

ORIGINAL ARTICLE

Coarctation of The Aorta: A Case-Series from a Tertiary Care Hospital

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Abstract

Background: Coarctation of the aorta is a congenital segmental narrowing of the aortic arch with severe hemodynamic repercussions and increased cardiovascular mortality. Early surgical correction and life-time echocardiographic follow-up must be performed to improve prognosis. However, this goal has been challenged by high rates of underdiagnosis, which delay surgical correction, and by recoarctation in up to one third of operated patients.

Objectives: The objectives of this study were: (i) to register the frequency of common clinical signs at diagnosis of coarctation of the aorta; (ii) to describe the course of echocardiographic parameters before and during the follow-up of coarctectomized subjects; (iii) to analyze the clinical prognosis of patients according to baseline characteristics, occurrence of recoarctation and associated malformations.

Methods: Case-series of 72 patients coarctectomized between June 1996 and November 2016 in a tertiary care hospital. Clinical, echocardiographic and surgical variables were considered. All patients were submitted to coarctectomy by posterolateral thoracotomy and end-to-end anastomosis. Data were classified as parametric or non-parametric by Kolmogorov-Smirnov test. Parametric data were expressed as mean and standard deviation, and non-parametric data as median and interquartile range. Continuous variables were analyzed using paired t-tests, and categorical variables were compared by chi-square test. For all analysis, a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS, version 20.0 (IBM, Chicago, IL, USA).

Results: The mean follow-up time was 5.8 years (range: 0-20 years). At diagnosis, most patients had heart murmur (88%), non-palpable pulse in the lower limbs (50%), left ventricular hypertrophy (78%), and bicuspid aortic valve (33%), with a mean aortic peak gradient of 55 mmHg. After surgical correction, those without recoarctation were less symptomatic (60 vs 4.5%; $p < 0.001$), had lower aortic peak gradient (54 ± 3.8 vs 13 ± 0.8 ; $p = 0.01$) and left ventricle mass (95 ± 9.2 vs. 63 ± 11 ; $p = 0.01$), and the most common complications were late hypertension (39.2%), and recoarctation (27.6%). Recoarcted patients did not show improvement of neither clinical nor echocardiographic variables. Age at repair and bicuspid aortic valve groups had comparable results with controls. Surgical procedure was safe; mean time of hospitalization was 10 days and mean surgery time 2.3 hours.

Conclusions: Coarctectomy improves cardiac symptoms and left ventricular hypertrophy, with a slight effect on the incidence of hypertension. Recoarctation occurs in one-third of patients and draws attention for the need of lifelong surveillance by echocardiography. (Int J Cardiovasc Sci. 2019; [online].ahead print, PP.0-0)

Keywords: Heart Defects, Congenital; Aortic Coarctation/surgery; Hypertrophy, Left Ventricular; Echocardiography / methods; Hypertension.

Introduction

Coarctation of the aorta (CoA), first described over 200 years ago, has for long been considered as a simple mechanical obstruction caused by a segmental narrowing

of the aortic arch.¹ It was only in the last decades that staggering results revealed that, beyond the anatomical malformation, CoA answers for a systemic vasculopathy with irreversible effects on endothelial function, arterial stiffness and left ventricular remodeling.²⁻⁴ As a

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result, although resection of the coarcted segment may prevent patients from dying by age of 30, even after this procedure, subjects remain at higher risk of hypertension and premature cardiovascular death.^{5,6}

This challenging phenomenon has led to an intense search for predictors of worse prognosis in repaired patients. In this direction, some have claimed that late repair is among the main risk factor for all-cause mortality in subjects undergoing resection of aorta coarctation.⁷ Importantly, late correction frequently occurs as a result of an underdiagnosis rate of over 62%, placing CoA as the most frequently misdiagnosed critical congenital heart disease.⁸ Besides, recoarctation occurs in one-third of patients, leading to a regression of the benefits of first surgical correction and, often, requiring reintervention. This complication demands a life-long surveillance by regular echocardiography in repaired patients.⁵ Finally, hypertension stands as the main complication in repaired subjects, hence representing a known risk factor for cardiovascular disease from an early age, with important long-term repercussions on mortality.⁹⁻¹¹

In this study, we retrospectively analyzed data of patients operated for CoA at a tertiary care hospital. The main goals of this study were: (i) to register the frequency of common clinical signs at diagnosis; (ii) to describe the course of echocardiographic parameters before and during the follow-up of coarctectomized subjects; (iii) to analyze the clinical prognosis of patients according to baseline characteristics, occurrence of recoarctation and associated malformations. A total of 417 patient-years follow-up was studied, revealing hypothesis-generating results.

