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Gender specific differences in functional capacity in asymptomatic patients with severe aortic stenosis

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SOUHRN

Ženské pohlaví je spojováno se zvýšeným rizikem nežádoucích příhod po chirurgické náhradě aortální chlopně, avšak s lepším výsledným stavem po katetrizační implantaci aortální chlopně (TAVI). Méně se toho již ví o rozdílech mezi pohlavími ve funkční kapacitě s těžkou aortální stenózou (AS). Cílem naší studie bylo zjistit, zda existuje rozdíl mezi pohlavími ve funkční kapacitě u skupiny asymptomatických pacientů s těžkou AS.
Metoda: Asymptomatičtí pacienti s těžkou AS byli zařazováni prospektivně a absolvovali kardiopulmonální zátěžové vyšetření (cardiopulmonary exercise testing, CPET) na bicyklovém ergometru (pacient v poloze na zádech, protokol RAMP, 15 W/min). Pacienti s prokázanou ischemií byli ze studie vyřazeni.
Výsledky: Do studie bylo zařazeno celkem 139 pacientů, z toho 61 žen. Při vstupním vyšetření nebyly mezi pohlavími nalezeny žádné rozdíly ve věku (66,11 vs. 64,8 roku; p = ns), echokardiografickými parametry závažnosti AS (V_{max} 4,53 vs. 4,53 m/s ani P_{mean} 52,27 vs. 53,42 mm Hg, vše p = ns), až na hodnoty AVA (0,75 ± 0,1 vs. 0,63 ± 0,17), EF LK (68,7 vs. 71,6 %), E/e' (12,6 vs. 14,3) a BNP (92,5 vs. 103 pg/ml), vše p = ns. Ženy měly vyšší hodnoty BMI (29,5 vs. 27,3; p = 0,018), nižší VO_{2max} (13,10 vs. 17,6 ml/kg/m^2; p = 0,001) a vyšší VE/VCO_2 slope (33,69 vs. 28,87; p = 0,004). K určení vztahu mezi klinickými a echokardiografickými charakteristikami s VO_{2max} byly provedeny univariační/multivariační lineární regresní analýzy. Proměnnými nezávisle spojenými s VO_{2max} byly ženské pohlaví (beta = –0,365; p = 0,002), V_{max} (beta = –0,341; p = 0,004), věk (beta = –0,239; p = 0,035) a BMI (beta = –0,246; p = 0,028)
Závěr: Ženské pohlaví je nejsilnější nezávislý prediktor snížené funkční kapacity, a to i po adjustaci na ostatní proměnné včetně BMI a echokardiografických markerů závažnosti AS. Ke zjištění, zda výše uvedená fakta nějak ovlivňují výsledný stav pacienta po onemocnění, je třeba provést další studie.

ABSTRACT

Female gender has been linked to increased risk of adverse events after surgical aortic valve replacement but with better outcome after TAVI. Less is known regarding functional capacity between the genders with severe AS. We investigated whether there is a gender difference in functional capacity in asymptomatic group of patients with severe AS.
Method: Asymptomatic patients with severe AS were prospectively enrolled and underwent cardiopulmonary exercise testing (CPET) on supine ergobicycle, ramp protocol, 15 W/min. Patients with test positive for ischemia were excluded.
Results: There were 139 patients, 61 women. There were no baseline gender differences in age (66.11 vs 64.8, p = ns), echo parameters of AS severity (V_{max} 4.53 vs 4.53 m/s, and P_{mean} 52.27 vs 53.42 mmHg, all p = ns) except AVA (0.75 ± 0.1 vs 0.63 ± 0.17), LVEF (68.7 vs 71.6%), E/e' (12.6 vs 14.3) and BNP (92.5 vs 103 pg/ml), all p = ns. Women had higher body mass index (29.5 vs 27.3, p = 0.018), lower VO_{2max} (13.10 vs 17.6 ml/kg/m^2,

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$p = 0.001$) and higher VE/VCO_2 slope (33.69 vs 28.87, $p = 0.004$). Univariable/multivariable linear regression analyses were used to test the relation between clinical and echocardiographic characteristics with VO_{2max}. The variables independently associated with the VO_{2max} were female gender (beta = –0.365, $p = 0.002$), V_{max} (beta= –0.341, $p = 0.004$), age (beta = –0.239, $p = 0.035$) and BMI (beta = –0.246, $p = 0.028$)

Conclusion: Female gender is the strongest independent predictor of decreased functional capacity, even when adjusting for other variables, including BMI and echo markers of AS severity. Further studies are needed to determine whether this finding affects the outcome of the disease

