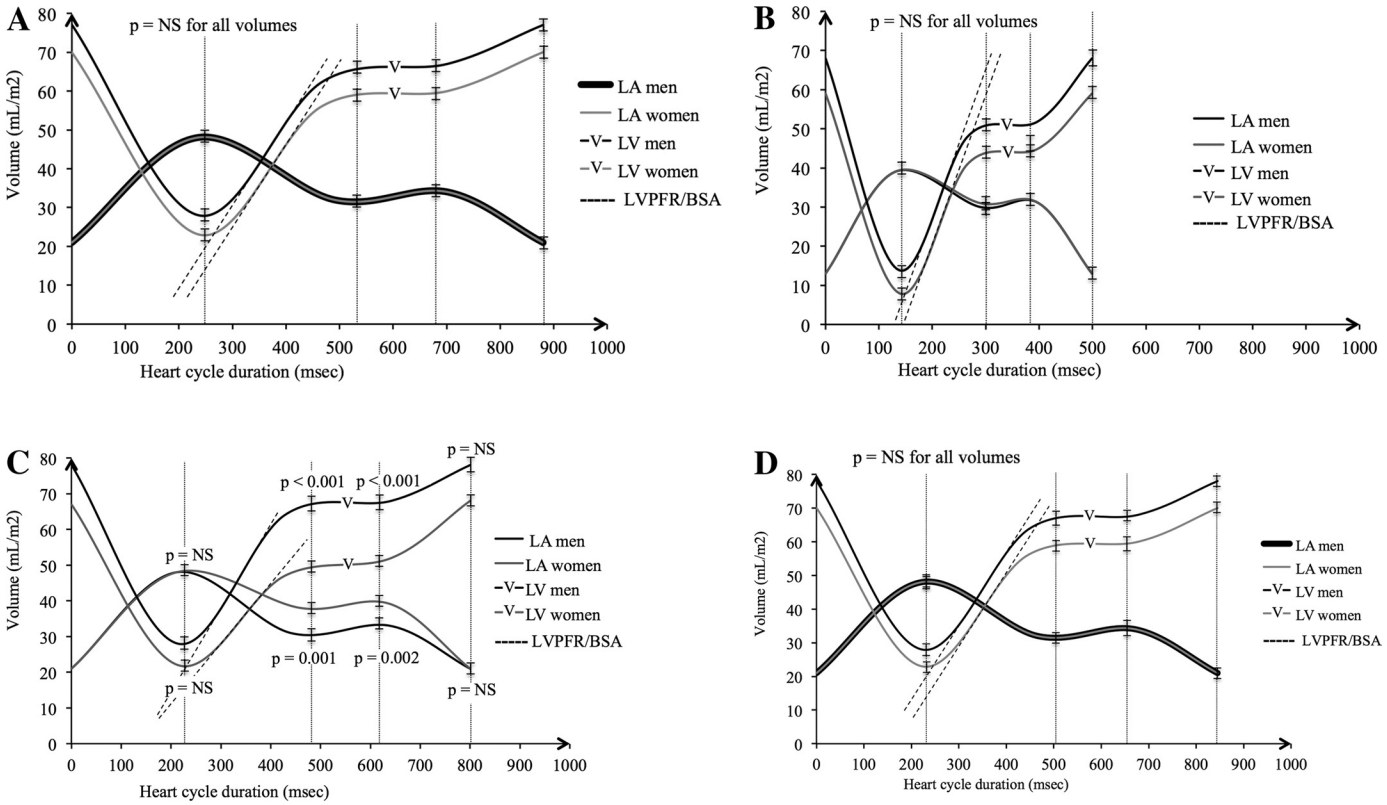

Fig. 4. Time-volume curves from mean values of LV and LA at rest (*A*), during dobutamine infusion (*B*), and 15 min (*C*) and 30 min (*D*) after termination of dobutamine infusion. Error bars represent SE.

prestress values (men vs. women, $P < 0.001$). Thirty minutes after dobutamine infusion, all LA parameters had normalized to prestress values in both groups.

DISCUSSION

To our knowledge, this is the first study to demonstrate a sex-specific difference in the LV response to catecholaminergic stress. The key finding in this study is that after termination of dobutamine infusion healthy elderly females experience a transient suppression in diastolic LV function. This is evident by a reduced LVPFR and an altered LA emptying pattern compared with healthy elderly men.

Sex Differences at Rest

Left heart chambers were larger in men; however, normalized to BSA there were no differences between the sexes. Others have found LVEF to be slightly higher in women (9, 21), and we also observed a trend of LVEF being marginally higher in the women; however, this was not statistically significant but in line with findings by Maceira et al. (15).

The Left Ventricle

In this study, we measured diastolic and systolic LV function at rest and during dobutamine stress, and, in accord with previous reports (15), we demonstrate that, despite good systolic reserve in healthy elderly, the aging heart has a reduced capacity for fast relaxation (3). During dobutamine stress, LVEF and LVPFR increased in both groups, demonstrating increased cardiac performance through both inotropy and lusitropy. Neither at rest nor during dobutamine stress did we observe differences in the LV parameters between the groups. However, as a new observation, we report that 15 min after termination of dobutamine infusion the LVPFR in the women did not return to prestress values as observed in men, but LVPFR decreased to a level significantly below prestress values. This demonstrates a distinct, late, adverse effect of dobutamine on LV diastolic function only seen in women.

