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ORIGINAL ARTICLE

RECOARCTATION AFTER SURGICAL CORRECTION OF COARCTATION OF THE AORTA IN CHILDREN AND ADOLESCENTS

REKOARKTACIJA NAKON HIRURŠKE KOREKCIJE KOARKTACIJE AORTE KOD DECE I ADOLESCENATA

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Abstract

Introduction: Coarctation of the aorta (CoA) is a narrowing of the thoracic aorta, most often localized at the junction of the *ductus arteriosus*. Data on risk factors for the development of recoarctation remain contradictory in the literature.
Aim: To determine the frequency of recoarctation and to identify risk factors for recoarctation after surgical correction of CoA.
Material and methods: The research included 94 patients who underwent surgery for coarctation of the aorta from 2012 to 2017. Demographic and clinical characteristics, preoperative, intraoperative, postoperative and echocardiographic parameters were observed. Pressure gradient over 25 mm Hg immediately after operation is considered predictor for recoarctation of the aorta. The data was processed using methods of descriptive and analytical statistics.
Results: The median age at the time of surgery was 2 months (4 days - 19 years). The dominant technique was extended end-to-end anastomosis (90.4%). Kaplan Meier survival analysis showed a higher incidence of recoarctation in the group of patients with immediate postoperative gradient > 25 mm Hg ($p < 0.001$). Also, Cox logistic regression showed higher immediate postoperative gradient to be a predictor (HR 4.57, $p = 0.009$, 95% CI 1.47 - 14.22). After correction for other cofactors, including sex, genetic syndrome, small body weight, administration of prostaglandine E1, presence of bicuspid aortic valve, surgical technique, it was shown that the group of patients with higher immediate postoperative gradient has 4-fold higher probability for recoarctation (HR 4.37, $p = 0.035$, 95% CI 1,11 - 17,16) .
Conclusion: Immediate postoperative pressure gradient > 25 mm Hg is an independent predictor for recoarctation after surgical correction of the coarctation of the aorta.

Keywords:
coarctation of the aorta,
recoarctation,
risk factors,
gradient

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Sažetak

Uvod: Koarktacija aorte predstavlja suženje torakalne aorte, najčešće lokalizovano na mestu pripajanja *ductus arteriosus*-a. U novorođenačkom i odojačkom uzrastu glavni modalitet lečenja je hirurgija, a u kasnijem uzrastu perkutane intervencije. Podaci o faktorima rizika za razvoj rekoarktacije u literaturi su kontradiktorni.

Cilj: Cilj rada je utvrđivanje učestalosti rekoarktacije i identifikovanje faktora rizika za razvoj rekoarktacije nakon operacije koarktacije aorte.

Materijal i metode: Istraživanje je obuhvatilo 94 pacijenata operisanih zbog koarktacije aorte u periodu od 2012. do 2017. godine. Posmatrane su demografske i kliničke karakteristike, preoperativni, intraoperativni, postoperativni i ehokardiografski parametri. Neposredni postoperativni gradijent veći od 25 mm Hg smatra se prediktorom postojanja rekoarktacije aorte. Podaci su obrađeni metodama deskriptivne i analitičke statistike.

Rezultati: Medijana uzrasta u vreme operacije je bila 2 meseca (4 dana - 19 godina). Dominantno je korišćena „*extended end-to-end*" anastomoza (90,4%). Kaplan-Majerova (*Kaplan-Meier*) analiza preživljavanja ukazuje na veću učestalost rekoarktacije aorte u grupi pacijenata sa neposrednim postoperativnim gradijentom > 25 mm Hg ($p < 0,001$). Takođe, Koksovom (*Cox*) logističkom regresijom kao prediktor je izdvojen veći neposredni postoperativni gradijent (HR 4,57, $p = 0,009$, 95% CI 1,47 - 14,22). Nakon korigovanja za druge faktore, uključujući pol, genetički sindrom, malu telesnu težinu, primenu prostaglandina E1, prisustvo bikuspidne aortne valvule i hiruršku tehniku, ustanovljeno je da grupa pacijenata sa većim neposrednim postoperativnim gradijentom na mestu anastomoze ima 4 puta veću verovatnoću da ima rekoarktaciju aorte (HR 4,37, $p = 0,035$, 95% CI 1,11 - 17,16).

