ORIGINAL ARTICLE

Chronotropic incompetence causes multiple organ complications in adults after the Fontan procedure

Magdalena Okólska[1], Maciej Skubera[2,3], Paweł Matusik[4], Wojciech Płazak[2,3],
Jacek Pająk[5], Beata Róg[1], Piotr Podolec[2,3], Lidia Tomkiewicz-Pająk[2,3]

1   Cardiology Outpatient Clinic, Department of Cardiovascular Diseases, John Paul II Hospital, Kraków, Poland
2   Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
3   John Paul II Hospital, Kraków, Poland
4   Department of Electrocardiology, John Paul II Hospital, Kraków, Poland
5   Department of Pediatric Heart Surgery and General Pediatric Surgery, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

BACKGROUND   Although patients undergoing the Fontan procedure (FP) present a normal or close-to--normal function of the systemic ventricle, they cannot generate cardiac output or exhibit similar exercise capacity as their healthy peers. This can be attributed to chronotropic incompetence and multiple organ complications.

AIMS   We evaluated the prevalence of chronotropic incompetence in adults after FP and assessed the relationship between heart rate reserve (HRR) and multiple organ complications.

METHODS   Data were obtained from 50 post-FP patients (mean [SD] age, 27 [6.6] years) and 30 healthy controls matched for age and sex. All patients were subjected to clinical examination, laboratory tests, echocardiography, cardiopulmonary exercise test, and chronotropic function evaluation.

RESULTS   Cardiopulmonary exercise test parameters were impaired in the post-FP group. Chronotropic incompetence was identified in 46 patients (92%), who also had a lower median (interquartile range) chronotropic index (0.55 [0.47–0.62] vs 0.93 [0.88–0.99]; P <0.001) and a greater median (interquartile range) HRR (32 [24–60] bpm vs 8 [1–14] bpm, P <0.001). A negative correlation was observed between HRR and peak oxygen uptake, and a positive one between HRR and the peak ventilatory equivalent for CO_2 and mean platelet volume. The study revealed the diagnostic utility of HRR in detecting an abnormal peak ventilatory equivalent for O_2, alkaline phosphatase levels, the ratio of aspartate transaminase to alanine transaminase levels, and mean platelet volume.

CONCLUSIONS   Chronotropic incompetence correlates with impaired exercise capacity, liver dysfunction, and platelet abnormalities in post-FP patients. Heart rate reserve may be a promising indicator of organ complications as well as a sign of future bradyarrhythmia and the need for cardiac pacing.

INTRODUCTION   The Fontan procedure (FP) remains the preferred treatment for most patients with single-ventricle physiology. This surgical procedure aims to restore the balance between pulmonary and systemic circulation and achieve normal or near-normal blood oxygenation. However, patients undergoing FP develop numerous cardiac and extracardiac complications over time. The commonly reported cardiac complications include systolic and diastolic single--ventricle dysfunction,[1] increased atrioventricular valve regurgitation, and arrhythmias,[2] and extracardiac complications comprise plastic bronchitis, chronic kidney disease, liver and thyroid dysfunction, thromboembolic complications, and exudative enteropathy.[3-6] Moreover, patients after FP have a decreased cardiac output and develop a progressive decline in exercise capacity.[2,7] Stroke volume (SV) and heart rate (HR) represent the determinants of cardiac output. The available data confirm the effect of impaired SV on reduced exercise capacity in this population.[8,9]

WHAT'S NEW?

Despite the normal or close-to-normal function of the systemic ventricle, patients undergoing the Fontan procedure cannot generate cardiac output or exhibit exercise capacity similar to that observed in their healthy peers. Impaired exercise capacity may result from widespread chronotropic incompetence and multiple organ complications. In this study, we demonstrated a relationship between heart rate reserve and selected complications affecting multiple organs. Heart rate reserve is a promising indicator of organ complications in patients after the Fontan procedure and may be helpful in selecting candidates for pacemaker implantation.

