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Atrioventricular Conduction Delay Predicts Impaired Exercise Capacity in Patients with Heart Failure with Reduced Ejection Fraction

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Background: Atrioventricular conduction delay (AVCD) impairs left ventricular (LV) filling and consequently leads to a reduction of cardiac output. We hypothesized that in patients with severely depressed LV function and coexisting intraventricular conduction disturbances (IVCD), AVCD can affect exercise performance. Therefore, we evaluated the association of AVCD and exercise capacity in patients with heart failure (HFREF) and coexisting IVCD.

Material/Methods: We included patients with stable, chronic HFREF, LVEF <35%, sinus rhythm, and QRS ≥120 ms. PR interval and peak oxygen consumption ($VO_{2\ peak}$) were specifically investigated. Multiple regression analysis was used to adjust the association between PR interval and $VO_{2\ peak}$ for possible confounders.

Results: Most (57.5%) of the 40 included patients [20% female, aged 63±12, 47.5% of ischemic etiology (IHD)] were in NYHA class III. Mean PR interval was 196±38.1 ms. There were 26 (65%) patients with PR interval ≤200 ms and 14 (35%) with >200 ms. Groups were similar in clinical, laboratory, echocardiographic parameters, QRS morphology, and treatment regimens. $VO_{2\ peak}$ was lower in patients with longer PR interval group as compared to shorter PR interval group (12.3±4.1 *vs.* 17.06±4.4, p=0.002). In the regression model, PR interval, female sex, and IHD remained important predictors of $VO_{2\ peak}$ ($_{partial}$=–0.50, p=0.003; $r_{partial}$=–0.48, p=0.005; $r_{partial}$=–0.44, p=0.01; R^2=0.61).

Conclusions: Delayed AV conduction contributes to decreased exercise capacity in patients with HFREF and coexisting IVCD.

MeSH Keywords: Atrioventricular Block • Exercise Test • Heart Conduction System • Oxygen Consumption

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Background

Cohort studies and clinical trials suggest that atrioventricular conduction delay (AVCD) carries a significant risk for adverse prognosis. Prolongation of PR interval on surface electrocardiogram (ECG) has been shown to be associated with a 1.24-fold increase in long-term risk for all-cause mortality, heart failure (HF), and atrial fibrillation in the general population [1]. In patients with ischemic heart disease (IHD), presence of AVCD was linked to an increased risk for both HF hospitalization and overall mortality [2]. HF patients with elongated PR interval present a >3-fold increase in risk for death, HF hospitalization, and deterioration [3-5]. Several studies have shown that cardiac resynchronization therapy (CRT) brings more benefit in terms of mortality and morbidity to patients with prolonged *vs.* normal PR interval, regardless of QRS duration and morphology [3–7].

While it has been shown that QRS duration of ≥120 ms in patients with HF with reduced ejection fraction (HFREF) is associated with more advanced myocardial disease, worse exercise capacity, and worse prognosis as compared to those with QRS <120 ms [8], the evidence on the relationship between AVCD and exercise capacity in this group of patients is very limited. Prolongation of atrioventricular (AV) conduction may impair left ventricular (LV) diastolic filling, the presence of AVCD in the severely diseased subset of HFREF patients with coexisting intraventricular conduction disturbances (IVCD) may lead to further reduction of already impaired cardiac output, escalate the severity of symptoms, and thereby decrease exercise capacity.

Correction of prolonged PR interval by CRT pacing may potentially attenuate this diastolic under-filling, improving overall LV hemodynamics. In fact, results of 1 trial's subanalysis showed that patients implanted with a CRT device who had baseline PR interval ≥180 ms exhibited significant increase in peak exercise oxygen consumption ($VO_{2\ peak}$) in comparison to those with PR <180 ms, who derived no benefit [9].

As decreased exercise capacity is one of the cardinal manifestations of HF, its measurement provides valuable pathophysiologic and clinical information. It directly reflects disease severity, allows prognostic stratification, and guides therapeutic decisions.

In the present study, we aimed to assess the impact of AVCD on exercise capacity in patients with HFREF and coexisting IVCD.

Material and Methods

Study group

We retrospectively included in this study consecutive patients with chronic HFREF, who were considered to undergo CRT device implantation at John Paul II Hospital in Cracow, Poland between 2013 and 2014.

Inclusion criteria were: New York Heart Association (NYHA) functional classes II–IV despite optimal medical therapy and coronary revascularization, without exacerbations within the past 3 months; LV ejection fraction (LVEF) ≤35%; sinus rhythm; and QRS duration ≥120 ms on 12-lead ECG. Exclusion criteria were: persistent atrial fibrillation and a history of any pacemaker or cardioverter defibrillator implantation; significant respiratory disease; and neurological or orthopedic disorders limiting exercise. Unstable, exacerbated patients presenting with pulmonary congestion or peripheral edema were also not included in the study.

