© Pediatr Med Rodz 2019, 15 (1), p. 47–56
DOI: 10.15557/PiMR.2019.0009

Małgorzata Kurpaska, Paweł Krzesiński, Grzegorz Gielerak, Beata Uziębło-Życzkowska, Małgorzata Banak, Małgorzata Maciorowska, Andrzej Skrobowski, Adam Stańczyk, Katarzyna Piotrowicz

Received: 18.09.2018
Accepted: 23.10.2018
Published: 31.05.2019

Reakcja układu sercowo-naczyniowego w trakcie wysiłku fizycznego u chorych z nadciśnieniem tętniczym – kliniczna charakterystyka pacjentów w badaniu ASSECURE

Cardiovascular response to exercise in hypertension – clinical characteristics of ASSECURE study participants

Klinika Kardiologii i Chorób Wewnętrznych, Wojskowy Instytut Medyczny, Warszawa, Polska
Adres do korespondencji: Małgorzata Kurpaska, Klinika Kardiologii i Chorób Wewnętrznych, Wojskowy Instytut Medyczny, ul. Szaserów 128, 04-141 Warszawa, tel./faks: +48 261 816 372, e-mail: mkurpaska@wim.mil.pl

Streszczenie

Cel: Nadciśnienie tętnicze prowadzi do postępującej dysfunkcji układu krążenia i niewydolności serca. Celem pracy była ocena wydolności fizycznej chorych z nadciśnieniem tętniczym z wykorzystaniem sercowo-płucnego testu wysiłkowego, wysiłkowej kardiografii impedancyjnej oraz 6-minutowego testu marszowego, ze szczególnym uwzględnieniem odpowiedzi hemodynamicznej na obciążenie wysiłkiem. **Metody:** 114 chorych (53,5% kobiet, wiek 55,7 ± 9,1 roku) oceniono pod względem zgłaszanych objawów, stężenia N-końcowego propeptydu natriuretycznego typu B (*N-terminal pro-B-type natriuretic peptide*, NTproBNP), wykładników echokardiograficznych oraz wydolności fizycznej za pomocą 6-minutowego testu marszowego i sercowo-płucnego testu wysiłkowego, a także parametrów hemodynamicznych za pomocą wysiłkowej kardiografii impedancyjnej. **Wyniki:** W badanej grupie 50% osób zgłaszało obniżenie tolerancji wysiłku, w tym 37,7% duszność wysiłkową. U 19,3% chorych stężenie NTproBNP przekroczyło wartość 125 pg/ml. Dysfunkcję rozkurczową stwierdzono u 8,8% z nich, ale kryteria rozpoznania niewydolności serca z zachowaną frakcją wyrzutową spełniło jedynie 6,2%. Obserwowano szeroki zakres szczytowego pochłaniania tlenu (peak VO_2) i dystansu 6-minutowego testu marszowego, odpowiednio 19,4 ± 5,2 ml/min/kg i 526,7 ± 112,0 m. Wysoki odsetek badanych prezentował obniżone parametry wydolności fizycznej: 56,1% osiągnęło peak VO_2 < 22 ml/min/m^2, a 45,9% – peak VO_2 < 80% wartości predykcyjnej; 37,3% badanych nie osiągnęło należnej wartości dystansu 6-minutowego testu marszowego. W wysiłkowej kardiografii impedancyjnej zarejestrowano na szczycie wysiłku: częstość rytmu serca 147,2 ± 22,4/min, objętość wyrzutową 110,2 ± 21,8 ml, pojemność minutową 15,9 ± 4,2 l/min, opór obwodowy 587,4 ± 168,0 dyn·s/cm^5. **Wnioski:** Objawy obniżonej tolerancji wysiłku i nieprawidłowe wyniki obiektywnej oceny wydolności fizycznej u pacjentów z niepowikłanym nadciśnieniem tętniczym są częste, chociaż niewielki odsetek tych chorych spełnia kryteria diagnostyczne niewydolności serca.

Słowa kluczowe: nadciśnienie tętnicze, niewydolność serca, sercowo-płucny test wysiłkowy, wydolność fizyczna, kardiografia impedancyjna

Abstract

Aim: Arterial hypertension leads to progressive cardiovascular dysfunction and heart failure. The aim of the study was to assess exercise capacity in hypertensives with the use of a cardiopulmonary exercise test, impedance cardiography and 6-minute walk test with special emphasis on haemodynamic response to exercise workload. **Methods:** 114 patients (53.5% women, 55.7 ± 9.1 years) were evaluated for reported symptoms, N-terminal pro-B-type natriuretic peptide (NTproBNP) levels, echocardiographic parameters and exercise capacity with 6-minute walk test, cardiopulmonary exercise test and haemodynamic parameters (by means of impedance cardiography). **Results:** 50% of patients had reported symptoms of impaired exercise tolerance, mostly dyspnoea on exertion (37.7%). NTproBNP levels exceeded 125 pg/mL in 19.3% of patients. Left ventricular diastolic dysfunction was found in 8.8% and heart failure was diagnosed in 6.2% of patients. A wide range of peak oxygen uptake (peak VO_2) and 6-minute walk test distance was observed: 19.4 ± 5.2 mL/min/kg and 526.7 ± 112.0 m, respectively. A major proportion of patients demonstrated decreased exercise capacity parameters: 56.1% achieving peak VO_2 < 22 mL/min/m^2; 45.9% achieving peak VO_2 < 80% of the predictive value; 37.3% achieving 6-minute walk test distance shorter than the predicted values. The impedance cardiography recorded at peak exercise: heart rate 147.2 ± 22.4 bpm, stroke volume 110.2 ± 21.8 mL, cardiac output 15.9 ± 4.2 L/min, peak systemic vascular resistance 587.4 ± 168.0 dyn·s/cm^5. **Conclusions:** Although a very small proportion of patients with uncomplicated arterial hypertension meet the criteria for being diagnosed with heart failure, the symptoms of impaired exercise tolerance as well as abnormal results of objective exercise capacity assessments are quite common in these patients.

Keywords: arterial hypertension, heart failure, cardiopulmonary exercise test, exercise capacity, impedance cardiography

INTRODUCTION

Arterial hypertension (AH) is a common condition and one of the key risk factors for cardiovascular diseases with poor prognosis[1–3]. Progressive cardiovascular dysfunction in patients with AH is both continual and individually diverse. Routine diagnostic methods often fail to objectify the symptoms of exercise intolerance to a degree sufficient to establish a definitive diagnosis of heart failure (HF). They are typically limited to the measurement of haemodynamic parameters at rest, which precludes detecting possible signs of cardiovascular dysfunction during exercise. As a result, the complaints of patients with uncomplicated AH are in many cases believed to be of a purely subjective nature. However, given the fact that exercise capacity is strongly associated with the quality of life and is an independent prognostic factor[4,5], it is practical to search for objective diagnostic methods that would help assess cardiovascular function during exercise. Such are the 6-minute walk test (6MWT) and cardiopulmonary exercise test (CPET), which are established as useful in patients with heart, lung, and musculoskeletal conditions as well as in healthy individuals and athletes[6–9]. Although they help measure exercise capacity, their potential to reflect the haemodynamic changes during exercise is limited. On the other hand, supplementing these tests with invasive haemodynamic evaluation is related with the risk of complications and requires extensive experience[10]. This is not so with impedance cardiography (ICG), the use of which in assessing exercise capacity in AH patients was demonstrated in our preliminary studies[11]. Therefore, the purpose of the presented study was to assess exercise capacity of hypertensive patients with special emphasis on haemodynamic response to exercise workload evaluated by ICG.