However, when SV, which depends on ejection fraction, is constant, cardiac output during exercise is mainly increased by faster HR. Exercise capacity is affected by systemic ventricle preload (which is determined by the volume of blood flowing through the heart) and pulmonary resistance.[2]

In general, chronotropic incompetence is defined as the inability to sufficiently increase HR in response to higher activity or demand. So far, only a few reports have analyzed the influence of an impaired chronotropic response on cardiac output, and thus on the exercise capacity of patients who underwent FP. In patients not presenting a clinically evident cardiac disease, the HR response to exercise is deemed a prognostic parameter beyond physical capacity. Chronotropic incompetence and slow HR reduction after exercise represent risk factors for sudden cardiac death and serious cardiac events in patients with cardiovascular diseases.[10] However, data on these conditions in those with adult congenital heart diseases are sparse.

What we see in clinical practice, patients undergoing FP—despite the normal or close-to-normal function of the systemic ventricle—remain unable to generate cardiac output or exhibit similar physical capacity as their healthy peers. This may be due to chronotropic incompetence and organ complications, which together lead to reduced exercise capacity in these patients.

In this study, we evaluated the prevalence of an abnormal HR response to exercise (chronotropic incompetence) in adults who underwent FP. We also assessed the relationship between heart rate reserve (HRR) and selected forms of multiple organ dysfunction.

PATIENTS AND METHODS Study participants

This retrospective study included adults over 18 years of age who underwent FP for the diagnosis of functional single ventricle and remain under care at the John Paul II Hospital, Kraków, Poland. The main exclusion criteria were as follows: asthma, pulmonary artery hypertension requiring vasodilator therapy, atrial fibrillation, atrial flutter, history of pacemaker placement, current infection, inflammation, pregnancy, diabetes, major trauma, therapy with vitamin K antagonists and β-blockers, malignancy, and history of alcohol abuse. The control group comprised healthy, age- and sex-matched volunteers.

The study was based on clinical, demographic, and anatomical characteristics derived from patients' medical records. Each patient was subjected to a physical examination and the assessment of body mass index, arterial oxygen saturation, and ejection fraction of the systemic ventricle. Body mass index was calculated as weight of the patient (kg) divided by the square of height (m²). Oxygen saturation was measured by pulse oximetry while breathing room air.

Echocardiography Ejection fraction of the single ventricle was assessed using the Simpson method. In addition, valvular competence was evaluated. The examination was performed by 2 independent, experienced cardiologists using echocardiography (Vivid 7, GE Medical Systems, Milwaukee, Wisconsin, United States), as described elsewhere.[1]

Cardiopulmonary exercise test To evaluate exercise tolerance, a cardiopulmonary exercise test (CPET) was performed using a modified Bruce protocol (Reynolds Medical System, ZAN-600, Hertford, United Kingdom). The following parameters were recorded during the test: time of exercise, 12-lead electrocardiogram, blood pressure, minute ventilation (VE), peak oxygen uptake (peak VO_2), respiratory exchange ratio (RER), peak ventilatory equivalent for oxygen (VE/VO_2), peak ventilatory equivalent for carbon dioxide (VE/VCO_2), breathing reserve, and oxygen saturation. Peak VO_2 was estimated as the highest value of oxygen uptake at peak exercise in milliliters per kilogram per minute and the percentage of the predicted value was calculated. Ventilatory anaerobic threshold was measured using the V-slope method. Oxygen pulse was determined by the amount of oxygen consumed per heartbeat. The VE/VO_2 parameter was defined as the amount of ventilation needed for the uptake of a given amount of oxygen, while VE/VCO_2, as the amount of ventilation needed for the elimination of a given amount of carbon dioxide. Finally, RER was calculated by dividing VO_2 by VCO_2.

Chronotropic incompetence Chronotropic index (CI) was determined by using the concept of the chronotropic metabolic relationship proposed by Wilkoff et al.[11] To calculate it, we used the following formula: (peak HR – resting HR)/(220 – age – resting HR). Chronotropic incompetence was confirmed if CI was lower than 0.8.