Zaključak: Nesporedni postoperativni gradijent > 25 mm Hg nezavisni je prediktor rekoarktacije aorte u dugoročnom praćenju nakon hirurški korigovane koarktacije aorte.

Ključne reči:
koarktacija aorte,
rekoarktacija,
faktori rizika,
gradijent

Introduction

Coarctation of the aorta (Coarctation of the Aorta - CoA) represents a narrowing of the thoracic aorta, which is most frequently localized at the junction of the *ductus arteriosus* (1). The location of the narrowing is variable; it is, however, most frequently positioned in the aortic isthmus, distally from the branching of the left subclavian artery. Coarctation of the aorta is relatively common and represents 6 - 8% of all congenital heart defects, with an incidence of 3 - 4 cases in 10.000 live births and two times higher rates in boys than in girls (1, 2).

Coarctation of the aorta can present as an isolated pathology or occur conjoined with other heart defects such as bicuspid aortic valve (60%), aortic arch hypoplasia (18%), ventricular septal defect (13%), mitral valve anomalies (8%), or subaortic stenosis (6%) (1). In addition to this, it has also been described that coarctation of the aorta can occur together with transposition of the great vessels, atrioventricular canal defect, Shone`s syndrome, and hypoplastic left heart syndrome in rarer cases (3-7).

Surgical correction of CoA is the main treatment option for newborns and infants. For patients of more advanced age, percutaneous interventions such as balloon angioplasty with or without stent placement are preferred (8). Surgical techniques that are used to correct this heart defect are end-to-end anastomosis, extended end-to-end anastomosis, and subclavian flap aortoplasty (9). Prostaglandin E1 is used preoperatively in newborns with the goal of maintaining an open ductus arteriosus or relaxing the aortic isthmus to ensure adequate distal perfusion and thus prevent worsening of the patient's condition until the procedure is performed (10).

Clinical presentation of CoA can vary, ranging from mild symptoms, which can frequently result in a late diagnosis, to rapid development of symptoms and signs of shock in newborns (11). In long-term postoperative follow up these patients can develop sequelae in the form of: arterial hypertension, recoarctations, aortic aneurysms, early development of coronary disease and sudden cardiac death (12-15).

Data in international literature on risk factors for the development of coarctation of the aorta are contradictory (9, 13, 16-19).

The aim of this study was to 1) establish the frequency of recoarctation of the aorta after surgical correction and 2) identify early parameters that indicate recoarctation of the aorta.

Material and methods

This research represents a single-center retrospective study conducted at the Department of Cardiology and Cardiac Surgery of the University Children's Hospital in Belgrade, Serbia. The study includes 107 consecutive patients who underwent primary surgical correction for coarctation of the aorta in the period from 2012 to 2017 (five-year period). Criteria for exclusion of patients were: intraoperatively established diagnosis of interrupted aortic arch, need for circulatory arrest during surgical correction, univentricular heart, and fatal outcome in the period of 30 days after the intervention. Patient data

was collected from the unified electronic registry of the Department of Cardiology and Cardiac Surgery at the University Children's Hospital.

Diagnosis of coarctation of the aorta was established based on echocardiography and is defined as a localized narrowing of the thoracic aorta with a flow acceleration of over 3 m/s registered by continuous Doppler techniques, along with a characteristic flow profile - diastolic prolongation in the descending and/or abdominal aorta.