METHODS

Study group

The study group comprised AH patients of both sexes, aged 40–75 years, recruited between September 2014 and September 2017. The exclusion criteria were: confirmed secondary AH; chronic kidney disease with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 calculated according to the MDRD (Modification of Diet in Renal Disease Study) equation; history of ischaemic heart disease; other severe comorbidities: left ventricular ejection fraction (LVEF) <50%; hypertrophic/dilated cardiomyopathy; clinically significant arrhythmias; non-sinus rhythm (including permanent cardiac pacing); clinically significant valvular disease; pre-existing diabetes mellitus; polyneuropathy; exercise-limiting peripheral vascular disease and/or musculoskeletal disorders; body mass index (BMI) of >40 kg/m^2; psychiatric conditions preventing full cooperation with the patient; pre-existing lung disease (asthma, chronic obstructive pulmonary disease, pulmonary embolism).

The study was conducted in accordance with the principles of Good Clinical Practice and Declaration of Helsinki, the study protocol had been approved by the local Bioethics Committee (approval No. 14/WIM/2014), and a written informed consent had been obtained from each patient. The study has been registered at ClinicalTrials.gov (NCT02634866).

Medical history and physical examination

Medical examination involved collecting history of any concomitant conditions, cardiovascular risk factors (for example smoking), and reported symptoms (especially the patient's subjective assessment of exercise capacity, including reduced exercise tolerance, dyspnoea, chest pain) as well as physical examination, including a thorough assessment of systolic (SBP) and diastolic blood pressure (DBP), signs of pulmonary congestion and/or oedema, and body measurements (height, weight, BMI).

Laboratory tests

Laboratory tests were conducted on fasting peripheral venous blood samples collected in the morning (7:00–8:30 am). The levels of the following parameters were evaluated: haemoglobin, D-dimer, N-terminal pro-B-type natriuretic peptide (NTproBNP), creatinine, urea and uric acid, fasting glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG). The eGFR was calculated based on the MDRD equation. The threshold values for total cholesterol, LDL, HDL, TG, fasting blood glucose, haemoglobin and D-dimer were based on the current European Society of Cardiology guidelines[1,2,12].

Echocardiography

Echocardiographic examinations were conducted with the Vivid S6 ultrasound system (GE Medical System, Wauwatosa, WI, USA), in standard parasternal, apical, and subcostal views. The following parameters were measured: cardiac chamber size, myocardial contractility, left ventricular wall thickness, ejection fraction, as well as valvular structure and function. Left atrial enlargement (LAE) was determined based on the left atrial volume index [LAVI (mL/m^2)] exceeding 34 mL/m^2[13]. Left ventricular hypertrophy (LVH) was diagnosed – in line with the current American Society of Echocardiography (ASE) recommendations[14] –based on the left ventricular mass indexed to body surface area (LVMI, left ventricular mass index of >95 g/m^2 for females and >115 g/m^2 for males). The left ventricular ejection fraction (LVEF) was assessed with Simpson's method. Left ventricular diastolic dysfunction (LVDD) was diagnosed according to the current recommendations[15] based on the presence of at least 2 of the following criteria: 1) mitral flow early (E) phase and mitral septal annulus early diastolic

DOI: 10.15557/PiMR.2019.0009

velocity (e') ratio (E/e') >14; 2) average e' <7 cm/s; 3) tricuspid regurgitation jet velocity (TRV) >2.8 m/s; 4) LAVI >34 mL/m^2. The left ventricular filling pressure was assessed and LVDD was graded based on the variables listed above and transmitral flow parameters E/A [mitral flow early (E) and late (A) phase ratio] and E in the following ranges: E/A ≤0.8, >0.8–<2, and ≥2; E ≤50 cm/s and >50 cm/s.

Six-minute walk test

The 6MWT was performed according to the 2002 American Thoracic Society guidelines[8]. The patients were instructed to walk as fast as they could at a comfortable pace along a 30-meter-long corridor marked every 10 meters. The total distance covered over 6 minutes (6MWTd) was rounded to 5 meters. The resulting absolute values were expressed as percentage of the predicted 6MWTd values, calculated individually for each patient based on reference equations introduced by Enright and Sherrill[6]:
Men: (predicted) 6MWTd = [7.57 × height (cm)] – [5.02 × age (year)] – [1.76 × weight (kg)] – 309 m
Women: (predicted) 6MWTd = [2.11 × height (cm)] – [2.29 × weight (kg)] – [5.78 × age (year)] + 667 m

Cardiopulmonary exercise testing

CPET was conducted in each patient in the morning (between 9 and 11 am), after they took their medications. The test was conducted on the Ergoselect cycle ergometer (Geratherm Respiratory GmbH, Germany), according to an individual ramp protocol (with the goal of reaching the target workload within 10 minutes). Prior to each test, oxygen and carbon dioxide sensors and the Ergoflow flow sensor (Geratherm Respiratory GmbH, Germany) were calibrated. Prior to each cardiopulmonary exercise test, resting spirometry was performed to exclude obstructive diseases [the first second of forced expiration/forced vital capacity, FEV_1/FVC and FEV_1] and measure vital capacity (VC). Each patient was subjected to a symptom-limited CPET protocol [with the exercise stopped at the onset of symptoms (fatigue, dyspnoea) or upon the patient's request][7]. The breath-by-breath analysis of respiratory gas exchange was performed with a Geratherm Ergostik system (Geratherm Respiratory GmbH, Germany). The following parameters were continuously monitored throughout the test and were assessed at the anaerobic threshold (AT) and at peak oxygen consumption (peak VO_2) time points and expressed as percentage of their respective predicted values: oxygen consumption [VO_2 (mL/kg/min)]; minute ventilation [VE (L/min)]; and ventilatory equivalents for carbon dioxide production (VE/VCO_2), breathing reserve (BR), oxygen (O_2) pulse (mL/min). Additionally, the following parameters were assessed: maximum achieved workload (Wmax); respiratory exchange ratio (RER); VO_2-work rate relationship (VO_2/WR (mL/min/W)]; maximum heart rate at peak exercise [HRmax (bpm)]; heart rate recovery [HRR (bpm)] at 1 minute after exercise; and exercise ventilatory efficiency (VE/VCO_2 slope). The heart's electrical function (12-lead ECG) and O_2 saturation were monitored continuously.
Peak VO_2 was expressed as the highest average value from the final 30 seconds of exercise. The predicted VO_2 value (VO_2pred) was estimated based on Wasserman's equation[16]. RER was defined as the highest average VCO_2/VO_2 value of the final 30 seconds of exercise. A regression equation was used to calculate the VE/VCO_2 slope, based on VE and VCO_2 values averaged every 10 seconds, obtained throughout the exercise period. BR was calculated as follows: BR = maximum voluntary ventilation (MVV = FEV_1 × 40) – peak VE. After CPET was completed, the AT was determined non-invasively with a V-slope method, based on the VO_2 and VCO_2 relationship[15], while the O_2 pulse was calculated as VO_2/HR. In line with the current recommendations[7,17], the following parameter values were considered abnormal: peak VO_2 <22 mL/min/kg, peak VO_2 <80% of the predicted value, VO_2 at the AT <40% of the predicted value, VE/VCO_2 slope >34, VO_2/WR <10 mL/min/W, O_2 pulse <85% of the predicted value, HRR <12 bpm, BR <11 L or <15% MVV.