Heart rate reserve was defined as the difference between maximal HR (HR_{max}) and peak HR (HR_{peak}). Maximal HR was calculated with

TABLE 1 Baseline characteristics of the study patients

Variable	Post-FP patients (n = 50)	Controls (n = 30)	P value
Age, y	27 (6.6)	29.9 (4.1)	0.82
Female sex, n (%)	16 (32)	9 (30)	0.89
Height, cm	171 (8.1)	174 (6.9)	0.06
Weight, kg	66.2 (12.2)	69.0 (9.3)	0.28
BMI, kg/m^2	22.7 (3.4)	22.7 (2.2)	0.97

Continuous data are presented as mean (SD) and categorical data, as number (percentage).
Abbreviations: BMI, body mass index; FP, Fontan procedure

TABLE 2 Cardiopulmonary exercise test results of post–Fontan procedure patients and controls

Variable	Post-FP patients (n = 50)	Controls (n = 30)	P value
Cardiopulmonary exercise test			
Exercise time, min	13.5 (3.4)	16.65 (2.7)	<0.001
Oxygen saturation at rest, %	91 (87–94)	97 (96–98)	<0.001
Oxygen saturation during exercise, %	85 (82–86)	96.5 (96–97)	<0.001
Peak VO$_2$ per kilogram, ml/kg/min	23.9 (7.6)	49.2 (7.3)	<0.001
Peak VO$_2$, %N	60.6 (17.5)	95.9 (4)	<0.001
VE/VCO$_2$	33.6 (5.2)	26.5 (2.9)	<0.001
VE/VO$_2$	33.5 (31.5–36)	28.85 (25.5–31)	<0.001
Peak RER	1 (0.1)	1.1 (0.9)	0.05
CI	0.55 (0.47–0.62)	0.93 (0.88–0.99)	<0.001
HRR	32 (24–60)	8 (1–14)	<0.001

Continuous data are presented as mean (SD) or median (interquartile range).

Abbreviations: CI, chronotropic index; HRR, heart rate reserve; %N, percentage of the predicted value; RER, respiratory exchange ratio; VE/VCO$_2$, peak ventilatory equivalent for carbon dioxide; VE/VO$_2$, peak ventilatory equivalent for oxide; VO$_2$, oxygen uptake; others, see TABLE 1

the formula: 220 – age. Accordingly, HRR was calculated using the following formula: $HRR = HR_{max} – HR_{peak} = 220 – age – HR_{peak}$.[12,13]

Laboratory tests Blood samples were collected from the antecubital vein from patients after overnight fasting (for at least 12 hours). The samples were evaluated for the following laboratory parameters: red blood cells, hemoglobin, hematocrit, red blood cell distribution width, white blood cells, platelets, mean platelet volume (MPV), N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) as well as liver function markers including serum protein electrophoresis data, international normalized ratio, and the levels of alanine transaminase (ALT), aspartate transaminase (AST), γ-glutamyltranspeptidase, alkaline phosphatase (ALP), total bilirubin, α-fetoprotein, creatinine, and cystatin C. Furthermore, we assessed liver dysfunction by calculating the following parameters with specific formulas: AST/ALT ratio, AST/platelet ratio index, Forns index, and MELD-XI score.[14]

Ethics This study was approved by the university ethics committee (1072.6120.110.2017). All patients provided written informed consent to participate in the study.