Surgical correction involved an approach via lateral thoracotomy or median sternotomy, depending on the anatomical characteristics of the aortic coarctation. Coarctation of the aorta was surgically corrected using end-to-end or extended end-to-end anastomosis techniques or patch plasty of the coarctation site. For each patient, demographic and clinical characteristics were observed: gender, age, age at the time of surgery, body weight and height, body weight at the time of surgery, presence of a genetic syndrome, and associated congenital heart defects. Preoperative, intraoperative, and postoperative parameters were observed: use of prostaglandin E1, presence of pulmonary arterial hypertension, invasively measured arterial blood pressure in the upper and lower extremities before and after surgical correction, difference in invasively measured pressures in the extremities, surgical technique, and clamp time during the surgical procedure. The presence of hypertension requiring the use of sodium nitroprusside in the intensive care unit after surgical correction was recorded. Echocardiographic parameters were analyzed: the presence of a bicuspid aortic valve, myocardial hypertrophy, and systolic dysfunction before and after surgical correction. Echocardiographically recorded dimensions were standardized using Z-scores. Doppler techniques were used to assess the pressure gradient at the site of obstruction before surgical correction, as well as the pressure gradient at the anastomosis site after surgical correction of the aortic coarctation. Arterial hypertension during follow-up was defined in one of the following ways: daily systolic load during 24-hour ambulatory blood pressure monitoring over 50%, recorded elevated arterial blood pressure values P > 95 for age in consecutive measurements, or documented initiation of antihypertensive therapy in the medical records.

Recoarctation of the aorta was defined by the first-time recorded flow velocity exceeding 3 m/s, registered using continuous Doppler techniques, along with a characteristic flow profile - diastolic prolongation in the descending and/or abdominal aorta. Mortality in long-term follow-up was defined as death occurring more than 30 days after the intervention.

Descriptive statistical methods, including chi-square and Student's t-test, were used for data processing. Kaplan-Meier survival curves were analyzed and compared based on the presence of aortic recoarctation in long-term follow-up, and groups were compared using the log-rank test. Cox regression was employed to assess the risk ratios between groups. Occurring p-values of < 0.05 were considered statistically significant, while p-values of < 0.001 were considered highly statistically significant. The selected confidence interval (CI) was 95%. The statistical analysis was conducted using the SPSS software package (Statistical Package for Social Sciences, version 23.0).

Results

A total of 107 patients were extracted from the unified electronic registry of the University Children's Hospital who underwent surgical correction of coarctation of the aorta (CoA) from 2012 to 2017. These patients were potentially suitable for inclusion in the study. After applying the exclusion criteria, a total of 94 patients were included in the research (**figure 1**).

Of the 94 (100%) patients, the majority were male (60%), and the median age at the time of the intervention was 2 months (ranging from 4 days to 19 years). Prostaglandin E1 was preoperatively prescribed for slightly more than one-third of the patients (35.2%). The majority of patients were neonates or younger than 2 years of age at the time of surgery (35.1% and 38.3%, respectively). Clinical and demographic characteristics of the study cohort are presented in **table 1**.

Preoperative echocardiographic assessment verified the presence of a bicuspid aortic valve in 59.8% of the patients. Also, of the entire cohort, almost 60% had myocardial hypertrophy, and 16% developed preoperative systolic dysfunction. Preoperative echocardiographic characteristics are presented in **table 2**.

Of all the analyzed surgical techniques, extended end-to-end anastomosis was predominantly used (90.4%) (**table 3**). Nearly one third of the patients (29%) in the cohort required postoperative administration of sodium nitroprusside. During follow-up, almost 40% of the patients developed arterial hypertension (**table 4**).