Impedance cardiography during exercise

ICG was conducted with the PhysioFlow device (Manatec, Paris, France) during CPET, according to the methodology consistent with another article[18]. The assessment is based on alterations in electric impedance caused by changes in chest volume during heart systole, which allows continuous monitoring (beat-to-beat) of heart rate [HR (bpm)], stroke volume [SV (mL)] and cardiac output [CO (L/min)]. However, this device does not require measuring the baseline thoracic impedance (Z0) or blood resistivity, but analyses signal morphology of impedance changes and offers advanced artifact elimination. For each patient the device was calibrated by conducting an assessment at rest, according to manufacturer's instructions (autocalibration procedure). CO and its components SV and HR are the most important in the assessment of exercise capacity and their reliability and accuracy are the best documented[18]. Systemic vascular resistance [SVR (dyn·s/cm^5)] was calculated as (mean arterial blood pressure minus central venous pressure)/CO × 80. We also measured the change (Δ) in these parameters between their values at peak exercise and those at the preceding period of rest.

Statistical analysis

The data was recorded, and the obtained results were analysed statistically with Statistica 12.0 software (StatSoft Inc., Tulsa, OK, USA). The results obtained for quantitative variables were expressed as means ± standard deviation (*SD*), while those obtained for qualitative variables were expressed as absolute values and percentages.

 DOI: 10.15557/PiMR.2019.0009

RESULTS

The assessments were conducted in a group of 114 patients with AH; their baseline characteristics are presented in Tab. 1. Most patients had well-controlled hypertension. A relatively large proportion of patients (50%) reported symptoms of reduced exercise tolerance; these were mostly dyspnoea on exertion (37.7%) and atypical chest pain (44.7%), with headaches, vertigo, and visual disturbances also relatively common. Most common treatments included angiotensin converting enzyme (ACE) inhibitors, beta-blockers, and diuretics.

Laboratory tests

The proportions of metabolic abnormalities associated with high cardiovascular risk in the study group were as follows: elevated fasting blood glucose, total cholesterol, LDL, and TG levels in 42.1%, 50.9%, 63.2%, and 31.6% of patients, respectively; low HDL levels in 10.5%; hyperuricemia in 26.3% of patients. Anaemia was diagnosed in 6 females (the lowest haemoglobin 11.1 g/dL). Although 13.1% of patients had a D-dimer level above the value excluding thromboembolic disease, none of them showed an increased clinical and echocardiographic probability of pulmonary embolism. NTproBNP levels exceeded the threshold value used for diagnosing HF in 19.3% of patients (Tab. 2).

Variable	Study group (*N* = 114)
Age (years), mean ± *SD*	55.7 ± 9.1
Men, *n* (%)	53 (46.5)
SBP (mm Hg), mean ± *SD*	128 ± 14
DBP (mm Hg), mean ± *SD*	80 ± 8
HR (bpm), mean ± *SD*	70 ± 10
BMI (kg/m^2), mean ± *SD*	29.3 ± 4.0
High (cm), mean ± *SD*	168.7 ± 9.6
Waist circumference (cm), mean ± *SD*	98.3 ± 10.4
Hip circumference (cm), mean ± *SD*	106.5 ± 6.8
Obesity, BMI >30 kg/m^2, *n* (%)	45 (39.5)
Smoking, *n* (%)	21 (18.4)
Symptoms	
Reduced exercise tolerance, *n* (%)	57 (50)
Dyspnoea during exercise, *n* (%)	43 (37.7)
Dyspnoea at rest, *n* (%)	5 (4.4)
Chest pain, *n* (%)	51 (44.7)
Peripheral oedema, *n* (%)	35 (30.7)
Headache, *n* (%)	48 (42.1)
Dizziness, *n* (%)	38 (33.3)
Vision disorders, *n* (%)	12 (10.5)
Palpitations, *n* (%)	37 (32.5)
Syncope, *n* (%)	5 (4.4)
Hypotensive treatment	
ACEI, *n* (%)	63 (55.3)
ARB, *n* (%)	20 (17.5)
BB, *n* (%)	45 (39.5)
Diuretic, *n* (%)	45 (39.5)
CB, *n* (%)	26 (22.8)

ACEI – angiotensin converting enzyme inhibitor; **ARB** – angiotensin receptor blocker; **BB** – beta-blocker; **BMI** – body mass index; **CB** – calcium blocker; **DBP** – diastolic blood pressure; **HR** – heart rate; **SBP** – systolic blood pressure; ***SD*** – standard deviation.

Tab. 1. Baseline characteristics of the study group

Echocardiography

Echocardiography revealed no clinically significant heart defects, regional contractility abnormalities, or decrease in LVEF. Although some diastolic parameters were abnormal in a major proportion of patients (e.g. e' <7 cm/s in 30.1%), only 8.8% of patients were diagnosed with (grade 1) diastolic dysfunction (Tab. 3). Only 7 patients (6.2%) were diagnosed with HF with preserved ejection fraction (HFpEF) on the basis of clinical findings, NTproBNP levels, and echocardiographic evidence.

Cardiopulmonary exercise testing

CPET was performed correctly in 107 patients. Nine of these patients failed to reach the AT and for this reason were excluded from detailed analysis.