All patients provided written informed consent to participate in this study. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee at Jagiellonian University in Cracow, Poland.

All measurements and patient medical records were prospectively acquired by the authors themselves.

Electrocardiography

Standard 12-lead ECGs were recorded in all patients at the paper speed of 25 mm/s, calibrated at 1.0 mV/cm. PR interval and the QRS duration were measured and the QRS morphology was analyzed according to practice guidelines [10]. AVCD was defined as PR interval >200 ms. Based on the PR interval length, we divided patients into 2 groups: (1) ≤200 ms and (2) >200 ms. Left bundle branch block (LBBB) was defined according to contemporary guidelines [11]. IVCD other than LBBB were classified as RBBB or non-specific IVCD (nsIVCD).

Cardiopulmonary exercise test

Exercise capacity was evaluated by means of cardiopulmonary exercise test (CPET) performed using a Reynolds Medical TMX425 TRACKMASTER treadmill unit with continuous measurement of oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) on a Reynolds Medical ZAN-600 respiratory gas analyzer. Modified Naughton protocol was applied to all patients [12,13]. VO_2, VCO_2, and VE were obtained by breath-by-breath analyses of the expired gas. $VO_{2\ peak}$ was defined as the highest value of oxygen uptake attained in the final 30 s of exercise. $VO_{2\ peak}$ was calculated as weighted terms (ml/kg per min) and as a percentage of predicted maximal exercise oxygen consumption (VO_{2max}) in relation to age and sex. Anaerobic threshold (AT) was defined as a submaximal VO_2 level where there is a nonlinear rise in VE and VCO_2 and expressed as ml/kg per minute. Respiratory exchange ratio (RER) was defined as the VCO_2/VO_2.

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Maximum age-predicted heart rate was calculated by the formula: 220 – age, and was used to determine the presence of chronotropic incompetence (CI), defined as failure to achieve 85% of age-predicted maximal heart rate [14,15].

Echocardiography

We used the commercially available Vivid 7 device (GE Medical System, Horten, Norway) equipped with a phased-array 3.5-MHz transducer to perform echocardiographic examinations. LVEF, as a measure of LV systolic function, was calculated using the Simpson biplane method [16]. The ratio of early diastolic mitral velocity to early diastolic velocity of the mitral annulus (E/e') was used as a measure of LV diastolic function [17].

Statistical analysis

Categorical variables were described as counts and percentages and continuous variables as means ± standard deviations or median and interquartile range. We used the unpaired Student's t-test for normally distributed variables, the Mann-Whitney U-test for non-normally distributed continuous data, and the chi-square test for categorical data to compare patients with and without AVCD. Pearson correlation coefficient (normal distribution) or Spearman rank correlation (non-normal distribution) were used to investigate associations between continuous variables. We examined correlations between (a) age, sex, etiology, LVEF, E/e' ratio, levels of creatinine and hemoglobin, QRS duration and morphology, PR interval and (b) the $VO_{2\ peak}$. Multiple stepwise linear regression analysis with the use of a manual forward variable elimination method was consecutively used to adjust the association between PR interval and $VO_{2\ peak}$ for possible confounders such as age, sex, HF etiology, LVEF, E/e' ratio, levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), creatinine and hemoglobin, QRS duration and morphology, and the presence of CI [18]. The significance level was set at $p<0.05$. Statistical analyses were performed with Statistica PL software [StatSoft, Inc. (2014). STATISTICA (data analysis software system), version 12. www.statsoft.com] and MedCalc version 11.6.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

Patients characteristics

Among 52 eligible patients, 11 were excluded due to missing CPET data and 1 due to lack of informed consent. The study group was composed of 40 participants. Clinical characteristics of the study participants are shown in Table 1, indicating recruitment of a typical group of community-based HFREF patients meeting established criteria for the CRT device implantation [19].

Most of the patients were male [32(80%)]. Most were in class III by NYHA [23(57.5%)], 22 (55%) were in class II, and 6 (15%) were in class IV. Ischemic etiology was present in 19 (47.5%). A substantial proportion of patients were treated in accordance with contemporary guidelines [20]. Thirty-nine patients used beta blockers (97.5%); 39 (97.5%) used angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; 36 (90%) used aldosterone receptor antagonist; and 37 (92.5%) used loop diuretics. The mean LVEF was 23.8±5.3% and the mean E/e' ratio was 15.1±5.7. Median QRS duration was 140 ms [120–160].

