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Original article

Iron deficiency and hematological changes in adult patients after Fontan operation

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ABSTRACT

Background: Growing evidence indicates that iron-deficiency anemia is common in patients with congenital heart diseases.

The aim of this study was to characterize hematologic changes and iron metabolism in adult Fontan patients. We also searched for the associations between these parameters and physical performance in the study group.

Methods and results: Thirty-two white Fontan patients with a mean age of 25 ± 4.5 years and 30 healthy control subjects matched for age and sex were studied. Complete blood count together with iron-related parameters was determined in plasma of peripheral venous blood. The cardiopulmonary exercise test was performed.

The Fontan patients had higher red blood cell counts ($6.0 \pm 2.1 \times 10^9/\mu l$ vs. $4.8 \pm 0.4 \times 10^9/\mu l$, $p < 0.001$), hemoglobin (16.7 ± 1.4 g/dl vs. 14.2 ± 1.3 g/dl, $p < 0.001$), hematocrit ($49 \pm 3.4\%$ vs. $42.1 \pm 3.1\%$, $p < 0.001$), red cell distribution width (RDW) ($14.3 \pm 2.4\%$ vs. $12.8 \pm 0.5\%$, $p < 0.001$), while mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were similar in both the groups. Compared to the controls, the Fontan patients had higher unsaturated iron binding capacity (46.1 ± 12.6 μmol/l vs. 38.4 ± 11.9 μmol/l, $p = 0.02$), total iron-binding capacity (62.8 ± 9.8 μmol/l vs. 57.8 ± 8.5 μmol/l, $p = 0.04$), lower transferrin saturation ($27.4 \pm 11.4\%$ vs. $34.6 \pm 13.4\%$, $p = 0.03$), and oxygen uptake, while iron and ferritin levels were comparable in both the groups. The multivariate model showed that $SatO_2$ and cystatin C were independent predictors of RDW, and alanine aminotransferase was an independent predictor of ferritin level. Interestingly RDW was an independent predictor of oxygen uptake.

Conclusion: Adult patients after Fontan operation despite having increased hemoglobin, hematocrit, and red blood cells have insufficient iron stores. Red cell distribution width is an indicator of iron deficiency in adult Fontan patients and it correlates with lower *exercise capacity*. Elevated ferritin levels in adult patients after Fontan surgery are associated with liver failure.

Introduction

The Fontan procedure, described for the first time in 1971, is presently a widely accepted method of treating patients with single ventricle heart [1]. The absence of the ventricle that pumps blood to the pulmonary bed results in restricted pulmonary venous return, which in turn causes a decrease in systemic ventricle preload [2]. Some patients demonstrate a gradual decrease in arterial blood saturation, increased hematocrit (HCT) values, and cyanosis. This is

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associated with the presence of abnormal arterial-venous fistulas in the pulmonary bed, intrahepatic venous shunts, increased pulmonary resistance, atrioventricular valve regurgitation, impaired systolic and diastolic function of the systemic ventricle, and intracardiac shunts, e.g. fenestration [3]. Earlier reports described the prevalence of cyanosis in adult patients after the Fontan procedure as 20–25% [4,5]. Erythrocytosis is a physiological increase in red cell number as a consequence of chronic hypoxia. This is a compensatory mechanism, leading to increase in tissue oxygen supply [6].

Iron-deficiency anemia is the most common type of anemia; it may result from blood loss, diet iron deficiency, abnormal absorption, and increased requirements. Hemoglobin (HGB) concentration is the most reliable indicator of anemia at the population level [7,8]. Previous investigations indicated high frequency of anemia in patients with congenital cyanotic heart defects [9]. More than one-third of patients with congenital cyanotic heart defects are believed to be iron deficient [10]. Collins et al. [11] reported that anemia is common in patients with complex congenital heart diseases and ventricular dysfunction, in particular those with Fontan physiology. Moreover, anemia is associated with increased mortality rates in this group of patients [10]. Numerous studies on anemia in patients with congenital heart defects and heart failure were performed in subjects with biventricular hearts [7,11–15]. The cause of anemia in adult patients after Fontan operation remains unclear, and its influence on exercise capacity has not been examined. To the best of our knowledge, there are few investigations addressing the assessment of hematological and iron-related parameters in adult Fontan patients.

The aim of this study was to characterize hematologic changes and iron metabolism in adult Fontan patients. We also searched for the associations between these parameters and physical performance in the study group.