Variable	Study group (*N* = 114)
HGB (g/dL), mean ± *SD*	14.4 ± 1.4
HGB <13.5 g/dL for men, <12 g/dL for female, *n* (%)	6 (5.2)
Creatinine (mg/dL), mean ± *SD*	0.86 ± 0.2
eGFR (mL/min/1,73 m^2), mean ± *SD*	75.1 ± 20.2
Urea (mg/dL), mean ± *SD*	34.2 ± 8.0
FG (mg/dL)[109], mean ± *SD*	102.0 ± 14.7
FG[109] ≥102 mg/dL, *n* (%)	48 (42.1)
T-C[101] (mg/dL), mean ± *SD*	204.6 ± 49.8
T-C[101] >190 mg/dL, *n* (%)	58 (50.9)
TG[100] (mg/dL), mean ± *SD*	143.0 ± 89.5
TG[100] >150 mg/dL, *n* (%)	36 (31.6)
LDL-C[101] (mg/dL), mean ± *SD*	141.3 ± 41.0
LDL-C[101] >115 mg/dL, *n* (%)	72 (63.2)
HDL-C[101] (mg/dL), mean ± *SD*	56.3 ± 14.5
HDL-C[101] <40 mg/dL for men, <46 mg/dL for female, *n* (%)	12 (10.5)
Uric acid[97] (mg/dL), mean ± *SD*	5.9 ± 1.4
Uric acid[97] >7 mg/dL, *n* (%)	30 (26.3)
D-dimers[106] (ug/mL), mean ± *SD*	0.39 ± 0.3
D-dimers[106] >0,5 ug/mL for patients ≤ 50 years, > age × 0.01 µg/mL for patients >50 years, *n* (%)	15 (13.1)
NTproBNP[104] (pg/mL), mean ± *SD*	159.6 ± 509.7
NTproBNP[104] >125 pg/mL, *n* (%)	22 (19.3)

Number of subjects examined in upper index.
eGFR – estimated glomerular filtration rate; **FG** – fasting glucose; **HDL-C** – high density lipoprotein cholesterol; **HGB** – haemoglobin; **LDL-C** – low density lipoprotein cholesterol; **NTproBNP** – N-terminal pro-B-type natriuretic peptide; ***SD*** – standard deviation, **TG** – triglycerides; **T-C** – total cholesterol.

Tab. 2. Laboratory tests

DOI: 10.15557/PiMR.2019.0009

Variable	Study group (*N* = 113)
RVEDd (mm), mean ± *SD*	29.8 ± 3.5
IVSDd (mm), mean ± *SD*	10.1 ± 1.2
LVEDd (mm), mean ± *SD*	47.7 ± 3.9
LA (mm), mean ± *SD*	37.6 ± 3.8
LAVI[108] (mL/m^2), mean ± *SD*	26.1 ± 7.7
Ao-asc (mm), mean ± *SD*	32.2 ± 3.2
LVMI[108] (g/m^2), mean ± *SD*	89.3 ± 19.0
LVEF[109] (%), mean ± *SD*	64.7 ± 3.9
e' avg[108] (cm/s), mean ± *SD*	8.3 ± 2.1
E/e' avg[105], mean ± *SD*	8.0 ± 3.0
TRV[75] (m/s), mean ± *SD*	2.3 ± 0.26
TRV[75] >2.8 m/s, *n* (%)	1 (0.0)
e' <7 cm/s[108], *n* (%)	34 (30.1)
E/e' >14 cm/s, *n* (%)	4 (3.5)
LAE[108], *n* (%)	18 (15.9)
Normal diastolic function of LV[113], *n* (%)	103 (91.2)
LVH[108], *n* (%)	19 (16.8)

Number of subjects examined in upper index.
Ao-asc – ascending aorta; **e'** – mitral septal annulus early diastolic velocity; **E/e'** – mitral flow early (E) phase and mitral septal annulus early diastolic velocity (e') ratio; **IVSDd** – intraventricular septum diastolic diameter; **LA** – left atrial diameter; **LAE** – left atrial enlargement; **LAVI** – left atrial volume index; **LV** – left ventricle; **LVEDd** – left ventricular end-diastolic diameter; **LVEF** – left ventricular ejection fraction; **LVH** – left ventricular hypertrophy; **LVMI** – left ventricular mass index; **RVEDd** – right ventricular end-diastolic diameter; ***SD*** – standard deviation; **TRV** – tricuspid regurgitant jet velocity.

Tab. 3. Echocardiography

Baseline spirometry revealed no clinically significant abnormalities, such as evidence of obstructive disease. The mean VC was 3.9 ± 1.1 L (106.2 ± 15.1% of the reference value), FEV_1 was 3.1 ± 0.9 L (103.4 ± 14.8% of the reference value), FEV_1/FVC was 81.4 ± 6.3% (104.4 ± 8.3% of the reference value).

A large proportion of patients demonstrated objective evidence of reduced exercise capacity (Tab. 4): with 45.9% of patients achieving peak VO_2 <80% of the predicted value, 32.6% of patients achieving O_2 pulse <85% of the predicted value, and 58.1% of patients demonstrating VO_2/WR of <10 mL/min/W. Moreover, 23.5% of patients showed a low heart rate recovery (HRR) of <12 bpm (Tab. 4). Some patients were treated with beta-blockers (n = 35), which significantly influenced maximum HR at peak exercise (treated vs. untreated: 134.4 ± 18.8 vs. 147.3 ± 21.0 bpm, p = 0.003) and HRR (32.9 ± 15.7 vs. 21.4 ± 15.7 bpm, p = 0.003), but not the % pred. peak VO_2 (76.7 ± 17.7 vs. 82.5 ± 16.3%, ns). The measured CPET parameters yielded a wide range of values. The mean peak VO_2 value was 19.4 mL/min/kg; however, the minimum value (10.6 mL/min/kg) was nearly 4 times lower than the maximum value (37.2 mL/min/kg). The workload at peak exercise ranged from 38% to 135% of the individually predicted peak values (Fig. 1). Electrocardiography at rest and during exercise revealed no evidence of ischaemia in any of the patients.

Variable	Study group (*n* = 98)
Peak workload (W), mean ± *SD*	141.1 ± 50.1
% pred. peak workload (%), mean ± *SD*	89.1 ± 19.5
AT VO_2 (mL/min/kg), mean ± *SD*	13.6 ± 3.7
% pred. AT VO_2 (%), mean ± *SD*	71.5 ± 12.0
Peak VO_2 (mL/min/kg), mean ± *SD*	19.4 ± 5.2
% pred. peak VO_2 (%), mean ± *SD*	80.5 ± 16.9
RER, mean ± *SD*	1.13 ± 0.09
Peak O_2 pulse (mL/beat), mean ± *SD*	11.3 ± 2.9
% pred. peak O_2 pulse (%), mean ± *SD*	95.1 ± 20.3
Peak VE/VCO_2, mean ± *SD*	30.8 ± 3.9
VO_2/WR (mL/min/W), mean ± *SD*	9.9 ± 2.4
VE (L/min), mean ± *SD*	59.1 ± 20.5
HRmax (bpm), mean ± *SD*	142.6 ± 21.1
HRR (bpm), mean ± *SD*	25.5 ± 18.7
VE/VCO_2 slope, mean ± *SD*	26.4 ± 3.8
BR <11 L or <15%, *n* (%)	4 (4.0)
Peak VO_2 <22 mL/min/kg, *n* (%)	55 (56.1)
% pred. peak VO_2 <80% of predicted value, *n* (%)	45 (45.9)
% pred. AT VO_2 <40% of predicted value, *n* (%)	0 (0)
VE/VCO_2 slope >34, *n* (%)	12 (12.2)
VO_2/WR <10 mL/min/W, *n* (%)	57 (58.1)
O_2 pulse <85% of predicted value, *n* (%)	32 (32.6)
HRR <12 bpm, *n* (%)	23 (23.5)