Statistical analysis Data were presented as number (percentage) for categorical variables, mean (SD) for normally distributed continuous variables, and median (interquartile range [IQR]) for continuous variables with nonnormal distribution. The Kolmogorov–Smirnov test was used to verify the normality of data distribution. Patients who underwent FP and controls were compared using the 2-tailed t test or the Mann–Whitney test for quantitative variables and the χ^2 test for qualitative variables. The diagnostic usefulness of HRR in predicting abnormal values of selected parameters of multiple organ complications (VE/VO$_2$, ALP, AST/ALT ratio, and MPV) was evaluated by receiver operating characteristic (ROC) curves with area under the curve (AUC) values. A cutoff value corresponding with the highest accuracy was determined, and the related sensitivities and
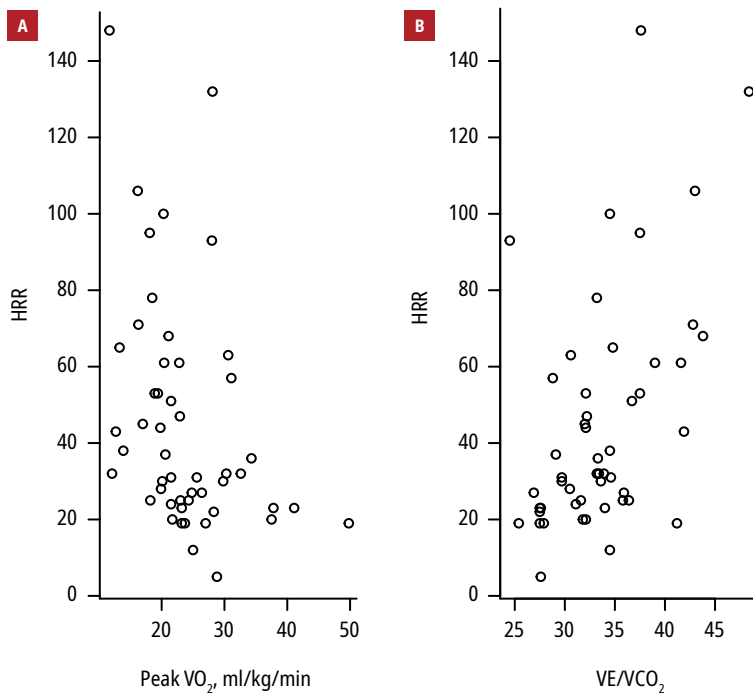
FIGURE 1 **A** – relationship between heart rate reserve (HRR) and peak oxygen uptake (VO$_2$); **B** – relationship between HRR and peak ventilatory equivalent for CO$_2$ (VE/VCO$_2$)
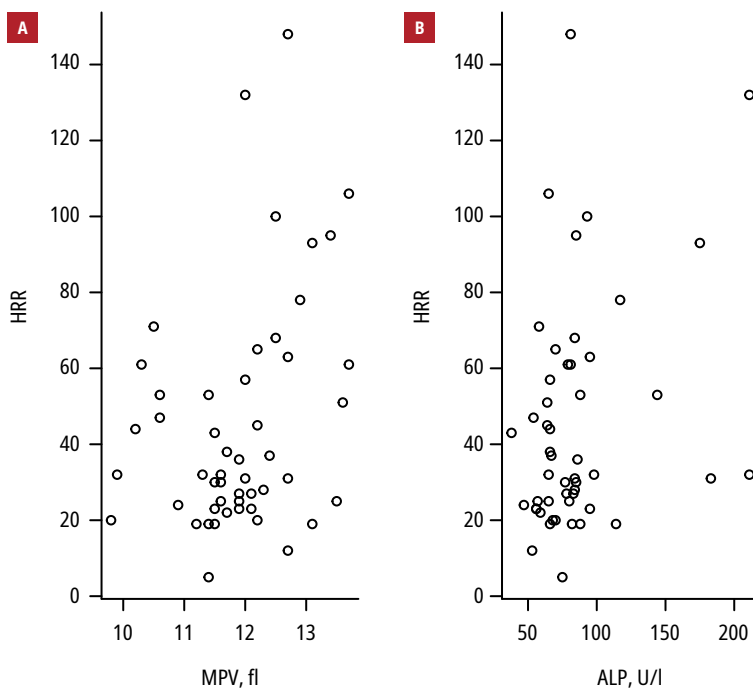
FIGURE 2 **A** – relationship between heart rate reserve (HRR) and mean platelet volume (MPV); **B** – relationship between HRR and alkaline phosphatase (ALP) levels

specificities as well as the Youden index were calculated. Relationships among clinical data, CPET results as well as chronotropic and biochemical parameters were assessed with Spearman rank correlation coefficients. All the analyses were performed using the IBM SPSS Statistics for Windows software, version 25.0 (IBM Corp., Armonk, New York, United States). A *P* value less than 0.05 was considered significant.

RESULTS **Patient characteristics** We enrolled 50 adult patients, including 34 men (68%), at a mean (SD) age of 27 (6.6) years. Patients who underwent FP did not differ from controls in terms of age, sex, and body mass index. Of the 50 patients in the FP group, 45 (90%) underwent total cavopulmonary connection (TCPC) and 5 (10%), direct right atrium–pulmonary artery connection (APC). There were 32 patients (64%) with fenestration and 18 (36%) without. The median (IQR) age of patients at the time of surgery was 4 (2–5) years, and the median follow-up after surgery was 19 (2–5) years. The mean (SD) systemic ventricular ejection fraction (SVEF) was 52% (9.1%). The baseline characteristics of the study groups are presented in TABLE 1.

