International Journal of Cardiology 220 (2016) 196–200

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Neurohormonal activation and exercise tolerance in patients supported with a continuous-flow left ventricular assist device

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ARTICLE INFO

Article history:
Received 20 June 2016
Accepted 26 June 2016
Available online 27 June 2016

Keywords:
Left ventricular assist device
Exercise intolerance
Biomarkers
Neurohormonal activation
Quality of life
Advanced heart failure

ABSTRACT

Background: Neurohormones play a key role in regulating hemodynamics in heart failure (HF) both at rest and during exercise. In contrast, little is known about the importance of neurohormonal regulation for exercise capacity in continuous-flow left ventricular assist device (CF-LVAD) patients. The aim of this study was to assess the relation between neurohormonal activation patterns in CF-LVAD patients and exercise capacity.
Methods: Plasma concentrations of the C-terminal portion of pro-arginine vasopressin precursor (copeptin), pro-adrenomedullin (proADM), pro-B-type (proBNP) and pro-atrial (proANP) natriuretic peptides were measured in 25 CF-LVAD patients (HeartMate II) in the morning prior to maximal cardiopulmonary exercise testing determining peak oxygen uptake (peak VO_2). Quality of life (QOL) was determined by questionnaires.
Results: Peak VO_2 was severely reduced averaging 13.0 ± 5.3 ml/kg/min and exhibited strong negative correlations with copeptin, $r = -0.61$ ($p = 0.001$) and proADM, $r = -0.56$ ($p = 0.005$). Additionally comparing patients with peak $VO_2 < 14$ vs ≥ 14 ml/kg/min demonstrated significant differences in copeptin and proADM concentrations, 2.8 ± 0.8 vs 2.1 ± 0.7 pmol/l ($p = 0.03$) and 1.0 ± 0.5 vs 0.7 ± 0.2 nmol/l ($p = 0.01$), respectively. In contrast natriuretic peptides were not associated with maximal exercise capacity. Lower QOL correlated with increasing proBNP.
Conclusion: Resting plasma levels of proADM and copeptin are significantly correlated with peak VO_2 in CF-LVAD patients. Future studies should address if interventions to lower the levels of these markers are associated with restoration of exercise tolerance.

1. Introduction

Continuous-flow left ventricular assist devices (CF-LVADs) are increasingly used to treat end-stage heart failure (HF), either as a bridge-to-transplant (BTT) or as so-called destination therapy (DT). Although CF-LVADs improve survival, several studies have shown that exercise capacity remains reduced after device implantation [1]. It is widely accepted that neurohormones play a key role in the regulation of hemodynamics in HF both at rest and during exercise [2–7]. In contrast, little is known about the importance of neurohormonal regulation for exercise capacity in HF patients supported with CF-LVADs.

Whereas dependence on adequate mechanical left ventricular support during exercise has been documented in CF-LVAD patients [8,9], several factors under neurohormonal influence, such as right ventricular function, and pulmonary -and peripheral vascular resistance, are likely to be involved in determining exercise capacity. Hence, analysis of the neurohormonal activation pattern in CF-LVAD patients, and in particular the association with exercise capacity, could improve our understanding of the physical limitations of this patient group and potentially identify targets for intervention. The aim of this study was to assess the relation between pre-specified neurohormonal markers and exercise capacity in CF-LVAD recipients.

2. Method

2.1. Study cohort and design

All included patients (n = 25) were ambulatory CF-LVAD recipients (HeartMate II [HM II], Thoratec, Pleasanton, California). Study interventions consisted of biomarker sampling, echocardiographic examination and maximal cardiopulmonary exercise testing (CPET). Self-reported quality of life (QOL) was determined by questionnaires. On a separate day a subset of the patients (n = 10) had repeat biomarkers assessed in relation to hemodynamic evaluation by right heart catheterization (RHC). We have previously reported on these hemodynamics in the subgroup ([10]), however, the relation with biomarkers have never been published for this group. The study was approved by the Ethics Committee of Copenhagen in accordance to the Helsinki declaration (Project no. H-1-2012-092/suppl. protocol) and was declared at ClinicalTrials.gov with identifier NCT02303236. All patients provided written informed consent.