Keywords:
Aortic stenosis
Asymptomatic
Functional capacity
Gender

Introduction

Risk stratification and treatment decisions in asymptomatic patients with isolated severe aortic stenosis (AS) are still a matter of debate and are addressed in ongoing randomized trials.[1–3] The prognosis of asymptomatic patients with AS is mainly defined by the severity of AS, left ventricular (LV) global systolic function and hemodynamic burden. However, pathophysiological response of the LV to chronic pressure overload in AS may be gender dependent. Female gender has been linked to increased risk of adverse events after surgical aortic valve replacement as compared to males (SAVR)[4] but with better outcome after transcatheter aortic valve implantation (TAVI).[5,6] Yet, less is known regarding difference in functional status between the men and women with severe AS. If the difference in LV pathophysiological adaptive response affects the onset of symptoms and timing of optimal intervention, than the objective indicators of the functional status of patients could be different between sexes with similar AS severity. So far, objective measures directly comparing cardiopulmonary exercise parameters in women vs men with severe AS is lacking. Cardiopulmonary exercise testing (CPET) is appropriate to be used as an objective tool for assessment of functional status and exercise tolerance[7] in patients with AS.

Therefore, we aim to investigate whether there is a gender difference in functional capacity, assessed through CPET, in asymptomatic group of patients with isolated severe AS.

Method

We have analyzed patients with asymptomatic severe AS (V_{max} > 4m/s, $P_{max} \geq 40$ mmHg, AVA < 1 cm^2) from the cohort screened for AVATAR trial eligibility (NCT02436655). Asymptomatic status was confirmed during exercise testing in each patient. AVATAR is a randomized trial designed to evaluate elective/early SAVR vs watchful waiting strategy in asymptomatic patients with severe AS; details of the trial have been previously given.[8] Blood sampling was performed at rest, before CPET.

The AVATAR trial has been approved by local ethical committees. All patients within this study have been screened for AVATAR trial participation and have given the informed consent.

Echocardiography

The diagnosis of severe AS was established according to standard echocardiography criteria.[9] All echocardiographic examinations were performed by two expert operators. Multiple views were recorded including parasternal long and short axis (basal, mid, apical), apical 2-, 3-, and 4-chamber and the subcostal view. LV internal dimension, posterior wall thickness, and interventricular septum thickness were measured at end-diastole, at a level immediately apical to the mitral valve leaflet tips, in two-dimensional parasternal long-axis view. The LV mass was calculated using the corrected formula of the American Society of Echocardiography and was indexed for body surface area.[10] AS was graded using the continuity equation[9] calculated as moderate aortic valve area (AVA; from 1.0 to 1.5 cm^2) or severe (AVA ≤1.0 cm^2). The subaortic diameter was measured from inner edge to inner edge at the level of the base of the aortic cusps in a parasternal long-axis frame frozen in mid systole. Pulsed-Doppler recordings were made in apical five-chamber view with the sample volume moved axially from the aortic annulus, 0.5–1 cm below the valve, recording V_{max} and velocity-time integral. Continuous wave recordings were made from all available transducer windows to obtain the Doppler signal most parallel with the direction of the stenotic jet flow, which provided the highest velocity recording. Continuous-wave signal was traced to obtain peak velocity, velocity-time integral, and peak and mean pressure difference. All acquired images were stored digitally for off-line analysis. The average of at least three cardiac cycles was computed for each measurement.

Cardiopulmonary exercise testing

The CPET analysis was done on semi-supine ergo-bicycle (Schiller CS 200, Germany) with Ramp 15 protocol (R15). First 3 minutes of pedaling were without workload. After that, there was incremental increase in workload, 15 W for every minute. During CPET special attention was paid on AS symptom onset. Test was stopped if emergence of symptoms was observed. Patients were encouraged to exercise as much as possible. During CPET, patients undergo 12 lead ECG monitoring, and blood pressure measurement every 3 minutes during exercise, at peak effort, and 3 minutes later during recovery. The criteria for interrupting test were severe chest pain, dizziness/syncope, ST-segment shift ≥2 mm (at least 0.08 seconds after J point) diagnostic for ischemia in the setting of LV hypertrophy, extreme dyspnea/fatigue, excessive increase (systolic blood pressure >240 mmHg, diastolic blood pressure >120 mmHg), or drop in blood pressure (≥20 mmHg).