AT – value at anaerobic threshold; **peak** – value at peak exercise; **% pred. peak** – percentage of predicted peak value; **% pred. AT** – percentage of predicted value at anaerobic threshold; **BR** – breathing reserve; **HRmax** – maximal heart rate; **HRR** – heart rate recovery; **RER** – respiratory exchange ratio; ***SD*** – standard deviation; **VCO_2** – carbon dioxide production; **VE** – ventilation; **VO_2** – oxygen uptake; **WR** – work rate.

Tab. 4. Values of selected CPET parameters measured in the study group

Reasons of reduced exercise capacity were categorised according to CPET algorithms[15,19] in poor effort (40 patients, reduced peak VO_2, VO_2 at AT >40% peak value, correct BR) or left ventricular dysfunction (36 patients, reduced peak VO_2, VO_2 at AT <75% pred. value, VE/VCO_2 <34). Coronary artery disease was suspected (decreased pulse O_2) and finally excluded by coronary angiography in only 4 subjects. The indices of restrictive lung disease (reduced peak VO_2, VO_2 at AT >40% peak value, low BR and frequency of breathing >50/min) were present in 1 patient and pulmonary vasculopathy in 2 cases (reduced peak VO_2, VO_2 at AT <75% pred. value, decreasing $P_{ET}CO_2$ during exercise).

Impedance cardiography during exercise

The haemodynamic parameters assessed via ICG during exercise also yielded a wide range of values (Tab. 5). At peak VO_2, mean SV was 110 mL (range 57–165 mL), mean HR was 147 bpm (80–200 bpm), and mean CO was 15.9 L/min (7.2–25.8 L/min). Changes in these parameters during exercise also varied widely. The average increase in HR was by 70 bpm (24–170 bpm) and in CO by 9.7 L/min (3.5–18.9 L/min). SV increased by 27.6 mL on

 DOI: 10.15557/PiMR.2019.0009

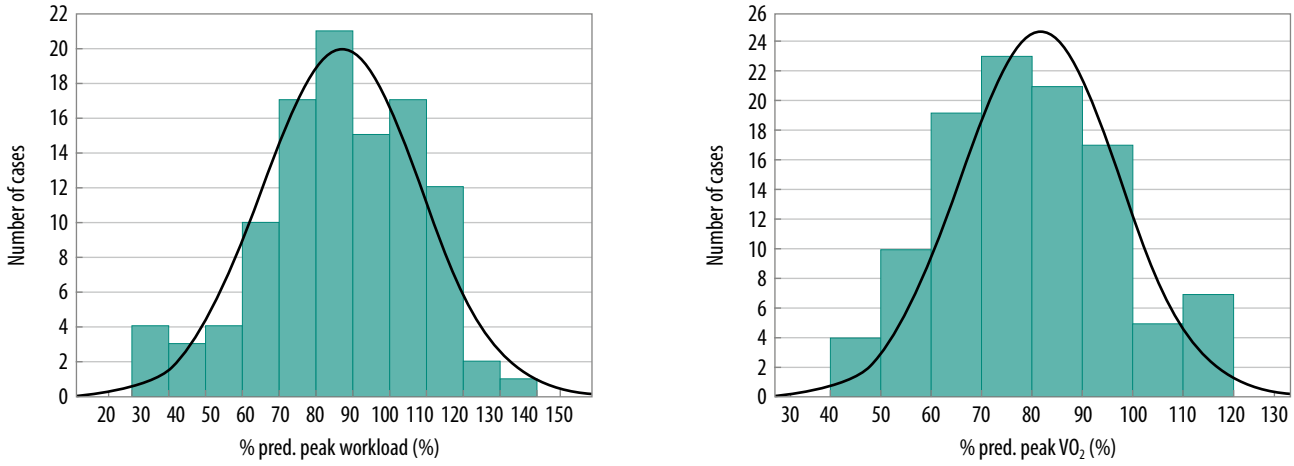

Fig. 1. Histograms: workload at peak exercise expressed as percentage of the predicted peak value (upper) and VO_2 at peak exercise expressed as percentage of the predicted peak value (lower)

average, with the maximum increase by 72.3 mL; however, there were also 4 patients whose SV at peak exercise was lower than that before exercise (with maximum recorded decrease of 7.2 mL). Two exemplary patterns of haemodynamic response to exercise are presented in Fig. 2. Patient 1 (with higher peak VO_2) was characterised by a progressive increase of both SV and HR, whereas patient 2 (with lower peak VO_2) presented with exercise plateau and even final decrease of SV.

6-minute walk test

The mean 6MWTd (n = 102) was 526.7 ± 112.0 m, which constituted 105.1 ± 23.3% of the predicted value. A relatively large proportion of patients (37.3%) failed to reach the predicted value (Fig. 3).

Variable	Study group (n = 98)
Baseline HR (bpm), mean ± *SD*	77.8 ± 10.7
Peak HR (bpm), mean ± *SD*	147.2 ± 22.4
Δ HR (bpm), mean ± SD	70.0 ± 22.4
Baseline SV (mL), mean ± *SD*	83.0 ± 15.3
Peak SV (mL), mean ± *SD*	110.2 ± 21.8
Δ SV (mL), mean ± *SD*	27.6 ± 14.8
Baseline CO (L/min), mean ± *SD*	6.4 ± 1.1
Peak CO (L/min), mean ± *SD*	15.9 ± 4.2
Δ CO (L/min), mean ± *SD*	9.7 ± 3.6
Baseline SVR (dyn·s/cm^5), mean ± *SD*	1268.6 ± 232.1
Peak SVR (dyn·s/cm^5), mean ± *SD*	587.4 ± 168.0
Δ SVR (dyn·s/cm^5), mean ± *SD*	−675.7 ± 285.4

Baseline – value at rest; **peak** – value at peak exercise; **Δ** – difference between values at peak exercise and those at rest; **CO** – cardiac output; **HR** – heart rate; ***SD*** – standard deviation; **SV** – stroke volume; **SVR** – systemic vascular resistance.