Materials and methods

Study population

Data were collected from medical records of patients operated for native coarctation of the aorta between June 1996 and November 2016 at the University of Campinas General Hospital (HC-UNICAMP), a tertiary care hospital in Brazil. The last visit to outpatient clinic occurred in November 2016. We compared clinical and echocardiographic data collected at the time of diagnosis and at the last outpatient clinic visit (in November 2016). Diagnosis of coarctation of the aorta was defined as a peak aortic gradient greater than 20 mmHg with compatible clinical history.

Clinical variables

Clinical variables included age, gender, antihypertensive medications and symptoms. Hypertension was defined as the use of antihypertensive drugs. Symptoms were classified according to the New York Heart Association (NYHA) criteria, and all other variables obtained from medical records. During follow-up, recoarctation was defined as a peak descending aorta gradient (DAG) greater than 20 mmHg after successful surgical correction at baseline.

Echocardiographic

Echocardiographic measurements were obtained by trained cardiologists using Vivid S6 (GE Vingmed Ultrasound, Horten, Norway) and EchoPAC version 8.0 (GE Healthcare). The following parameters were considered: left ventricular (LV) end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), posterior wall diastolic thickness (PW), aortic root diameter (ARD), peak DAG, left atrial diameter (LAD) and LV mass (LVM). All variables, except for DAG and ejection fraction (EF), were indexed by body surface calculated by DuBois formula. LV hypertrophy was defined as LV mass values above the 95th percentile for respective age and gender, according to validated guidelines.¹² For comparative purposes, we considered the first echocardiographic test performed before surgical correction as “baseline”, and the last echocardiographic examination after surgery as the “last” examination.

Operative technique

Medical registries including operative notes, data on perioperative hemodynamics and complications of all patients operated at our hospital were collected for analysis. In our study, all patients have undergone coarctectomy by posterolateral thoracotomy and an end-to-end anastomosis as previously described.¹³ Briefly, in this procedure, a left posterolateral thoracotomy is completed with sparing of the serratus anterior muscle in the third to fourth intercostal space. Then, the lung is retracted inferiorly and medially, exposing the aorta which is further mobilized. Then, a proximal clamp is placed at the base of the left subclavian artery or proximal to the carotid bifurcation, and a distal clamp is placed below the second intercostal space. Finally, the narrowed segment is resected, and an end-to-end anastomosis performed.

Complications include injury to adjacent structures, such as the common thoracic duct, leading to chylothorax.¹³ Also, paraplegia may occur in 0.5% of cases, especially in those requiring prolonged cross-clamping time or presenting with distal hypotension.¹³ Lately, up to one-third of operated patients may develop recoarctation, which worsens the prognosis and require prompt intervention. If uncomplicated, the procedure should take from 2 to 3 hours, with a mean cross-clamping time of 17 minutes.¹⁴

Missing data

Only data collected from the medical records of our hospital and only tests performed at our institution were considered for analysis. Therefore, patients diagnosed or followed in other centers and referred to the HC-UNICAMP for surgical correction, had missing data and were lost to follow-up. To tackle this issue, data is presented according to the total number of tests available.

Statistical analysis

Kolmogorov-Smirnoff test was applied to classify data as parametric or non-parametric. Parametric data were expressed as mean and standard error, and non-parametric data as median and interquartile range. Categorical variables were expressed as number of cases and prevalence (%). Continuous variables were analyzed using paired t-tests, and categorical variables were compared by chi-square test. For all analysis, a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS, version 20.0 (IBM, Chicago, IL, USA).

Results

We identified 72 patients who underwent CoA surgical correction at the HC-UNICAMP between June 1996 and November 2016. Patients were followed for a mean time of 5.82 years, ranging from 0 to 20 years. The mean age at surgery was 5.64 ± 1.31 years, ranging from 0.1 to 27 years, and 51.6% of patients were operated in their first year of life. Demographic data is summarized in Table 1.