Cardiopulmonary exercise test results Compared with controls, patients in the FP group had more frequently decreased peak VO$_2$ (82% vs 0%; *P* <0.001), increased VE/VCO$_2$ (98% vs 77%; *P* = 0.004), and increased VE/VO$_2$ (14% vs 0%; *P* = 0.004). Detailed CPET results obtained for FP and control groups are presented in TABLE 2. Chronotropic incompetence was identified in 46 patients (92%) after the Fontan procedure. Post-FP patients had a lower median (IQR) chronotropic index (0.55 [0.47–0.62] vs 0.93 [0.88–0.99]; *P* <0.001) and higher median (IQR) HRR (32 [24–60] bpm vs 8 [1–14] bpm; *P* <0.001) than controls. We observed a negative correlation between HRR and peak VO$_2$ (*R* = –0.4; *P* <0.001) (FIGURE 1A) and a positive correlation between HRR and VE/VCO$_2$ (*R* = 0.49; *P* <0.001) (FIGURE 1B).

Biochemical test results We found elevated ALP levels in 6 patients (12%) and an increased AST/ALT ratio in 21 (42%). Furthermore, increased MPV was observed in 14 patients (28%) and elevated NT-proBNP levels (exceeding 125 pg/ml) in 27 (54%). Laboratory parameters determined for both FP and control groups are presented in TABLE 3.

We observed a positive correlation between HRR and MPV (*R* = 0.3; *P* = 0.04) (FIGURE 2A) and a trend toward a positive correlation between HRR and ALP levels (*R* = 0.24; *P* = 0.09) (FIGURE 2B). Also, a tendency toward a positive correlation was noted between HRR and NT-proBNP levels (*R* = 0.26; *P* = 0.07). A similar association was observed for SVEF values, as we found a trend toward a negative correlation between HRR and those values (*R* = –0.24; *P* = 0.09). We did not observe any correlation between HRR and parameters relevant to liver fibrosis such as the AST/ALT ratio, AST/platelet ratio index, Forns index, and MELD-XI score.

Receiver operating characteristic curve analysis The results of ROC curve analysis regarding the ability of HRR to predict liver

TABLE 3 Laboratory parameters in patients after the Fontan procedure and controls

Variable	Post-FP patients (n = 50)	Controls (n = 30)	P value
NT-proBNP, pg/ml	140.5 (72–331)	24.5 (6–35)	<0.001
RBC, × 10^9/μl	5.6 (0.5)	4.9 (0.5)	<0.001
Hemoglobin, g/dl	16.3 (1.9)	14.7 (1.3)	<0.001
Hematocrit, %	48.3 (6.4)	43 (3.3)	<0.001
RDW, %	13.2 (12.8–13.9)	12.4 (12–12.6)	<0.001
Platelets, × 10^3/μl	159.6 (61.7)	228.2 (38.1)	<0.001
PDW, fl	15.8 (2.7)	12.2 (2.3)	<0.001
MPV, fl	11.9 (1)	10.4 (1)	<0.001
Cystatin C, mg/l	0.9 (0.8–1.1)	0.9 (0.8–0.9)	0.007
Creatinine, mg/dl	0.9 (0.8–1)	0.9 (0.7–1)	0.67
eGFR, ml/min/1.73 m^2	108.5 (97–123)	111 (105–124)	0.53
AST, IU/l	24 (20–29)	19.5 (17–22)	<0.001
ALT, IU/l	25 (20–34)	20.5 (17–23)	0.01
GGTP, IU/l	73 (52–120)	15.5 (14–18)	<0.001
Bilirubin, μmol/l	17.9 (13.6–24.5)	12 (7.7–17)	<0.001
α-Fetoprotein, ng/ml	2.8 (1.9–4.1)	2.3 (1.9–3.4)	0.14
ALP, IU/l	78.5 (65–88)	67 (55–89)	0.08
Total protein, g/dl	75.7 (71.4–78.6)	75 (73–78.6)	0.95
PT, s	13.8 (13.1–17.2)	11.9 (11.4–12)	<0.001
INR	1.2 (1.2–1.6)	1 (1–1.1)	<0.001
AST/ALT ratio	1 (0.8–1.1)	0.9 (0.8–1.1)	0.67

Continuous data are presented as mean (SD) or median (interquartile range).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGTP, γ-glutamyltranspeptidase; INR, international normalized ratio; MPV, mean platelet volume; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; PDW, platelet distribution width; PT, prothrombin time; RBC, red blood cells; RDW, red cell distribution width; others, see TABLE 1