Expiratory gases were collected on a breath-by-breath basis and analyzed by metabolic cart (Schiller CS 200, Germany). Ventilatory anaerobic threshold (VAT) was determined by the 'V-slope' analysis on oxygen consumption (VO_2) vs. carbon dioxide production (VCO_2). The values of VO_2 at VAT and at peak exercise (peak VO_2) are expressed as ml O_2/kg/min during the 30 seconds in which the examined event occurred and printed using rolling averages every 10 seconds. Ventilatory efficiency/VCO_2 slope was measured by excluding data points after the onset of maximal hyperventilation at the maximal effort. The respiratory exchange ratio 1.10 at the end of the CPET test was considered as the achievement of the maximal effort.

Results

Data were analyzed in 139 patients, 61 women and 78 men. The most frequent form of AS was degenerative AS (80.5%, while 15.6% had bicuspid AS) and the most frequent comorbidity associated with AS was hypertension (90.9%), while 20.7% had diabetes mellitus. Mean age was 66.73±10.32, mean gradient was 52.75±12.23 mmHg,[2] mean AVA was 0.69±0.17 cm^2, while mean LVEF was 69.25±7.16%. There were no baseline gender differences in age, LVEF, brain natriuretic peptide (BNP), and in most echo parameters of AS severity except of aortic valve area (AVA) (Table 1). Females had higher body mass index, lower maximal oxygen consumption (VO_{2max}), lower O_2 pulse, higher VE/VCO_2 slope, worse relationship between O_2 consumption and workload and also achieved significantly lower workload during testing while reached similar maximal heart rate (Table 2). Univariable and multivariable linear regression analysis were used to test the relation between various clinical and echocardiographic characteristics with VO_{2max} (Tables 3 and 4). The variables independently associated with the VO_{2max} were female (beta = –0.365, p = 0.002), V_{max} (beta = –0.341, p = 0.004), age (beta = –0.239, p = 0.035) and BMI (beta = –0.246, p = 0.028) (Table 4).

Statistical analysis

The normality assumption for continuous variables was evaluated by the Kolmogorov–Smirnov test. Normally distributed variables are presented with mean ± standard deviation, and variables that did not show a normal distribution are presented as the median value and interquartile range. Categorical variables are reported as counts with percentages. Continuous variables were compared using the two-sided Student's t test for normal distributed, or Mann-Whitney U test for non-normal distributed variables. Differences in categorical variables were tested by χ^2 test or Fisher test, as appropriate. Univariable logistic regression analysis was used to test the relation between various clinical and echocardiographic characteristics with VO_{2max}. To select covariates independently associated with VO_{2max}, significant univariable predictors were reassessed by a multivariable logistic analysis, with values for inclusion and elimination set at p <0.10.

Table 1 – Elementary, echocardiographic, and laboratory parameters in comparison according to gender

Parameters	Male	Female	p
Age	66±11.6	64±8.4	0.718
BMI	27±3.5	29±5.1	0.018
EF biplane (%)	68±7.4	71±6.7	0.062
SVi (ml/m^2)	43.79±13.08	39.26±10.84	0.043
LVd mass index (g/m^2)	164.7±38.65	150.8±31.66	0.146
LVESV (ml)	36.7±14.8	27.5±12.3	0.014
LVEDV (ml)	121.3±33.97	102.2±30.3	0.028
Relative wall thickness (cm)	0.471±0.057	0.494±0.065	0.063
BNP pg/ml Median (interquartal range)	92.5 (104.75)	103 (111.75)	0.832
E/e'	12.6±5.59	14.3±6.47	0.105
TAPSE (cm)	2.23±0.60	2.13±0.43	0.362
PASP (mmHg)	29.4±9.50	31.3±7.55	0.492
V_{max} (m/s)	4.53±0.36	4.53±0.35	0.974
P_{mean} (mmHg)	52.27±12.09	53.42±12.52	0.590
P_{max} (mmHg)	81.75±16.20	81.60±14.38	0.955
AVA ($cm^{2)}$)	0.75±0.15	0.63±0.17	<0.001
AVAi (cm^2/m^2)	0.38±0.08	0.35±0.09	0.025
Zva (mmHg/ml/m^2)	4.65±1.31	5.14±1.5	0.064

AVA – aortic valve area; BMI – body mass index; BNP – brain natriuretic peptide; E/e' – ratio between early mitral inflow velocity and mitral annular early diastolic velocity; EF – ejection fraction; LVESV/LVEDV – left ventricular end-diastolic and end-systolic volume; PASP – pulmonary artery systolic pressure; P_{max} – maximal gradient across aortic valve; P_{mean} – mean gradient across aortic valve; SVi – indexed stroke volume; TAPSE– tricuspid annular plane systolic excursion; V_{max} – maximal velocity across aortic valve; Zva – valvulo-arterial impedance.