Tab. 5. Values of the selected ICG parameters analysed in the study group

DISCUSSION

Our findings showed that although a relatively large proportion of patients with AH reported symptoms of exercise intolerance, relatively few of these patients could in fact be diagnosed with HFpEF. Exercise capacity varied widely in our theoretically relatively homogeneous study group. A large proportion of patients with uncomplicated AH failed to achieve predicted values for the parameters of normal cardiovascular response to exercise. Moreover, the recorded changes in the CPET parameters associated with left ventricular function may, in some cases, suggest a significantly impaired haemodynamic adaptation to exercise.

Hypertension was generally well controlled in the study group. However, there was a high prevalence of metabolic risk factors for cardiovascular disease. The proportion of obese patients was high and similar to that reported in other studies in similar patient populations[3,20,21]. There were also a number of cases with abnormal levels of fasting blood glucose, total cholesterol and all its fractions. These findings are consistent with those of large population studies[3,22], which suggests that our study group was representative for the entire population of patients with uncomplicated AH.

Despite the high number of patients with typical HF manifestations, considerable occurrence of single factors, including echocardiographic abnormalities (LVH 16.8%; LVDD 8.8%), and elevated NTproBNP levels in one out of five patients, the co-occurrence of these criteria, which would be a basis for diagnosing HFpEF, was found in only 7 patients. Reduced exercise capacity, elevated natriuretic peptide levels, and the presence of diastolic dysfunction, with no grounds to diagnose HFpEF in AH patients, were also reported by others[23–27].

Both the 6MWT and CPET demonstrated a wide range of exercise capacity (6MWTd, maximum workload achieved during CPET). The values of the individual cardiovascular function parameters, including peak VO_2, also ranged

DOI: 10.15557/PiMR.2019.0009

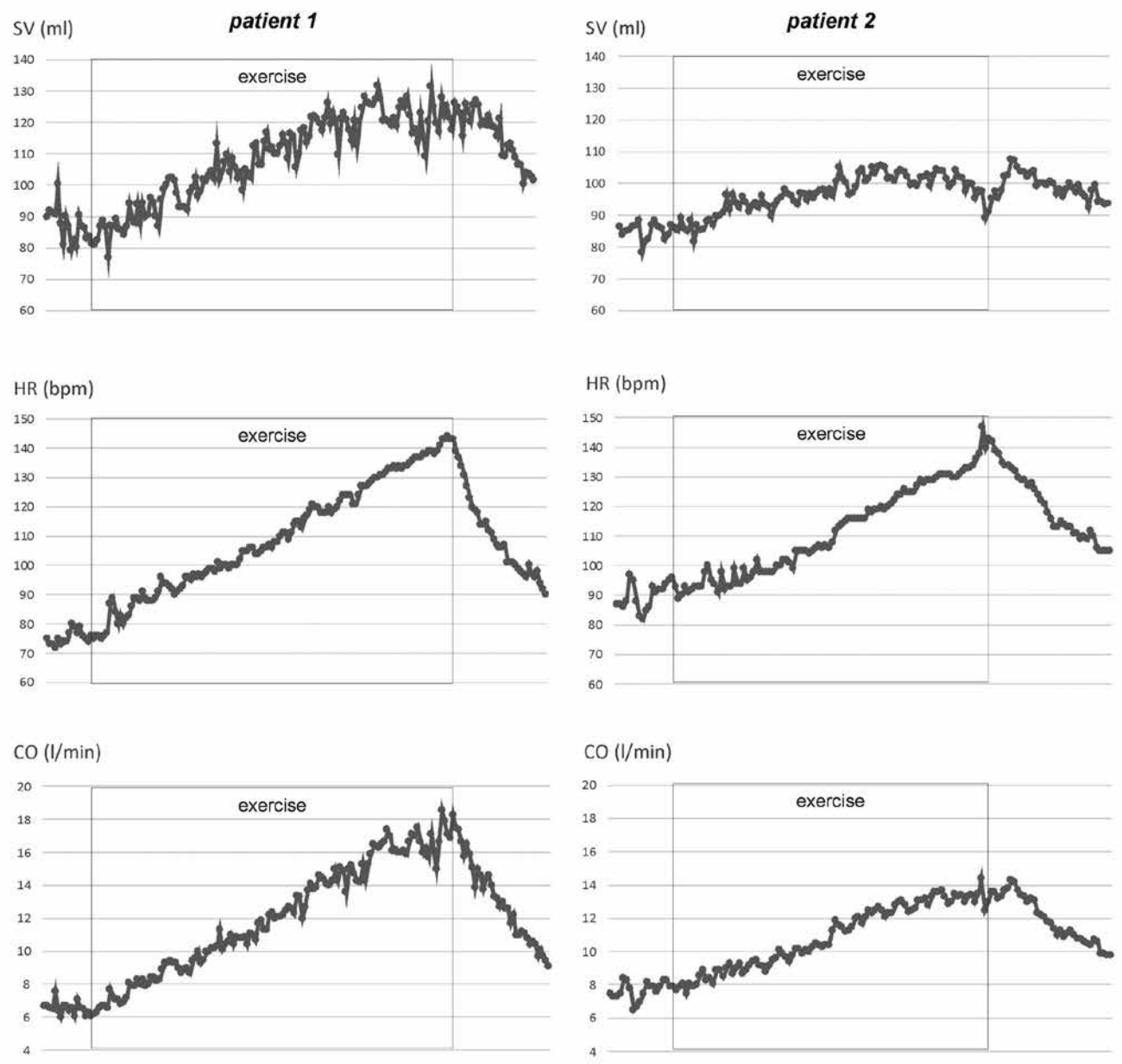

Fig. 2. Exemplary records of exercise cardioimpedance cardiography (PhysioFlow, Manatec, France) with different patterns of SV change:
1) patient 1 (left charts): a 56-year-old woman [with resting BP 123/72 mm Hg; peak VO_2 21.9 mL/min/kg (115% of predicted value); exercise time 12'07"; LVEF 70%, normal left ventricular diastolic function and myocardial mass] – significant progressive increase of SV (from 87 mL at rest to 126 mL at peak exercise);
2) patient 2 (right charts): a 50-year-old woman [with resting BP 121/80 mm Hg; peak VO_2 18 mL/min/kg (72% of predicted value); exercise time 7'52"; LVEF 67%, normal left ventricular diastolic function and myocardial mass] – initial increase with final decrease of SV (from 88 mL at rest, through 100–105 mL plateau between minute 4 and 6 of exercise, to 95 mL at peak exercise)
BP – *blood pressure;* **CO** – *cardiac output;* **HR** – *heart rate;* **LVEF** – *left ventricular ejection fraction;* **SV** – *stroke volume;* **VO_2** – *oxygen uptake; exercise period limited by the box*

across a wide spectrum. Many patients failed to achieve the predicted values for these parameters. There have already been reports of an association between AH and low peak VO_2 values[28]. Interestingly, low peak VO_2 values were also reported in asymptomatic patients with normal exercise capacity, who exhibited cardiovascular risk factors[29].
The obtained mean values of measured CPET parameters place our study group between healthy individuals and patients diagnosed with HF. In comparison with the findings by Garcia et al.[30], the VE/VCO_2 and HRR values recorded in our study were closer to those of healthy individuals, whereas the O_2 pulse and peak VO_2 values were closer to those of patients with HFpEF. However, our finding that the VO_2/WR relationship – a parameter independent of sex, age, height or physical fitness[31] – was low in 58% of patients is of note. This may indicate an