Mean PR interval was 196±38.1 ms. There were 26 (65%) patients with PR interval ≤200 ms and 14 (35%) with PR interval >200 ms. Comparisons of these 2 groups are presented in Table 1. Groups did not differ in terms of demographic, clinical, laboratory, echocardiographic parameters, or treatment regimens. QRS duration was shorter in patients with AVCD. Prevalence of LBBB, RBBB, and nsIVCD was similar in both groups.

CPETs were performed without serious complications, chest pain, or ischemic ECG changes in all patients and were terminated if there was shortness of breath or general fatigue. Detailed CPET parameters are shown in Table 2. Exercise effort achieved by study patients was considered diagnostic with a median RER of 1.04 [0.97–1.14]. Mean $VO_{2\ peak}$ was 15.4±4.8 ml/kg/min. Patients with PR interval >200 ms had lower $VO_{2\ peak}$,% of predicted VO_{2max}, exercise duration, and load in comparison to patients with PR interval ≤200 ms and expressed a trend towards decreased ventilatory response to exercise (VE/VCO_2).

CI was present in 17 (42.5%) patients. Patients with CI had lower $VO_{2\ peak}$ and longer PR interval as compared to those without (12.9±4.8 ml/kg/min *vs.* 17.2±4.1 ml/kg/min, p=0.004, respectively) and (217.6±32.2 ms *vs.* 180±34.5 ms, p=0.001, respectively).

In relation to the PR interval at rest, decrease of its duration on exercise was observed in 15 (37.5%) patients and remained unchanged in the remaining 25. Neither exercise-induced elongation of PR interval nor occurrence of higher degree AV block was seen in any of the patients. No differences in $VO_{2\ peak}$ were observed in those with decreased and unchanged PR interval on exercise (16.1±3.6 ml/kg/min *vs.* 14.9±5.4 ml/kg/min, p=0.47, respectively).

Investigation for associations showed that age, ischemic etiology, PR interval, and the presence of CI were significantly correlated with $VO_{2\ peak}$ (Table 3). The correlation between PR interval and $VO_{2\ peak}$ was negative, indicating that patients with AVCD had lower $VO_{2\ peak}$. In the multiple stepwise linear

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Table 1. Clinical characteristics of the study patients.

Variable	All patients (n=40)	PR interval ≤200 ms (n=26)	PR interval >200 ms (n=14)	p-value
Age	63±12	63.2±13.5	62.6±9.1	0.86
Women/men [n (%)]	8 (20)/32 (80)	4 (15.4)/22 (84.6)	4 (28.6)/10 (71.4)	0.56
BMI [kg/m^2]	26.4±4.05	26.1±4.4	27.3±3.3	0.34
Ischemic/Non-ischemic [n (%)]	19 (47.5)/21 (52.5)	10 (38.5)/16 (61.5)	9 (64.3)/5 (35.7)	0.12
NYHA [n (%)]				0.34
– II	11 (27.5)	9 (34.6)	2 (14.3)	
– III	23 (57.5)	14 (53.8)	9 (64.3)	
– IV	6 (15)	3 (11.6)	3 (21.4)	
NT-proBNP [pg/ml]	1904 [811–3503]	1847 [503–3267]	2274 [1433–4723]	0.25
Hb [g/dl]	14.5 [13.5–15.4]	14.4 [13.5–15.5]	14.9 [14–15.3]	0.6
Creatinine [umol/l]	87.5 [75.5–100.5]	87.5 [76–104]	85.5 [75–96]	0.73
LVEF [%]	23.8±5.3	23.8±5.3	23.8±5.4	0.98
E/e'	15.1±5.7	14.4±6.2	16.7±4.2	0.27
HR [beats per minute]	71.5±8.8	71.1±9.1	72.6±8.6	0.59
PR interval [ms]	196±38.1	173.5±23.1	237.8±20.8	<0.001
QRS duration [ms]	140 [120–160]	160 [140–160]	135 [120–140]	0.04
LBBB/nsIVCD [n (%)]	23 (57.5)/17 (42.5)	16 (61.5)	7 (50)	0.71
Beta blocker [n (%)]	39 (97.5)	25 (96.1)	14 (100)	0.75
ACE inhibitor [n (%)]	39 (97.5)	25 (96.1)	14 (100)	0.75
Spironolactone [n (%)]	36 (90)	22 (84.6)	14 (100)	0.32
Loop diuretics [n (%)]	37 (92.5)	23 (88.5)	14 (100)	0.49

BMI – body mass index; NYHA – New York Heart Association; NT-proBNP – N-terminal prohormone of brain natriuretic peptide; Hb – hemoglobin; LVEF – left ventricular ejection fraction; E/e' – ratio of early diastolic mitral velocity to early diastolic velocity of the mitral annulus; HR – heart rate; LBBB – left bundle branch block; nsIVCD – non-specific intraventricular conduction disturbances; ACE – angiotensin converting enzyme.

regression model, PR interval, female sex, and ischemic etiology remained important predictors of exercise capacity in the studied group.