TABLE 4 Receiver operating characteristic curve analysis testing the ability of heart rate reserve to predict liver dysfunction as well as hematological and cardiopulmonary exercise test parameter values

Variable	AUC	95% CI	P value	Cutoff point	Sensitivity	Specificity	Youden index
Abnormal VE/VO$_2$ >40	0.73	0.51–0.96	0.05	41	0.86	0.65	0.51
Abnormal ALP >40 U/l	0.71	0.53–0.88	0.04	31	1.00	0.48	0.48
Abnormal AST/ALT ratio >1.1	0.67	0.52–0.82	0.04	26	0.91	0.48	0.39
Abnormal MPV >12.5 fl	0.74	0.56–0.93	0.009	59	0.64	0.89	0.53

Abbreviations: AUC, area under the curve; others, see TABLES 2 and 3

dysfunction as well as hematological and CPET parameters are shown in TABLE 4. The analysis revealed the significant diagnostic usefulness of HRR to detect the abnormal value of 4 parameters. The highest AUC value was noted for abnormal MPV (AUC, 0.74), and the lowest value, for an abnormal AST/ALT ratio (AUC, 0.67). The ROC curve analysis of the ability of HRR to detect the abnormal values of VE/VO$_2$, ALP levels, the ASP/ALT ratio, and MPV are presented in FIGURE 3.

DISCUSSION Our study demonstrated a significant influence of chronotropic incompetence on exercise capacity in post-FP individuals. We also found a relationship among HRR and selected parameters of multiple organ dysfunction in adults who underwent the Fontan procedure.

A CPET is a widely acknowledged diagnostic tool, as it provides information about not only the patient's exercise capacity but also prognosis, including the need for heart transplant.[15]
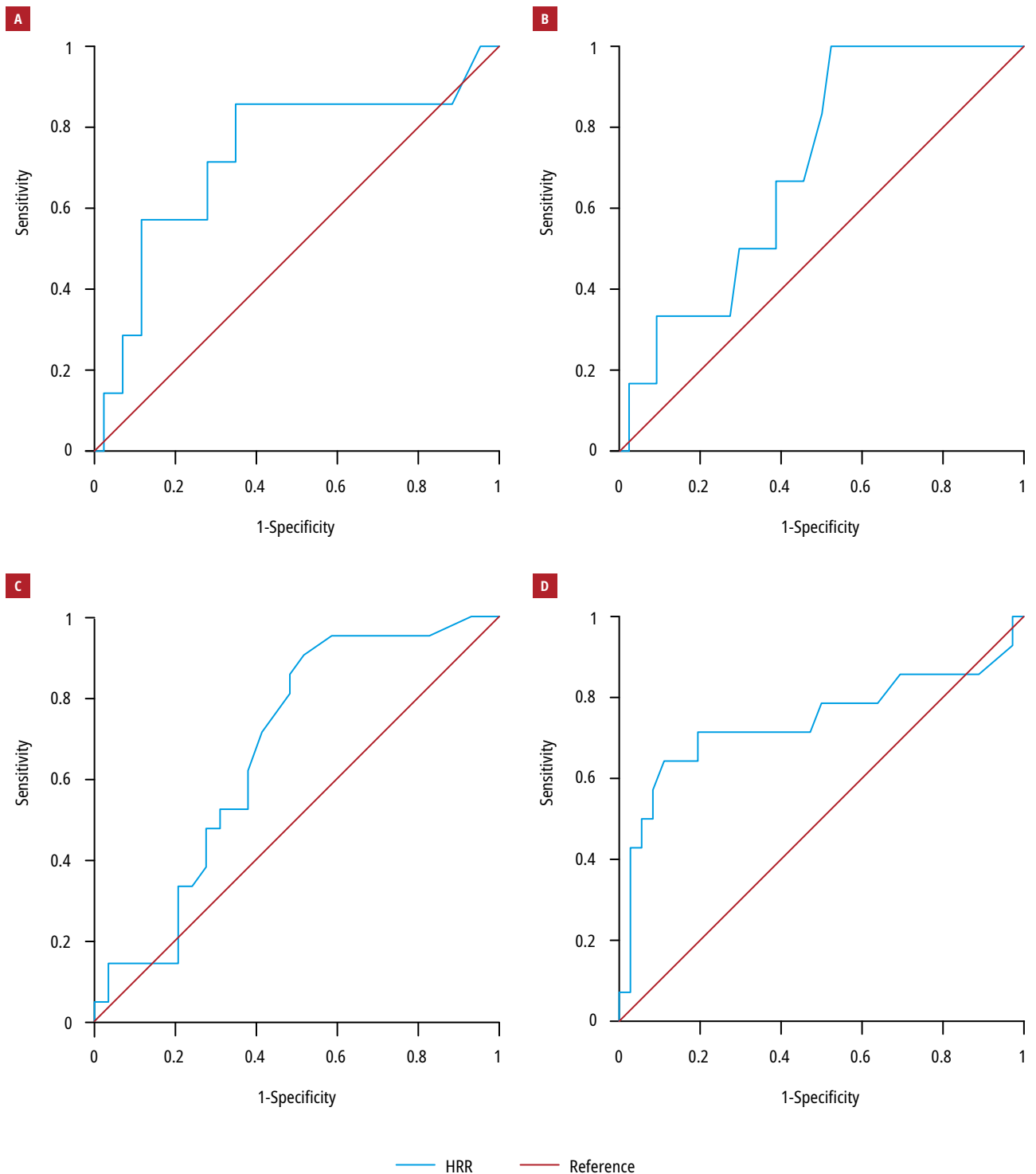
FIGURE 3 Receiver operating characteristic curve analysis of heart rate reserve (HRR) for the detection of: **A** – abnormal peak ventilatory equivalent for oxygen (VE/VO$_2$); **B** – abnormal levels of alkaline phosphatase (ALP); **C** –abnormal ratio of aspartate transaminase (AST) to alanine transaminase (ALT); **D** – abnormal mean platelet volume