 DOI: 10.15557/PiMR.2019.0009

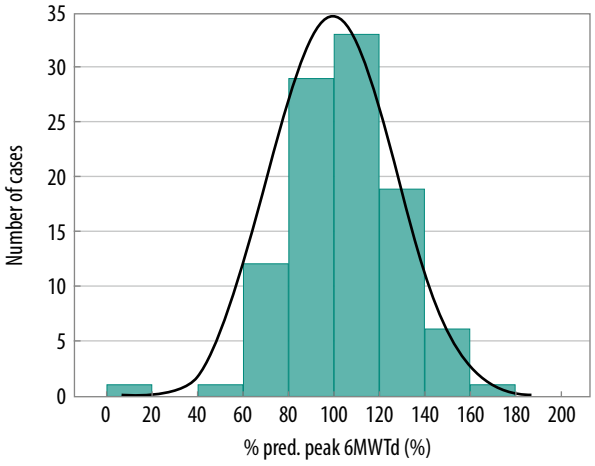

Fig. 3. Histogram of the distance covered during the 6MWT expressed as percentage of the predicted distance

important role of anaerobic mechanisms in adapting to exercise, which was observed in patients with cardiovascular dysfunction[32]. Reduced exercise capacity was also indicated by a major proportion of patients who failed to reach the predicted 6MWTd.

Exercise ICG helped assess the role of individual mechanisms in the haemodynamic response to exercise and detect differences between populations and changes of evaluated parameters over time[18]. An increasing oxygen demand typically leads to an increase in HR and SV and a decrease in SVR, the purpose of which is to increase CO and tissue perfusion while maintaining acceptable blood pressure values[32]. Our study showed that these parameters ranged across a wide spectrum at peak exercise. This is consistent with earlier reports[33–38], which showed that haemodynamic parameter values depended on patients' age, sex, fitness level, and – unsurprisingly – their clinical status. The mean values of these parameters at peak exercise fell to the lower limit of the normal range recommended for healthy individuals (peak SV 110.2 ± 21.8 mL vs. 100–140 mL and peak CO 15.9 ± 4.2 L/min vs. 15–25 L/min)[29] and were similar to those reported in earlier studies[39,40]. In comparison to the findings reported by Fukuda et al.[38] the changes in haemodynamic parameters (HR, CO) observed in our study group were comparable with those in patients with uncomplicated AH; moreover, the increase in SV observed in our study group was comparable to that reported by Fukuda in patients with HFpEF. It is noteworthy that in our study there were patients whose SV at peak exercise was lower than the resting value.

These abnormalities are most likely due to subclinical complications of AH. High blood pressure leads to detrimental arterial and myocardial remodelling, which contributes to the development of haemodynamic disturbances. Arterial stiffness may be either a result of vascular adaptation to non-physiological haemodynamic conditions or the primary cause of hypertension[41]. A long-term adaptation of the myocardium to an increased afterload may lead to LVH and LVDD[42,43]. Initially, an abnormal relaxation pattern and elevated filling pressure of the left ventricle may occur only during exercise; however, symptomatic HF – which is associated with both functional and structural left ventricular wall stiffness – develops over time[42]. In such cases, if the potential of CO to increase by an increase in SV is limited, the effect is detrimental, as the only mechanism of adapting to the increasing cardiac load would be an increase in HR.

CLINICAL IMPLICATIONS

The coexistence of a subjective reduction in exercise tolerance, objective decline in exercise capacity, and abnormal haemodynamic response to exercise in patients with AH requires further studies aiming to determine the mutual relationship of these phenomena and their association with cardiovascular risk. ICG may be a valuable complement to CPET. Additionally, it can help identify abnormal ventricular-arterial coupling, which may be associated with the reported symptoms.

LIMITATIONS

We are aware that the small sample size is a limitation of the study. Therefore, the invasive haemodynamic assessment (heart catheterisation) was not performed, and we cannot definitively exclude pulmonary hypertension and preload failure related to impaired venous return to the left atrium[10]. However, echocardiography results were not suggestive of significantly increased pulmonary pressures. Another limitation is that we did not perform diagnosis to exclude asymptomatic ischaemic heart artery disease, such as myocardial scintigraphy or coronarography, in all subjects. However, no signs and symptoms suggesting cardiac ischaemia, such as LV wall motion abnormalities, electrocardiogram findings, were noted. Our study comprised mostly middle-aged hypertensives without any other serious comorbidities and our results should not be extrapolated to the general population. On the other hand, the strength of our results is that we recruited subjects without other serious chronic diseases, including those taken into account in the differentiation of dyspnoea.

CONCLUSIONS

Although symptoms of reduced exercise tolerance as well as abnormal results of objective exercise capacity assessments are common in patients with uncomplicated AH, a very small proportion of these patients meet the current criteria for being diagnosed with HF. The experience from this study suggests that ICG may reveal impaired haemodynamic adaptation to exercise. The clinical value of this method in identifying pathophysiological substrate for exercise intolerance and its prognostic value should be further investigated.

DOI: 10.15557/PiMR.2019.0009

Summary Table	
What is known about the topic	What this study adds
1. The knowledge about differences in exercise tolerance and haemodynamic response to exercise in patients with uncomplicated atrial hypertension is still limited	1. A very small proportion (6.2%) of patients with uncomplicated hypertension meet the criteria for being diagnosed with heart failure, however, the symptoms of impaired exercise in those patients are quite common (50%) 2. A large proportion of patients with uncomplicated hypertension (45.9%) demonstrated objective evidence (with CPET and 6MWT) of reduced exercise capacity 3. ICG revealed individual differences in haemodynamic response to exercise, including abnormal changes in stroke volume at the middle and final stage of exercise (plateau and even decrease)

Conflict of interest

The authors declare no conflict of interest.

Funding/Support and role of the sponsor

The study was supported by the Ministry of Science and Higher Education/Military Institute of Medicine, Warsaw, Poland (grant no. 336/WIM).