Outcomes

The average follow-up time in the study was 6 years, and 12 (11.28%) patients developed recoarctation of the

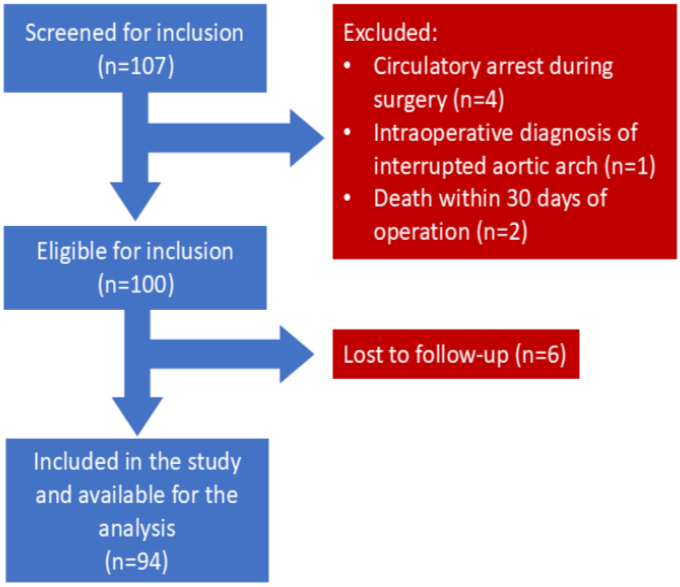

Figure 1. The study flow chart

aorta. By using Cox regression, it was established that an immediate postoperative gradient > 25 mm Hg is a statistically significant factor (HR 4.57, p = 0.009, 95% CI 1.47 - 14.22). After adjusting for other factors including gender, genetic syndrome, low body weight, use of prostaglandin E1, presence of a bicuspid aortic valve, and surgical technique, it was found that the group of patients with a higher immediate postoperative gradient at the anastomosis site has a fourfold greater tendency to develop recoarctation (HR 4.37, p = 0.035, 95% CI 1.11 - 17.16) (**figure 2**).

Table 1. Demographic and clinical characteristics in patients with and without recoarctation of the aorta during follow-up after surgical correction

	All patients (n = 94)	Recoarctation of the aorta (n = 12)	No recoarctation of the aorta (n = 82)	p
Gender (male, %)	60.0	50.0	61.0	0.537
Age at the time of surgery (years, SD)	2.2 ± 4.2	3.7 ± 3.2	1.9 ± 1.6	0.169
Age ≤ 28 days (%)	35.1	50.0	32.9	0.333
Age ≥ 29 days to < 2 years (%)	38.3	16.7	42.7	0.117
Age ≥ 2 years to < 5 years (%)	12.8	8.3	12.1	0.997
Age ≥ 5 years to < 18 years (%)	12.8	25.0	11.0	0.179
Age ≥ 18 years (%)	1.1	-	-	-
Weight at the time of surgery (kg, SD)	11.7 ± 11.2	15.1 ± 15.0	11.2 ± 10.4	0.453
Weight < 2.5 kg (%)	12.0	9.1	11.5	0.996
Genetic syndrome (%)	13.0	25	12.3	0.365
PGE1 Administration (%)	35.2	50.0	36.3	0.525
Pulmonary hypertension (%)	29.7	50.0	29.1	0.187

Table 2. Preoperative echocardiographic characteristics of patients with and without recoarctation after surgical correction

	All patients (n = 94)	Recoarctation of the aorta (n = 12)	No recoarctation of the aorta (n = 82)	p
LVEDD (mm, SD)	24.9 ± 10.35	26.7 ± 13.8	24.9 ± 9.6	0.556
LVEDD (Z score, SD)	-0.01 ± 1.96	-0.4 ± 1.9	0.1 ± 1.7	0.393
LVESD (mm, SD)	15.1 ± 6.25	16.4 ± 7.3	15.1 ± 5.9	0.500
LVESD (Z score, SD)	-0.1 ± 1.9	-1.0 ± 1.3	-0.6 ± 2.1	0.420
FS (%, SD)	38.7 ± 8.4	36 ± 6.0	38.0 ± 8.0	0.440
IVS (mm, SD)	7.7 ± 10.3	6.1 ± 2.4	7.9 ± 9.2	0.638
ZZ (mm, SD)	6.4 ± 7.8	5.7 ± 2.6	6.5 ± 6.2	0.788
Aortic annulus (mm, SD)	11.4 ± 9.3	11.0 ± 7.0	11.4 ± 9.7	0.890
Aortic annulus (Z score, SD)	2.0 ± 13.2	0.1 ± 2.7	2.3 ± 14.0	0.595
Bicuspid aortic valve (%)	59.8	83.3	57.5	0.117
Ascending aorta (mm, SD)	13.8 ± 13.3	13.0 ± 8.6	14.2 ± 12.3	0.852
Site of coarctation (mm, SD)	3.2 ± 3.2	2.5 ± 1.2	3.3 ± 4.0	0.589
Systolic dysfunction (%)	15.4	16.7	16.5	0.999
Myocardial hypertrophy (%)	58.8	70.4	56.0	0.507
Pressure gradient (mm Hg, SD)	49.6 ± 22.9	54.3 ± 28.5	48.6 ± 22.1	0.429