The results of the present study corroborate a well-known observation that patients with Fontan physiology have decreased exercise capacity. Compared with controls, patients in the FP group presented lower exercise time, lower saturation both at rest and during exercise, lower peak VO$_2$ per kilogram as well as lower peak VO$_2$ (expressed as the percentage of the predicted value). Of the post-FP patients, 98% had increased VE / VCO$_2$. These results are in line with previous studies and show that exercise limitation is a common finding in this particular group of patients.[2,15,16] The reasons for the reduced exercise performance in patients after FP seem to be associated with a combination of various mechanisms. One of them might be the lack of the ability to increase and maintain cardiac output in response to increased workload.[2]

Chronotropic incompetence is a widespread disorder among patients undergoing FP, being

a result of sinus node damage that occurs during surgery or structural alterations developed owing to hemodynamic changes following FP. In the present study, these were detected in 46 patients (92%). Diller et al[17] found that, within a group of patients with adult congenital heart diseases, chronotropic incompetence was most commonly observed among patients who underwent FP.[17] Some authors have also noted an abnormal chronotropic response during exercise in patients who were treated with FP.[18,19] Heart rate during exercise is determined by sinus node function, the local effect of autonomic innervation, circulating catecholamines, and increased ventricular preload.[20] In our study patients, the ejection fraction was close to normal. In such situation, increased HR likely accounts for the main mechanism contributing to increased cardiac output during exercise. We observed that even though the post-FP patients underwent a diagnostic CPET (RER, 1.04), they had lower peak oxygen consumption and HRR was moderately associated with VO_2 and VE/VCO_2. Furthermore, we established an exact HRR value of 41 or higher that indicated individuals expected to have worse VE/VO_2. Therefore, HRR might be used as another parameter suggesting potential benefits from rate-responsive cardiac pacing in post-FP patients with chronotropic incompetence, which influences physical activity in everyday life.