Discussion

AVCD is a cardiac conduction system dysfunction, which is manifested by lengthening of PR interval on surface ECG. Duration of PR interval tends to increase with age. Prevalence of AVCD varies among different groups of patients. It becomes more common among patients with IHD and HF [2,21].

There is emerging evidence suggesting that, contrary to what was conventionally believed, prolongation of PR interval carries a risk for unfavorable prognosis. In a meta-analysis of 14 population-based studies that evaluated clinical outcomes in relation to the length of PR interval, with a total number of 400 750 participants, elongated PR interval was associated with a 1.24-fold increase in risk for all-cause mortality, a 1.39-fold increased risk for heart failure or LV dysfunction, and a 1.45-fold increased risk for atrial fibrillation [1].

Similarly in the existence of cardiac disease. In patients with IHD, presence of AVCD was linked to an increased risk for both heart failure hospitalization (2.33-fold) and overall mortality (1.58-fold) over a period 5-year follow-up [2]. A longitudinal

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Table 2. Cardiopulmonary exercise tests parameters.

Variable	All patients (n=40)	PR interval ≤200 ms (n=26)	PR interval >200 ms (n=14)	p-value
Time of exercise [sec]	548±240	623±213	409±231	0.005
Exercise load [METs]	5.4 [3.5–6.3]	5.4 [4.4–6.3]	3.9 [2.5–5.4]	0.005
$VO_{2\ peak}$ [ml/kg/min]	15.4±4.8	17.06±4.4	12.3±4.1	0.002
% pred VO_2 max [%]	57.5 ±19.1	63.6±19.9	46.8±11.9	0.01
AT (mL/kg/min)	10.5 [7.1–12.6]	11.5 [8.0–16.7]	7.2 [6.6–10.7]	0.03
VE/VCO_2	31.25 [27.5–36.5]	30.2 [27.3–34.4]	32.3 [28.2–39.5]	0.22
RER	1.04 [0.97–1.14]	1.02 [0.98–1.08]	1.08 [0.88–1.15]	0.74
CI [n (%)]	17 (42.5)	7 (27)	10 (71.4)	0.006

$VO_{2\ peak}$ – peak oxygen uptake;% pred $VO_{2\ max}$ – percentage of predicted maximal exercise oxygen consumption; AT – anaerobic threshold; VE/VCO_2 – minute ventilation to carbon dioxide production ratio; RER – respiratory exchange ratio; CI – chronotropic incompetence.

Table 3. Association between clinical, laboratory, electro- and echocardiographic variables and $VO_{2\ peak}$.

Variable	Univariate analysis		Multivariate analysis (R^2=0.61)	
	r-value (CI)	p-value	$r_{partial}$-value	p-value
Age [years]	– 0.49 (–0.70 to –0.22)	0.001		
Sex [0 – male; 1 – female]	– 0.25 (–0.52 to –0.06	0.11	–0.48	0.005
Etiology [0 – non-ischemic; 1 – ischemic]	– 0.54 (–0.73 to –0.28)	0.003	–0.44	0.01
PR interval [ms]	– 0.52 (–0.71 to –0.25)	0.0006	–0.50	0.003
QRS duration [ms]	0.16 (–0.16 to 0.45)	0.32		
LBBB [0 – absent; 1 – present]	0.05 (–0.36 to 0.26)	0.76		
CI [%]	– 0.44 (–0.66 to –0.15)	0.004		
LVEF [%]	0.19 (–0.12 to 0.48)	0.22		
E/e’	– 0.008 (–0.33 to 0.32)	0.96		
Creatinine [umol/l]	– 0.26 (–0.5 to 0.05)	0.09		
Hb [g/dl]	0.07 (–0.25 to 0.37)	0.68		
NT-proBNP [pg/ml]	– 0.29 (–0.55 to 0.03)	0.07		

$VO_{2\ peak}$ – peak oxygen consumption; LBBB – left bundle branch block; CI – chronotropic incompetence; LVEF – left ventricular ejection fraction; E/e’ – ratio of early diastolic mitral velocity to early diastolic velocity of the mitral annulus; Hb – hemoglobin; NT-proBNP – N-terminal prohormone of brain natriuretic peptide.

observational study of patients with idiopathic dilated cardiomyopathy disclosed a 3.1-fold higher risk for all-cause mortality related to the presence of AVCD [22]. As in patients with chronic HFREF and coexisting IVCD, delay in AV conduction led to a 1.4-fold to >3-fold increase in risk for death, HF hospitalization, and deterioration [4–6].