At diagnosis, 51 (87.9%) patients had a heart murmur and 23 (48.9%) had no palpable pulse in the lower limbs. Out of the 18 electrocardiographic tests performed, 12

Table 1 - Baseline characteristics of patients (n = 72) who underwent surgical correction of coarctation of the aorta at the HC-UNICAMP between June 1996 and November 2016

Demographic data	
Age at surgery, years	5.64 ± 1.31 (0.1 to 27)
Male, %	41 / 72 (56.9)
Follow-up time, years	5.82 ± 0.86 (0.02 to 20)
Clinical data	
Symptomatic, %	36 / 60 (60)
Hypertensive, %	27 / 46 (58.7)
Heart murmur, %	51 / 58 (87.9)
Absence of lower limbs pulse, %	23 / 47 (48.9)
Surgical data	
Hospitalization, days	10.3 ± 1.07 (4 to 32)
Surgery time, hours	2.3 ± 0.09 (1.5 to 3.5)
Clamping time, min	15.9 ± 6 (8 to 38)

Data expressed as mean \pm SE (range) or n/total (%).

(67%) patients with LV overload were detected, and of 14 patients who underwent complementary cardiovascular imaging investigation beyond echocardiogram, two (14%) had a chest X-ray, one (7%) had a chest computed tomography and six (43%) underwent computed tomography angiography. Besides, among those taking antihypertensive medications at baseline (58%), the most frequent classes were thiazide diuretics (35.6%), beta-blockers (27.1%) and inhibitor of angiotensin-converting enzyme inhibitors (22%). Use of vasodilators (5.1%) and angiotensin receptor blocker (1.7%) were far less common (Table 2).

At baseline, the mean peak DAG was 55 mmHg, and 19 (78%) of patients had LV hypertrophy. The most common echocardiographic findings were bicuspid aortic valve (BAV) (32.8%), persistent arterial duct (31%) and interventricular communication (19%). Mitral valve insufficiency was present in 13.8% of patients. Noteworthy, pulmonary artery hypertension occurred in 12.1% of patients. Less common findings are summarized in Table 3.

All patients underwent surgical correction of CoA by left thoracotomy followed by end-to-end anastomosis.

Table 2 - Number of antihypertensive medications

	Baseline (n = 46)	Last exam		
		Control ^a (n = 34)	Recoarctation ^b (n = 14)	Bicuspid aortic valve ^c (n = 16)
0	19 (41.3)	21 (61.8)	3 (21.4)*	7 (43.8) [‡]
1	15 (32.6)	8 (23.5)	6 (42.9)	6 (37.5)
2	5 (10.9)	3 (8.8)	3 (21.4)	2 (12.5)
3	7 (15.2)	2 (5.9)	2 (14.3)	1 (6.3)

Values are n (%). *p = 0.011 compared with control; chi-square test; [‡]p = 0.53 compared with control; chi-square test; ^a Patients without bicuspid aortic valve (BAV) at diagnosis and without recoarctation in the last echocardiographic test; ^b absence of BAV at diagnosis, and presence of recoarctation in the last echocardiographic test; ^c BAV at diagnosis, and absence of recoarctation in the last echocardiographic test; NYHA: New York Heart Association classification for heart failure symptoms; BAV: bicuspid aortic valve.

Table 3 - Baseline echocardiographic variables

Findings	
Peak aortic gradient, mmHg	55 ± 3.2 (20 to 103)
Left ventricular hypertrophy, %	19/25 (76)
Bicuspid aortic valve, %	19/58 (32.8)
Persistent arterial duct, %	18/58 (31)
Interventricular communication%	11/58 (19)
Patent foramen ovale, %	9/58 (15.5)
Mitral valve insufficiency, %	8/58 (13.8)
Interatrial communication, %	7/58 (12.1)
Aortic valve insufficiency, %	7/58 (12.1)
Pulmonary artery hypertension, %	7/58 (12.1)
Tricuspid valve insufficiency, %	6/58 (10.3)
Aortic stenosis, %	3/58 (5.2)

Data expressed as mean ± SE (range) or n/total (%)

The mean time of surgery and hospitalization was 2.3 hours and 10 days, respectively, and mean cross-clamping time was 15.9 minutes. Of 51 patients operated, three patients had chylothorax, with no other surgical complications being reported. Among those who did not have recoarctation during follow-up, surgical correction greatly decreased peak DAG (54 vs 13 mmHg; p < 0.001) and symptoms (60 vs 4.5%; p < 0.001), but not hypertension (58 vs 38%; p = 0.17) (Figure 1). Besides, a

significant reduction in LVM, LVEDD, LVESD, PW, ARD and LAD was observed in these patients when compared to baseline values (Figure 2 and Table 4).