In the present study, we noted elevated levels of single biochemical markers (such as γ-glutamyltranspeptidase, total bilirubin, international normalized ratio, and ALP) as well as an increased AST/ALT ratio. Moreover, we found relationships among increased levels of ALP, the AST/ALT ratio, and HRR. An increase in HRR to up to 26 allowed for the prediction of an increase in the AST/ALT ratio in post-FP patients. Further increase in HRR to up to 31 was found in individuals with elevated ALP levels. The fact that chronotropic incompetence and reduced cardiac output increase central venous pressure may explain this observation. A chronic increase in central venous pressure and impaired liver perfusion observed in Fontan circulation leads to liver dysfunction and widening of the liver sinuses. This is manifested by increased values of parameters relevant for liver dysfunction and the development of Fontan-associated liver disease.[6] In conclusion, chronotropic dysfunction manifested by increasing HRR can be a marker to identify people with impaired liver function. Similar observations were made by Italian researchers, who assessed pediatric post-FP patients. They found hepatic abnormalities in up to 53% of patients and reported that liver dysfunction correlated with decreased HR and a low cardiac index.[5] Of note, mechanisms associated with hepatological disorders are complex and unclear and require further research.

In our study, post-FP patients presented with various significant hematological disorders not seen in controls. We investigated abnormalities in the platelet parameters and found a reduced platelet count in 38% of patients. Increased MPV was noted in 28% of patients and was associated with HRR. Moreover, we observed that an HRR of up to 59 showed diagnostic usefulness in detecting patients with abnormal MPV. The association between MPV and HRR may be explained by the fact that increased HRR results in reduced cardiac output. This in turn leads to impaired organ perfusion and increased venous congestion in the liver, spleen, and marrow.[21] Impaired marrow perfusion can cause disturbances in thrombopoiesis. On the other hand, splenomegaly, liver cirrhosis, and portal hypertension (which are frequently observed in Fontan circulation) may be responsible for increased platelet destruction.[22] In patients with fenestration (64% in our study), a right-to-left shunt might additionally account for thrombocytopenia and changes in MPV, resulting in the delivery of megakaryocytes into the arterial system circulation, thus bypassing the lungs where the megakaryocyte cytoplasm is fragmented into platelets.[23] The association between HRR and the analyzed biochemical and morphological parameters was nonsignificant; however, we believe that it is worth being analyzed.

In the present study, 45 patients (90%) in the FP group underwent TCPC and 5 (10%), direct APC. The presence of fenestration did not have any influence on HRR. The available data indicate that it is often necessary to implant a pacemaker in patients undergoing TCPC as opposed to those undergoing APC.[24,25] However, a team from Boston demonstrated that the incidence of arrhythmia and pacemaker implantation did not differ between patients undergoing TCPC and those treated with APC.[26] A possible explanation for this finding may be the fact that the development of chronotropic incompetence and the need for pacemaker implantation are determined not only by structural changes in the heart but also by a combination of other hemodynamic parameters and organ complications associated with Fontan circulation. However, further research is needed to elucidate this issue.

Study limitations Several limitations of our study need to be acknowledged. First, it was a retrospective study. Second, the number of patients in the study group was small and relatively heterogeneous, as it included patients with intracardiac and extracardiac conduits as well as varied ventricular geometry. However, Fontan physiology was the predominant feature of all patients. Systemic ventricular ejection fraction in the FP group was lower than in controls,

yet it was close to normal. The present study did not include the results of invasive diagnostic workup. The ROC curve analysis showed significant results, but the number of patients in the study group was small. However, the values of sensitivity and specificity of the methods used in the study indicated that the HRR parameter may have a predictive value. Nevertheless, further analysis of a larger number of patients is needed.

Conclusions   To sum up our findings, chronotropic incompetence may cause complications and, in some cases, correspond with them. Our findings demonstrated that patients with chronotropic incompetence have impaired exercise capacity, liver complications, and platelet alterations. Parameters relevant for chronotropic incompetence (for HRR calculation) can be measured during any exercise test. In the present study, we used data from CPET, which is a recommended method for the clinical evaluation of exercise capacity in adults with congenital heart disease.[27] We believe that HRR, as a relatively simple and generally available diagnostic parameter measured during CPET, may be a promising indicator to identify patients with expected specific organ complications. Moreover, chronotropic incompetence parameters and HRR may be a sign of future bradyarrhythmia in patients with Fontan physiology and indicate the need for regular follow-ups in the case of cardiac pacing. Nevertheless, every single decision about performing FP should be made with great caution, considering the patient's age, potential need for epicardial pacing, and possible complications at long-term follow-up. There is a need for further research to explore the combination of dynamic physiological variables such as chronotropic performance parameters and biomarkers related to multiple organ complications in order to improve risk assessment in patients undergoing FP.

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