Materials and methods

Study participants

All the study patients were recruited consecutively at the John Paul II Hospital in Krakow, Poland, between August 2012 and December 2012. Patients were eligible if they were aged ≥18 years, had Fontan physiology, and were in stable clinical condition for at least 3 months before enrollment to the study. The main exclusion criteria were renal insufficiency, neoplasmatic diseases, infection, inflammation, major trauma within the past three months, pregnancy, diabetes, and alcohol abuse. In addition, 30 age- and sex-matched healthy volunteers were recruited. None of the participants were on iron supplementation or were phlebotomized.

Study protocol

Clinical and demographic variables were extracted from the patients' medical records. In every patient we assessed laboratory parameters, body mass index, arterial oxygen saturation, and ejection fraction of the systemic ventricle. Body mass index was calculated as mass (kg)/height (m)^2. Ejection fraction of the single ventricle (EFSV) was assessed using the Simpson method (Vivid 7, GE Medical Systems No 4183V7, Milwaukee, WI, USA). Cardiopulmonary exercise test (CPET) was performed using a modified Bruce protocol (ZAN-600 type USB No. 6660161). During the test, electrocardiogram, blood pressure, clinical symptoms, and duration of exercise were recorded. The monitored gas parameters included exercise time (*T*, min), peak oxygen uptake (VO_{2peak}, ml/kg/min and %predicted value) and oxygen uptake at anaerobic threshold (VO_{2AT}, %predicted value). Oxygen saturation ($SatO_2$, %) was measured by pulse oximetry in the room air.

The study protocol was approved by the local Ethical Committee and each subject granted informed consent to participate in the investigation.

Laboratory investigations

Blood samples were collected from the antecubital vein between 07:00 h and 09:00 h, after overnight fasting for at least 12 h. White blood cells (WBC), platelet count, red blood cells (RBC), HCT, HGB, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, total protein, alanine aminotransferase (ALT), creatinine, gamma-glutamyltranspeptidase (GGTP), alkaline phosphatase (ALP), C-reactive protein (CRP), uric acid, creatinine, estimated glomerular filtration rate (eGFR), cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP), bilirubin, and international normalized ratio (INR) were assayed using routine laboratory techniques. Hyaluronic acid (HA) levels were measured with a commercial enzyme-linked immunosorbent assay (ELISA) kit (R&D systems, Minneapolis, MN, USA) according to the manufacturer's instructions. This sandwich assay uses human recombinant aggrecan as the immobilized capture phase for HA in the subject's serum sample and is designed to measure >35 kDa molecules of HA. Mean intra-assay coefficient of variation was 5.9%. Iron concentration values (normal range: men 6.6–26 μmol/l, women 11–28 μmol/l) and unsaturated iron-binding capacity (UIBC) (normal range: 20–62 μmol/l) were determined by the colorimetric method. Total iron-binding capacity (TIBC) (normal range: 45–70 μmol/l) was calculated as TIBC (μmol/l) = Iron (μmol/l) + UIBC (μmol/l). Transferrin saturation (TSAT) (normal range: 20–40%) was calculated as TSAT (%) = iron (μmol/l)/TIBC (μmol/l) × 100. Ferritin (normal range: 30–400 μg/l) was determined by the latex particle-enhanced immunoturbidimetric method (Cobas 6000, Roche, Rotkreuz, Switzerland). Anemia was defined as HGB concentration <13 g/dl in males and <12 g/dl in females [9].

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical variables are described as counts and percentages. Patients after Fontan operation and controls were compared using the Mann–Whitney *U*-test for the continuous variables and with the chi square test for categorical variables. Correlations between the individual parameters were calculated using the Spearman rank test. Factors that determine RDW, ferritin level, and VO_{2peak} were analyzed using multiple logistic regression analysis. A *p*-value <0.05 was considered statistically significant. The statistical analyses were performed with the PQStat version 1.4.2.324 software (Poznań/Plewiska, Poland).

Results

Group characteristics

We enrolled 32 Fontan patients (11 men, 20 women) aged 25 ± 4.5 years. The mean age at Fontan operation was 5.3 ± 3.5 (2–14) years. The mean follow-up time was 19.6 ± 5.2 (15–30) years. Underlying cardiac malformations were as follows: 14 (44%) patients with tricuspid atresia, 10 (31%) patients with pulmonary atresia and ventricular septal defect, two (6%) patients with double outlet right ventricle and left ventricular hypoplasia, and six subjects (19%) with right ventricular hypoplasia. Modification of the Fontan operation included direct right atrium–pulmonary artery connection in four (12%) patients and total cavopulmonary connection (TCPC) by means of intraatrial lateral tunnel in the remaining