Importantly, during follow-up, 16 (27.6%) patients had recoarctation (Figure 3). The mean follow-up period before detection of recoarctation was 5.6 years, and half of the cases occurred after 3.6 years of follow-up. Last recoarctation event was identified after 15 years of follow-up. Overall, patients with recoarctation were more likely to be symptomatic (4.5 vs 64%; p < 0.001) and hypertensive (38 vs 78%; p = 0.011) when compared to those without recoarctation (Table 5). In addition, compared to baseline, there was no significant change in peak gradient or in LVM (Table 5).

Noteworthy, patients with BAV at diagnosis had comparable results with controls during follow-up. Also, age at surgery and gender did not affect the outcomes (data not shown).

Discussion

In this case series, we evaluated data from 72 patients operated for coarctation of the aorta and followed for up to 20 years in tertiary hospital in Brazil. Our main objectives were to identify the most frequent clinical findings that could benefit from early diagnosis, to describe the course of echocardiographic measures following surgical correction, and to detect the occurrence of recoarctation and its impact on prognosis. Our main findings were the following: (i) heart murmur is present in most patients; (ii) in addition to peak DAG, LV mass and diameters also decreased after surgical correction;

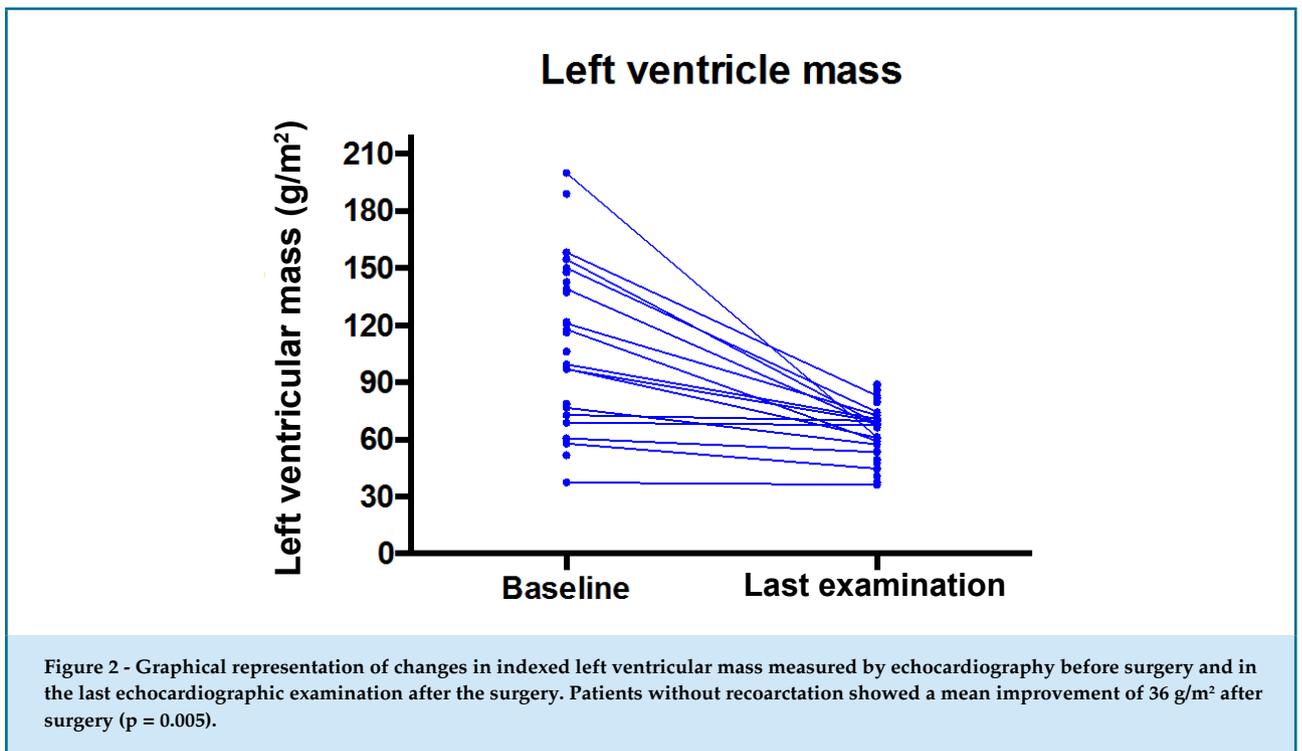
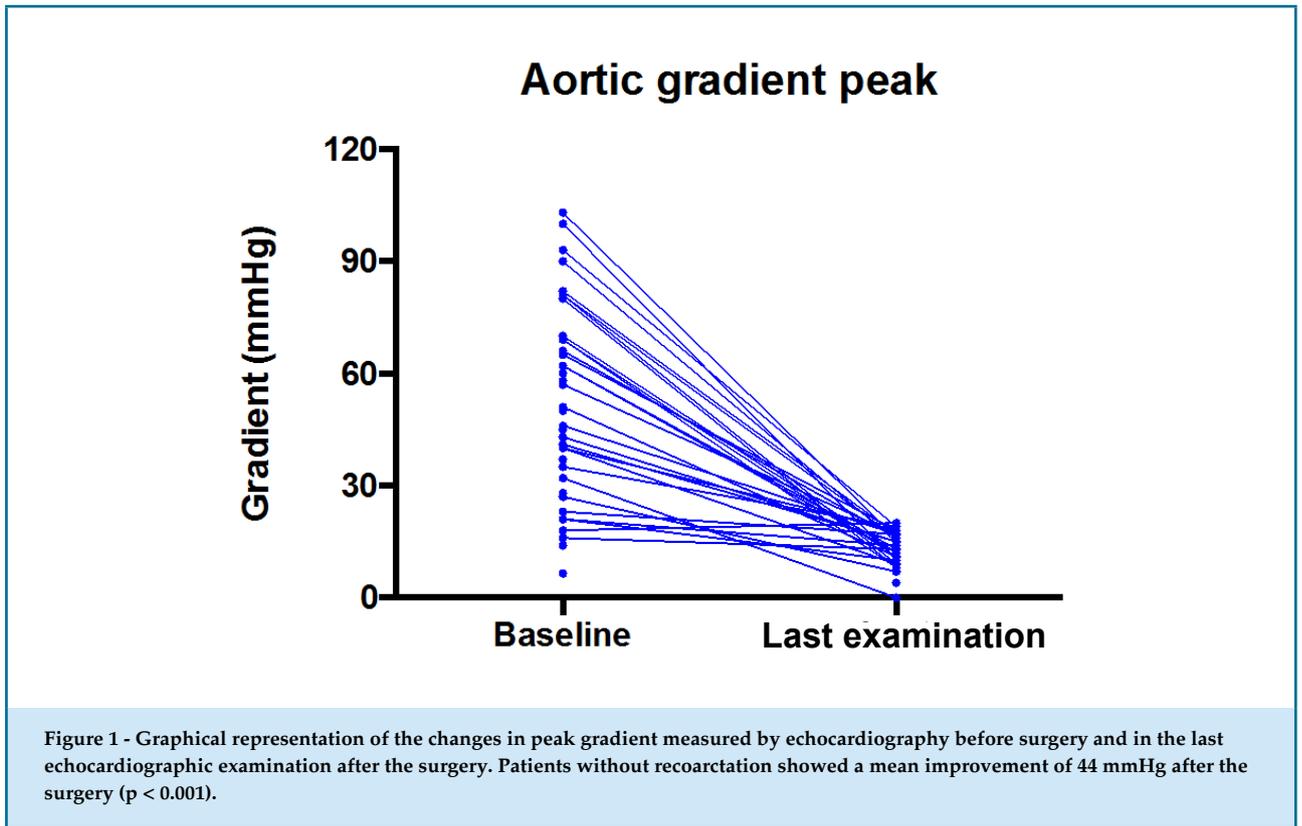