Table 2 – Comparing parameters of cardiopulmonary exercise testing between genders

Parameters	Male	Female	*p*
VO_{2max} (mL/kg/min)	17.64±4.61	13.10±3.32	<0.001
O_2 pulse (ml/beat)	12.03±3.07	7.91±1.93	<0.001
VE/VCO_2 slope	28.87±5.57	33.69±7.50	0.004
Achieved workload (Watts)	112.91±30.66	71.64±22.17	<0.001
Maximal heart rate (bpm)	126.84±19.37	131.18±23.28	0.271
dVO_2dWR (mL/min/Watt)	9.08±4.77	4.65±2.93	<0.001
$PETCO_2$ (mmHg)	36.71±6.77	35.30±8.05	0.481

dVO_2dWR – relationship between oxygen consumption and workload; $PETCO_2$ – extrapolated end-tidal carbon dioxide tension; VO_{2max} – maximal oxygen consumption; VE/VCO_2 slope – ratio between pulmonary ventilation and carbon dioxide production.

Table 3 – Univariate logistic regression analysis for relation to VO_{2max}

VO_{2max}	B	Beta	*p*	CI 95%
Female	4.534	–0.365	<0.001	2.442–6.625
Age	–0.177	–0.306	0.010	–0.310 to –0.044
BMI	–0.366	–0.327	0.012	–0.646 to –0.085
EF biplane	0.046	0.052	0.669	–0.167–0.258
SVi	0.083	0.050	0.106	–0.019–0.184
LVd mass index	0.005	0.039	0.833	–0.046–0.056
LVESV	0.094	0.245	0.200	–0.053–0.240
LVEDV	0.022	0.143	0.460	–0.039–0.083
BNP	–0.011	–0.217	0.162	–0.028–0.005
NTproBNP	–0.001	–0.163	0.334	–0.003–0.001
E/E"	93.536	0.304	0.011	21.965–165.107
TAPSE	1.232	0.140	0.259	–0.930–3.394
SPDK	0.232	0.283	0.215	–0.146–0.610
V_{max}	–3.849	–0.264	0.029	–7.282 to –0.416
P_{mean}	–0.035	–0.089	0.469	–0.130–0.061
P_{max}	–0.078	–0.195	0.108	–0.173–0.018
AVA	10.283	0.385	0.001	4.277–16.288
AVAi	17.859	0.320	0.008	4.871–30.846
Zva	–0.780	–0.246	0.046	–1.545 to –0.014
S'mean	28.376	0.094	0.440	–44.468–101.219
SWL	–0.027	–0.080	0.515	–0.109–0.055
ELI	13.007	0.358	0.003	4.530–21.484

AVA – aortic valve area; BMI – body mass index; BNP – brain natriuretic peptide; EF – ejection fraction; ELI – energy loss index; LVESV/LVEDV – left ventricular end-diastolic and end-systolic volume; PASP – pulmonary artery systolic pressure; P_{max} – maximal gradient across aortic valve; P_{mean} – mean gradient across aortic valve; S' – systolic velocity of mitral annulus; SVi – indexed stroke volume; SWL – stroke work loss; TAPSE – tricuspid annular plane systolic excursion; V_{max} – maximal velocity across aortic valve; Zva – valvulo-arterial impedance.

Statistical analyses were performed using the statistical package for social sciences, version 21 (SPSS, Chicago, Ill). Statistical significance was defined as $p < 0.05$.

Discussion

Our study showed that female gender is the strongest independent predictor of decreased functional capacity, even when adjusting for other variables, including age, body mass index, and echo markers of AS severity in asymptomatic patients with severe AS. It is the first study to directly compare the functional capacity assessed through the CPET parameters in group of asymptomatic opposite sex patients with severe AS. CPET is an expression of the functional health of the combined cardiovascular, pulmonary and skeletal muscle systems,[11] and as such it serves as an objective measure of functional status and capaci-

Table 4 – Multivariate logistic regression analysis for relation to VO_{2max}

VO_{2max}	B	Beta	*p*	CI 95%
Female	3.389	–0.365	0.002	1.453–5.924
Age	–0.140	–0.239	0.035	–0.269 to –0.010
BMI	–0.312	–0.246	0.028	–0.589 to –0.035
V_{max}	–5.609	–0.341	0.004	–9.294 to –1.924
e/E'	–	–	0.892	–
AVA	–	–	0.589	–
AVAi	–	–	0.819	–
Zva	–	–	0.752	–
ELI	–	–	0.494	–