The Left Atrium

Previously, we showed how minor differences in LV diastolic function are reflected in the LA emptying pattern (3). During dobutamine stress, we observed a substantial decrease in LA passive emptying volume and a corresponding compensatory increase in LA active emptying volume in both groups compared with rest, which is in line with our previous report. Fifteen minutes after termination of dobutamine infusion, the women had a sustained altered LA emptying pattern, suggesting compromised diastolic function. Fifteen minutes after termination of dobutamine infusion, the LA emptying volumes in the women were almost as affected as during dobutamine stress. Not until 30 min after termination of dobutamine infusion did the LA parameters recover to prestress values in the women. This is contrasted by the early recovery of the LA emptying pattern 15 min after termination of dobutamine infusion seen in men.

By extending the study 30 min after termination of dobutamine infusion, we found a transitory adverse effect on LV filling seen only in women. The reduced diastolic function was seen as a significant decrease in LVPFR and altered LA

emptying pattern. Dobutamine increased LVPFR with 27 ± 3% in both men and women, but with abrupt termination of dobutamine infusion women experienced a pronounced transitory rebound decrease in LVPFR (−22 ± 3%) below prestress values. No rebound effect was seen in men, who after 15 min had normalized LVPFR to prestress values. One could speculate that the findings were due to dobutamine-related reduced preload in women; however, dobutamine has a half-life of 2.4 min and was expected to have been cleared from the blood before image acquisition 15 min after termination of infusion. Furthermore, there were no group differences in the LVEDV in any state (Fig. 4), also suggesting similar preloads. Altered pressures and filling in the LA could also be a plausible explanation of the findings, but in healthy subjects the major determinant of LA emptying dynamics is the relaxational properties of the LV. Therefore the transient rebound decreased LVPFR seen in women 15 min after termination of dobutamine infusion most likely represents a degree of myocardial stiffening.

Perspectives and Clinical Implications

There are several reports of Takotsubo cardiomyopathies in postmenopausal females precipitated by dobutamine infusion (2, 4, 7, 17), supporting the suggestion that women respond differently to dobutamine than men. The striking predominance of women with Takotsubo cardiomyopathy indicates a biological susceptibility to stress-related cardiac dysfunction. The mechanism underlying the association between excess catecholaminergic stimulation and myocardial stunning as seen in Takotsubo cardiomyopathy is unknown. Explanations may involve epicardial coronary spasm (12), microcirculatory dysfunction (8, 23), calcium overload (5, 16), or myocardial lipotoxycity (24). We suggest that delayed recovery of LV diastolic function after prolonged stress may be a contributing factor; as well, this would challenge the overall cardiac efficiency. However, whether this observed sex-related difference translates into a clinically relevant difference needs to be proved.

We have in this study found that normal, healthy, elderly women show a profoundly different postinfusion cardiac response to dobutamine compared with men. The normal dose of dobutamine used in the intensive care setting ranges from 2.5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. However, it is sometimes necessary to use a higher dose to achieve an adequate hemodynamic effect. After termination of higher-dose dobutamine infusion one can expect a lingering effect on LV diastolic function in elderly women, and proper weaning off the drug should be considered.

Limitations

The duration of dobutamine infusion in this study was short. It would be of interest to see the cardiac effects on long-term dobutamine infusion as in the setting of intensive care. This study may only weakly resemble the sudden supraphysiological catecholamine surge precipitating Takotsubo cardiomyopathy, and we can only extrapolate from dobutamine's effect on LV function seen in this study. The data do not give an answer on whether the findings relate to sex differences directly to dobutamine, or solely that the female heart has prolonged recovery to stress in a broader sense. We did not measure dobutamine clearance in the subjects; therefore, one should be careful extrapolating the current results to physiological changes. Since dobutamine half-life is ~2.4 min, it is reasonable to presume that there was no residual dobutamine effect 15 min after termination. cMRI earlier than 15 min after termination could potentially give a more distinct description of diastolic recovery between the sexes. In fact, there is a risk that a similar diastolic "dip" in men could have been missed as a result of the chosen cMRI time point (T15). However, the current study design had the purpose of assessing cardiac function when dobutamine was cleared (concentration was <1% of the initial concentration; $T_{1/2}$ 2.4 min). The authors acknowledge the small study population. A larger sample could make the results more broadly applicable and reduce the risk of type II errors. Further studies of the pathophysiology with higher catecholamine levels, longer stimulation, and more subjects would be of great interest.

Conclusion

Dobutamine infusion causes greater stress to the aging female heart. This is revealed with abrupt termination of dobutamine infusion where the left heart recovers fast in men but women experience a transient rebound stiffening of the left ventricle with reduced diastolic relaxation. This is the first report of a sex-specific cardiovascular response to catecholamines, and it renders some support to the hypothesis that catecholamine stimulation is a key player in the development of Takotsubo cardiomyopathy, which mainly affects women.

GRANTS

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: K.A.A., K.K.I., P.L.M., 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. and K.K.I. 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., J.T.L., P.L.M., T.E., and N.G.V. approved final version of manuscript.

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