References

1. Mancia G, Fagard R, Narkiewicz K et al.; Task Force Members: 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31: 1281–1357.
2. Ponikowski P, Voors AA, Anker SD et al.; Authors/Task Force Members; Document Reviewers: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891–975.
3. Zdrojewski T, Rutkowski M, Bandosz P et al.: Prevalence and control of cardiovascular risk factors in Poland. Assumptions and objectives of the NATPOL 2011 Survey. Kardiol Pol 2013; 71: 381–392.
4. Kitzman DW: Exercise intolerance. Prog Cardiovasc Dis 2005; 47: 367–379.
5. Kim ES, Ishwaran H, Blackstone E et al.: External prognostic validations and comparisons of age- and gender-adjusted exercise capacity predictions. J Am Coll Cardiol 2007; 50: 1867–1875.
6. Enright PL, Sherrill DL: Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998; 158: 1384–1387.
7. Balady GJ, Arena R, Sietsema K et al.: American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research: Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010; 122: 191–225.
8. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111–117.
9. Fletcher GF, Ades PA, Kligfield P et al.: American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention: Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013; 128: 873–934.
10. Berry NC, Manyoo A, Oldham WM et al.: Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. Pulm Circ 2015; 5: 610–618.
11. Kurpaska M, Krzesiński P, Gielerak G et al.: Hemodynamical conditions of exercise capacity in patients with arterial hypertension – preliminary report. Lek Wojsk 2015; 93: 244–252.
12. Konstantinides SV, Torbicki A, Agnelli G et al.; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC): 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35: 3033–3069.
13. Lang RM, Badano LP, Mor-Avi V et al.: Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28: 1–39.e14.
14. Marwick TH, Gillebert TC, Aurigemma G et al.: Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). Eur Heart J Cardiovasc Imaging 2015; 16: 577–605.
15. Nagueh SF, Smiseth OA, Appleton CP et al.; Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri: Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016; 17: 1321–1360.
16. Wasserman K, Hansen JE, Sue DY et al.: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. Lippincott Williams & Wilkins, Philadelphia 2004.
17. American Thoracic Society; American College of Chest Physicians: ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211–277.
18. Gordon N, Abbiss CR, Maiorana AJ et al.: Intrarater reliability and agreement of the physioflow bioimpedance cardiography device during rest, moderate and high-intensity exercise. Kinesiology (Zagreb) 2018; 50 Suppl 1: 140–149.
19. Dumitrescu D, Oudiz RJ, Karpouzas G et al.: Developing pulmonary vasculopathy in systemic sclerosis, detected with non-invasive cardiopulmonary exercise testing. PLoS One 2010; 5: e14293.
20. Zdrojewski T, Szpakowski P, Bandosz P et al.: Arterial hypertension in Poland in 2002. J Hum Hypertens 2004; 18: 557–562.
21. Krzesiński P, Hałas K, Gielerak G et al.: [Cardiovascular risk and inflammatory markers in patients with hypertension]. Pol Merkur Lekarski 2015; 38: 70–76.
22. Drygas W, Niklas AA, Piwońska A et al.: Multi-centre National Population Health Examination Survey (WOBASZ II study): assumptions, methods, and implementation. Kardiol Pol 2016; 74: 681–690.
23. Lubien E, DeMaria A, Krishnaswamy P et al.: Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002; 105: 595–601.
24. Parekh N, Maisel AS: Utility of B-natriuretic peptide in the evaluation of left ventricular diastolic function and diastolic heart failure. Curr Opin Cardiol 2009; 24: 155–160.

25. Krzesiński P, Uziebło-Życzkowska B, Gielerak G et al.: Echocardiographic assessment and N-terminal pro-brain natriuretic peptide in hypertensives with metabolic syndrome. Adv Clin Exp Med 2017; 26: 295–301.
26. Seki S, Tsurusaki T, Kasai T et al.: Clinical significance of B-type natriuretic peptide in the assessment of untreated hypertension. Circ J 2008; 72: 770–777.
27. Gharavi AG, Diamond JA, Goldman AY et al.: Resting diastolic function and left ventricular mass are related to exercise capacity in hypertensive men but not in women. Am J Hypertens 1998; 11: 1252–1257.
28. Goodman JM, McLaughlin PR, Plyley MJ et al.: Impaired cardiopulmonary response to exercise in moderate hypertension. Can J Cardiol 1992; 8: 363–371.
29. Aspenes ST, Nilsen TI, Skaug EA et al.: Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. Med Sci Sports Exerc 2011; 43: 1465–1473.
30. Garcia EL, Menezes MG, Stefani C de M et al.: Ergospirometry and echocardiography in early stage of heart failure with preserved ejection fraction and in healthy individuals. Arq Bras Cardiol 2015; 105: 248–255.
31. Straburzyńska-Migaj E: Testy spiroergometryczne w praktyce klinicznej. Wydawnictwo Lekarskie PZWL, Warszawa 2010.
32. Górski J (ed.): Fizjologiczne podstawy wysiłku fizycznego. Wydawnictwo Lekarskie PZWL, Warszawa 2006.
33. Vella CA, Robergs RA: A review of the stroke volume response to upright exercise in healthy subjects. Br J Sports Med 2005; 39: 190–195.
34. Agostoni P, Vignati C, Gentile P et al.: Reference values for peak exercise cardiac output in healthy individuals. Chest 2017; 151: 1329–1337.
35. Park S, Ha JW, Shim CY et al.: Gender-related difference in arterial elastance during exercise in patients with hypertension. Hypertension 2008; 51: 1163–1169.
36. Krzesiński P, Stańczyk A, Gielerak G et al.: Sex determines cardiovascular hemodynamics in hypertension. J Hum Hypertens 2015; 29: 610–617.
37. Krzesiński P, Stańczyk A, Gielerak G et al.: The hemodynamic patterns in hypertensive men and women of different age. J Hum Hypertens 2016; 30: 177–185.
38. Fukuda T, Matsumoto A, Kurano M et al.: Cardiac output response to exercise in chronic cardiac failure patients. Int Heart J 2012; 53: 293–298.
39. Fagard RH, Pardaens K, Staessen JA et al.: Prognostic value of invasive hemodynamic measurements at rest and during exercise in hypertensive men. Hypertension 1996; 28: 31–36.
40. Chiba Y, Maehara K, Yaoita H et al.: Vasoconstrictive response in the vascular beds of the non-exercising forearm during leg exercise in patients with mild chronic heart failure. Circ J 2007; 71: 922–928.
41. Kass DA: Ventricular arterial stiffening: integrating the pathophysiology. Hypertension 2005; 46: 185–193.
42. Phillips SA, Vuckovic K, Cahalin LP et al.: Defining the system: contributors to exercise limitations in heart failure. Heart Fail Clin 2015; 11: 1–16.
43. Palmieri V, Russo C, Palmieri EA et al.: Isolated left ventricular diastolic dysfunction: implications for exercise left ventricular performance in patients without congestive heart failure. J Am Soc Echocardiogr 2006; 19: 491–498.
44. Lewartowski B: Patofizjologia rozkurczowej niewydolności serca. Kardiol Pol 2008; 66: 1096–1101.

DOI: 10.15557/PiMR.2019.0009 PEDIATR MED RODZ Vol. 15 No. 1, p. 47–56