AVA – aortic valve area; BMI – body mass index; CI – confidence interval; E/e' – ratio between early mitral inflow velocity and mitral annular early diastolic velocity; ELI – energy loss index; V_{max} – maximal velocity across aortic valve; VO_{2max} – maximal oxygen consumption; Zva – valvulo-arterial impedance.

ty. Although women generally tend to have lower VO_2 values compared to men in our study the groups were well matched, the severity of AS and the frequency of comorbidities were the same, thus the interaction analysis between sex and AS on VO_{2max} directly demonstrated that females indeed have risk for impaired functional capacity. Our finding also implicates that for same severity of AS AVR may be considered earlier in women in comparison to men.

Although LV hypertrophy regression occurs relatively early post AVR (up to 20–30%), normalization of myocardial structure and function is not always possible.[12] Thus, timely recognition of myocardial fibrosis and latent myocardial inability to significantly enhance its function in exertion is important. Fairbairn and coworkers in their study showed that in most patients with significant AS there was preoperative evidence of myocardial fibrosis.[13] In their study they also hypothesized that even if reverse LV remodeling occurs post AVR the fibrosis is irreversible and thus limits potential functional capacity improvement. In other words, the AVR may be successfully performed but the recovery is suboptimal as the optimal time for the operation was missed, and thus certain symptoms, such as fatigue, could persist after the intervention. In this sense females seem to be at greater risk than males. Studies have demonstrated that females have significantly lower increase in functional capacity in comparison to males following cardiac rehabilitation after acute cardiac event or with regard to chronic heart disease.[14,15]

For a given aortic valve area and/or mean gradient females tend to have higher amount of fibrosis and a greater proportion of dense connective tissue in aortic valve as compared to males.[16,17] Women also appear to obtain a greater degree of diffuse fibrosis during chronic pressure overload. Demonstrated with cardiac MRI (CMRI), women often have smaller LV cavity size and more pronounced concentric remodeling/hypertrophy[18,19] compared with men who have AS of similar severity and with similar comorbidities. This has been confirmed in our study, as females had smaller end-diastolic and end-systolic LV volumes, lower indexed stroke volume, and borderline higher relative wall thickness. Females also had smaller LV outflow tract diameter and consequently smaller AVA. The observed LV geometric changes with increased wall thickness relative to left ventricular diameter, tends to reduce wall stress and thereby myocardial metabolic demand, yet this adaptive response is not necessarily always beneficial to the patient. Beside the fact that low-flow severe AS has been associated with increased AS-related morbidity and mortality,[20,21] the smaller the LV cavity and the more pronounced the concentric LV remodeling is, the more decreased is exercise capacity.[22] Saeed et al. demonstrated in 316 patients with moderate or severe AS that exercise capacity was lower in women than men, and the determinants of exercise capacity differed among genders,[23] with women having smaller LV dimensions in this study. In our study females achieved significantly lower workload during exercise and also had almost all cardiopulmonary parameters worse than males.

A prospective study by Singh et al.[24] found that females had earlier onset of symptoms in comparison to males for a similar indexed aortic valve area. However, it is challenging to attribute symptoms to AS, especially in the elderly, thus, relying entirely on symptom onset to guide the timing of AVR is problematic for either gender. Aortic stenosis is an insidious disease and hence every effort should be made to perform a thorough analysis, assess the actual clinical status, especially in risk groups, and determine adequate risk stratification.[25,26] This can halt the otherwise inevitable progression of systolic deterioration by timely sending the patient to AVR and unloading the LV. With regard to this fact, CPET might be of help as an objective indicator of functional and symptomatic status. According to our results gender-specific AS risk-evaluation strategy should be considered.

Study limitations

The number of analyzed patients is relatively low and as such it might be difficult to generalize the results. However, it is still the largest number of asymptomatic AS patients that were analyzed in the context of gender-related functional capacity. The fact that patients were screened and included in the randomized study allowed the study groups to be equal in the majority of baseline characteristics. Although the screening and inclusion of patients was prospective (within the AVATAR trial) the results of this study were presented as part of the subsequent analysis.

Conclusion

Female gender is the strongest independent predictor of decreased functional capacity, even when adjusting for other variables, including body mass index and echo markers of AS severity. Further and larger studies are needed to evaluate the mechanisms of gender differences in patients with AS and to determine whether this finding affects the course and outcome of the disease.

Conflict of interest

Nothing to report.

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