Table 4 - Echocardiographic measures before and after surgical correction according to groups

	Baseline (n = 40)	Last exam		
		Control (n = 40)	Recoarctation (n = 16)	Bicuspid aortic valve (n = 11)
DAG, mmHg	54 ± 3.8	13 ± 0.8**	35 ± 5.9	11 ± 1.1**
LVM, g/m ²	95 ± 9.2	63 ± 11**	56 ± 5.1	55 ± 3.8
LVEDD, cm/m ²	72 ± 5.5	41 ± 3.2**	46 ± 7.3*	49 ± 6.3*
LVESD, cm/m ²	45 ± 3.7	25 ± 2.2**	29 ± 5.6*	29 ± 4.2*
PW, cm/m ²	15 ± 1.8	8 ± 0.7**	10 ± 2.1	9 ± 1.6**
ARD, cm/m ²	35 ± 2.3	23 ± 1.5**	26 ± 3.4	26 ± 2.7**
LAD, cm/m ²	48 ± 3.8	28 ± 2.5**	33 ± 5	36 ± 5.7
LV hypertrophy, %	22/28 (78.6)	0/27 (0)	0/7 (0)	0/6 (0)

Values are mean ± SE. **p* < 0.05; ***p* < 0.01 compared with baseline; paired T-test. DAG: peak descending aorta gradient; LVM: left ventricular mass; LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; PW: posterior wall diastolic thickness; ARD: aortic root diameter; LAD: left atrial diameter.