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http://dx.doi.org/10.1016/j.ijcard.2016.06.245
0167-5273/

2.2. Exercise protocol

Cardiopulmonary exercise testing was performed on one of two comparable systems on upright ergometer bicycles (Ergoline D-72475 Bitz, Germany or Schiller CS-200, Schiller AG, Bar, Switzerland). Calibration before each test for gas, ambient conditions and flow, according to manufacturer's instructions, was performed. Breath-by-breath respiratory gas was analyzed measuring oxygen consumption (VO_2), carbon dioxide excretion (VCO_2) and expiratory minute ventilation (V_E). Peak oxygen uptake (peak VO_2) was calculated as ml/kg/min. The participants were encouraged to keep cycling until exhaustion and were monitored with pulse oximetry and continuous 12-lead electrocardiogram during exercise.

2.3. Biomarker measurements and analysis

Blood samples were drawn from an intravenous catheter placed in the antecubital vein in the morning prior to other study interventions. Specimens were immediately put on ice and centrifuged. Plasma was stored at −80 °C until analysis. The banked plasma was analyzed in a batch by a core laboratory that was blinded to clinical patient data. White blood cell (WBC) count and C-reactive protein (CRP) were evaluated as markers of inflammation, pro-B-type (proBNP) and pro-atrial (proANP) natriuretic peptides as markers of myocardial stress, and lastly the C-terminal portion of pro-arginine vasopressin precursor (copeptin) and pro-adrenomedullin (proADM) as broader neurohormonal responses to heart failure. All precursor hormones were measured by automated methods; proBNP on the Cobas platform (Roche, Germany) and proANP, copeptin and proADM on a Kryptor Compact Plus (thermos-Fisher, Germany). The analytical performance of the methods has been validated previously [11,12].

2.4. Self-assessed health status

Quality of life was evaluated by the Minnesota living with heart failure (MLWHF) questionnaire and stated both with global score (MLWHF-G) and physical dimension score (MLWHF-P: point 2–7 + 12–13). Mental health was determined by the Major Depression Inventory (MDI) questionnaire (no symptoms, mild, moderate or severe).

2.5. Echocardiographic examination

Echocardiography was performed according to current guidelines [13] on an Philips iE33 cardiac ultrasound system (Philips Healthcare, Best, the Netherlands). Pulsed – and continuous wave Doppler images were acquired in the parasternal long-axis view and the apical 4 chamber view. LV dimensions were measured from parasternal M-mode images. AV opening was assessed in both the parasternal long-axis view and the apical view. At least ten consecutive cardiac cycles were reviewed, and the frequency of AV opening recorded as a proportion.

2.6. Right heart catheterization

Central venous pressure (CVP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO) and mixed venous blood oxygen saturation (SvO_2) were measured by RHC, via the right internal jugular vein, using a Swan-Ganz catheter (PAC VIP, Edwards Lifesciences, CA, USA). Cardiac output was measured three times by standard thermodilution using injection of cold isotonic glucose solution (5%) and the average result was recorded. Systemic – and pulmonar vascular resistance (SVR and PVR) were subsequently calculated as SVR = (mean arterial pressure − CVP)/CO and PVR = (mPAP-PCWP) / CO, respectively.

2.7. Statistical analysis

Statistical analysis was carried out using SAS 9.4 Statistical Software (Cary, NC, USA). If indicated, due to deviation from the normal distribution, concentrations of biomarkers were log-transformed. Comparison between groups was performed using two-sided paired or unpaired Student's *t*-test or ANOVA as appropriate. The association between continuous variables was described using correlation coefficients, Spearman's rank or Pearson correlation coefficient, as appropriate. Statistical significance was defined by a two-tailed P-value <0.05. Data is presented as mean ± standard deviation unless otherwise stated.

3. Results

3.1. Study cohort

Patients were predominantly men, aged 54 ± 14 years, suffering from non-ischemic cardiomyopathy (Table 1). Average CF-LVAD support duration was approximately one year, (BTT) being the most common indication. The aortic valve remained closed in 17 out of 25 patients at an average baseline pump speed of 9272 ± 299 rpm. All patients but one received β-blocking therapy - the exception digoxin.