Table 3. Intraoperative characteristics of patients with and without recoarctation of the aorta

	All patients (n = 94)	Recoarctation of the aorta (n = 12)	No recoarctation of the aorta (n = 82)	p
Extended end-to-end anastomosis (%)	90.4	75.0	92.7	0.087
Clamp time (min, SD)	22.75 ± 9.71	31.5 ± 15.40	24.3 ± 16.2	0.168
Difference in invasively measured systolic pressure GE/DE before correction (mm Hg, SD)	30.6 ± 26.4	34.3 ± 21.7	29.1 ± 23.5	0.344
Difference in invasively measured systolic pressure GE/DE after correction (mm Hg, SD)	6.7 ±7.4	9.1 ± 7.4	7.7 ± 6.4	0.787

Table 4. Postoperative echocardiographic characteristics of patients with and without recoarctation of the aorta

	All patients (n = 94)	Recoarctation of the aorta (n = 12)	No recoarctation of the aorta (n = 82)	p
LVEDD (mm, SD)	25.1 ± 8.4	26.3 ± 12.2	24.9 ± 7.7	0.658
LVEDD (Z score, SD)	-0.3 ± 1.0	-0.6 ± 1.0	0.2 ± 0.9	0.630
LVESD (mm, SD)	14.7 ± 5.2	15.0 ± 7.4	14.7 ± 4.8	0.881
LVESD (Z score, SD)	0.1 ± 1.2	0.2 ± 1.3	-0.4 ± 1.0	0.742
FS (%, SD)	40.3 ± 9.3	41.6 ± 3.8	39.1 ± 9.3	0.508
Immediate postoperative pressure gradient (mm Hg, SD)	19.4 ± 11.1	26.3 ± 6.1	18.9 ± 11.6	**0.041**
Immediate postoperative pressure gradient > 25 mm Hg	17.0	50.0	13.0	**0.007**
Any postoperative complication (%)	30.1	16.7	28.4	0.503
Use of Na-nitroprusside (%)	29.0	31.3	28.6	0.999

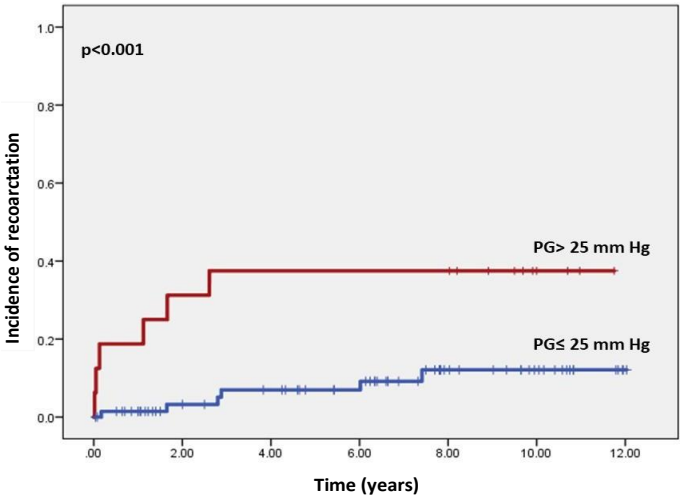

Figure 2. The cumulative Kaplan-Meier curve illustrates the occurrence of recoarctation of the aorta after surgery in relation to the immediate postoperative gradient measured by continuous Doppler