Interventional trials with implantable pacing devices conducted in patients with HFREF and a wide QRS complex have not only generated substantial data on such therapy, but also provided insight into the clinical meaning of PR interval prolongation, raising the question of whether ACVD is solely a marker of poor prognosis in this population, or a potentially correctable pathology.

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In a subgroup analysis of the COMPANION trial, patients receiving CRT with a baseline prolonged PR interval ≥200 ms derived the most benefit as compared to patients with a baseline normal PR interval [4]. A post hoc analysis of the MADIT-CRT study showed that non-LBBB patients with prolonged PR interval implanted with a CRT-D had a significant reduction in the cumulative probability of HF and death, but patients with normal PR interval had increased incidence of HF or death after initiation of resynchronization therapy [5]. A substudy from the CARE HF trail demonstrated that, although prolongation of PR interval was a predictor of worse prognosis in both optimal medical treatment and CRT groups, normalization of PR interval by resynchronization therapy significantly improved the outcome [3].

The interest in restoring normal AV conduction in patients with HFREF comes from the observation that prolonged PR interval results in AV dyssynchronization, which impairs diastolic LV filling by delaying mitral valve closure and creating diastolic mitral regurgitation [23]. Specifically, in patients with HFREF with coexisting IVCD in whom prolongation of QRS is associated with more advanced myocardial disease and worse LV function [8], such ineffective contribution of the atrial systole to the stroke volume would further decrease cardiac performance. As opposed to our study, in the ReThinQ trial subanalysis, PR interval of patients with HFREF but without IVCD (QRS <130 ms) was not associated with exercise capacity [9]. We hypothesized that patients with less severe LV disease could compensate for increased duration of PR interval and therefore it does not influence the exercise capacity. On the contrary, patients with more severely diseased LV who have IVCD are more sensitive to delay in AV conduction; therefore, PR prolongation further decreases exercise capacity.

In addition to the stroke volume, cardiac output is dependent on the HR. Presence of CI in patients with HFREF is an important determinant of reduced exercise capacity and is relatively common in patients with AVCD [24].

These detrimental hemodynamic and chronotropic effects of elongated PR interval in already-existing HFREF not only impair prognosis but may also escalate the severity of symptoms and hence are poorly tolerated by this group of patients. Optimization of AV conduction has therefore been suggested to augment the hemodynamic response to single or bi-ventricular pacing in HFREF patients [25–27]. In fact, results of the ReThinQ trial subanalysis showed that implantation of a CRT device in patients with PR interval ≥180 ms was associated with a significant increase in $VO_{2\ peak}$ as compared to those with PR <180 ms, who derived no such benefit [9]. However, several studies have shown that presence of AVCD in patients with HFREF is associated with a more advanced stage of the disease and the risk for this *a priori* "sicker" subset of HFREF patients is not compensated by the positive effect of CRT on restoring AV synchrony [7,28,29].

We showed that patients with HFREF and coexisting IVCD, who additionally suffered from AVCD, exhibited worse exercise capacity compared to those with normal AV conduction. This reduction in exercise capacity appeared to be irrespective of echocardiographic parameters of LV systolic or diastolic function. In line with previous observations, ischemic etiology and older age were related to a reduction in exercise capacity [30–32]. In addition to a study reporting that in HFREF patients with QRS ≥120 ms, wider QRS was not associated with a further decrease in $VO_{2\ peak}$ [8], our results suggest that prolongation of PR interval may actually be a more powerful predictor of exercise intolerance than QRS width and morphology in this group of patients.

Conclusions

Delayed AV conduction contributes to decreased exercise capacity in patients with HFREF and coexisting IVCD.

Limitations

This study was a retrospective analysis, but the study population came from a prospective registry designed to evaluate the role of echocardiographically-assessed different types of dyssynchrony on exercise capacity in HFREF patients with wide QRS complexes. It was a single-center investigation with a limited number of participants. Despite this drawback, we believe that the consistency of the results validates the observations. As the study group was strictly specified, the results of our study should not be extrapolated to other HFREF patient populations. Long-term follow-up and large-scale prospective studies are needed to validate our results.

Strengths

Our results add to the limited body of literature on the impact of AVCD on exercise capacity in this distinctively debilitated group of HFREF patients, furthering the hypothesis that correction of AVCD in this group of patients can improve their exercise capabilities.

Statement

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