Table 1
Baseline characteristics.

Clinical characteristics		
	Age (years)	54 ± 14
	Height (cm)	182 ± 6
	Weight (kg)	90 ± 14
	ICM/NICM	8/17
	Male/female	23/2
	Beta-blocker/Digoxin	24/1
Pump characteristics		
	Support duration	355 ± 421
	Pump speed (rpm)	9272 ± 299
	DT/BTT/BTD	7/17/1
Exercise parameters		
	Peak VO_2 (ml/kg/min)	13.0 ± 5.3
	RER	1.13 ± 0.1
	APMHR	166 ± 14
	Resting HR	77 ± 12
	Maximal HR	132 ± 23
	HRR	0.62 ± 26
	Maximal load (watt)	97 ± 42
	Exercise duration (s)	434 ± 189
Biomarkers		
	Hemoglobin (mmol/l)	7.9 ± 1.2
	White blood cell count ($\times 10^9$/l)	8.1 ± 3.3
	C-reactive protein (mg/l)	8.1 ± 7.7
	proBNP (pmol/l)	194.6 ± 113.8
	proANP (pmol/l)	274 ± 108
	proADM (nmol/l)	0.9 ± 0.4
	Copeptin (pmol/l)	16.4 ± 12.3
	Creatinine (umol/l)	92.8 ± 24.7
	eGFR (ml/min/1.73 m^2)	73.0 ± 17.1
	LDH (U/l)	384,0 ± 152.9
	Haptoglobin (g/l)	<0.2
Echocardiographic parameters		
	LVEDD (cm)	6.3 ± 1.2
	TAPSE (cm)	1.3 ± 0.5
	LVEF (%)	17 ± 10
	AV (closed/open/partly open)	17/5/3
Quality of life		
	Total MLWHF (U)	40 ± 24
	Physical MLWHF (U)	16 ± 10
Mental health		
	MDI (no symptoms/mild/moderate/severe)	19/3/2/1

Data are mean ± standard deviation or proportions. Abbreviations: ICM = Ischemic cardiomyopathy, NICM = non-ischemic cardiomyopathy, DT = destination therapy, BTT = bridge-to-transplant, BTD = bridge to decision, RER = respiratory exchange ratio, APMHR = age predicted maximal heart rate, HR = heart rate, HRR = heart rate reserve eGFR = estimated glomerular filtration rate, LDH = lactate dehydrogenase, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, TAPSE = tricuspid annular plane systolic excursion, LVEF = left ventricular ejection fraction, AV = aortic valve, MLWHF = Minnesota living with heart failure, MDI = Major depression inventory.

3.2. Biomarkers and exercise parameters

White blood cell count was 8.1 ± 3.3 × 10^9/l, plasma concentrations of CRP 8.1 ± 7.7 mg/l, proBNP 194.6 ± 113.8 pmol/l, proANP 274 ± 108 pmol/l, proADM 0.9 ± 0.4 nmol/l and copeptin 16.4 ± 12.3 pmol/l. Maximal exercise capacity was severely reduced with peak VO_2 averaging 13.0 ± 5.3 ml/kg/min corresponding to 44 ± 16% of predicted for age, weight and gender. Respiratory exchange ratio (RER) was 1.13 ± 0.1, maximal heart rate 132 ± 23 bpm, exercise duration 434 ± 189 s and maximal workload 97 ± 42 W, Table 1.

Peak VO_2 exhibited strong negative correlations with proADM, r = −0.56 (p = 0.005) and logCopeptin, r = −0.61 (p = 0.001). In contrast natriuretic peptides were not associated with peak VO_2, logproANP, r = −0.21 (p = 0.3) and logproBNP, r = −0.32 (p = 0.1), Fig. 1. Plasma concentrations of biomarkers in patients with peak VO_2 < 14 vs ≥ 14 ml/kg/min are shown in Fig. 2. Hemoglobin level was