Discussion

In this study, after surgical correction of coarctation of the aorta (CoAo), recoarctation of the aorta occurred in 11.28% of patients, which is consistent with the literature, stating that recoarctation develops in 10 - 20% of cases (20). The research by Rinske Ijsselhof and colleagues (8) showed a difference in the distribution of aortic recoarctation and reintervention among different age groups of children, with 10.3% of operated patients in the neonatal age requiring reintervention, while among those aged 29 days to 6 months at the time of surgical correction, 4.7% required reoperation. However, in this research, age at the time of surgery did not prove to be a risk factor for the development of recoarctation. Six studies (16,17,21-24) also analyzed the impact of age at the time of CoAo surgery as a risk for recoarctation, where only two studies in multivariate analysis demonstrated that a younger age at the time of surgery discreetly increases the risk of recoarctation.

Dias and colleagues identified a body weight of less than 2.5 kg as an independent risk factor for the development of re-coarctation in their study (25). In contrast, lower body weight at the time of surgery did not prove to be an independent predictor in our cohort. This is consistent with the findings of McElhinney and colleagues (16), as well as Sudarshan and colleagues (26).

Amélia Lehnert and colleagues (21) demonstrated a correlation between the use of prostaglandin E1 (PGE1) and an increased incidence of aortic recoarctation, which is not in agreement with this study after incorporating PGE1 into the Cox regression model. This association was explained by the fact that the opening of the ductus arteriosus leads to changes in the aortic isthmus, thereby masking the edges of resection during the surgery (27). However, in the study, the use of prostaglandin infusion did not emerge as a statistically significant risk factor during follow-up.

In this research, 90.4% of patients underwent extended end-to-end anastomosis, which is the most commonly used surgical technique for CoAo (17,28-30). A statistically significant higher frequency of this surgical technique was found in the group of patients without recoarctation of the aorta, which can be explained by the extensive removal of ductal tissue and the fact that prosthetic materials are not used in this procedure. Additionally, this approach involves a wide resection edge, which allows for adequate growth of the transverse aorta (28, 31).

Arterial hypertension is a common occurrence after CoAo surgery and occurs in about 35 - 70% of cases. In this study, 39.4% of patients developed arterial hypertension during long-term follow-up (32). The etiology is not fully understood, but it is believed to arise from endothelial dysfunction, reduced compliance of the aortic wall, and irregular blood flow, along with irregularities in the renin-angiotensin system (33-36).

Immediately after CoAo surgery, transthoracic measurement of the aortic pressure gradient is performed using Doppler echocardiography, which ideally would display laminar flow and a pressure gradient of less than 25 mm Hg, representing the threshold value. An accelerated systolic flow with a pressure gradient greater than 25 mm Hg serves as an early indicator of the presence of aortic recoarctation, as shown by Osama M. Eldadah and colleagues (37).

In this study, there is a statistically significant higher number of patients in the group with aortic recoarctation whose immediate postoperative pressure gradient measured by continuous Doppler is greater than 25 mm Hg, compared to the group without aortic recoarctation. Furthermore, in the Cox logistic regression, the immediate postoperative pressure gradient over 25 mm Hg emerged as a statistically significant factor, and after adjustment for co-factors, it was also identified as an independent predictor, with a fourfold increased risk of developing recoarctation during long-term follow-up.

Limitations of the study include a small number of participants, the fact that the study is retrospective and represents a single-center study, as well as the lack of data encountered during the data collection process.

Conclusion

The immediate postoperative gradient of over 25 mm Hg is an independent predictor for the development of recoarctation of the aorta during long-term follow-up. This finding may contribute to better risk stratification, monitoring, planning, and earlier detection of recoarctation of the aorta, thus leading to improved outcomes in the long-term follow-up of this patient population.

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