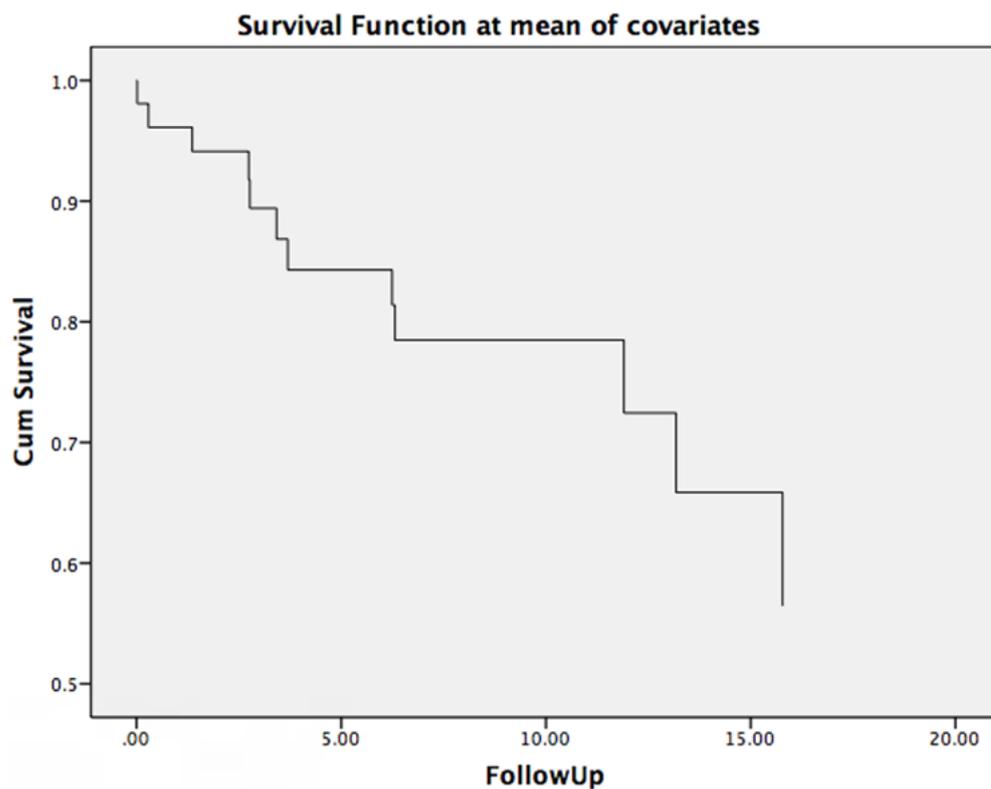


Figure 3 - Graphical representation of recoarctation episodes during follow-up. Values are presented as cumulative survival (%) and follow up (years after surgery).

Table 5 - Clinical variables before and after surgical correction

NYHA	Baseline (n = 60)	Last exam		
		Control ^a (n = 22)	Recoarctation ^b (n = 14)	Bicuspid aortic valve ^c (n = 11)
I	24 (40)	21 (95.5) [*]	5 (35.7) [*]	10 (90.9) [#]
II	14 (23.2)	1 (4.5)	8 (57.1)	1 (9.1)
III	12 (20)	-	1 (7.1)	-
IV	10 (16.7)	-	-	-

Values are n (%). #p < 0.001 compared with baseline; chi-square test; *p < 0.001 compared with control; chi-square test; ^a patients without bicuspid aortic valve at diagnosis and without recoarctation in the last echocardiographic test; ^b absence of BAV at diagnosis, and presence of recoarctation in the last echocardiographic test; ^c BAV at diagnosis, and absence of recoarctation in the last echocardiographic test; NYHA: New York Heart Association classification for heart failure symptoms; BAV: bicuspid aortic valve.

(iii) recoarctation is a late finding in operated subjects and significantly impacts prognosis.

In our study, most patients who underwent CoA surgical correction had systolic heart murmur with posterior radiation at diagnosis, and half of them had hypertension, cardiac symptoms, and no palpable pulse in the lower limbs. Of note, these findings were achieved by proper physical examination and history-taking, which can guide complementary investigation focused on early diagnosis. Yet, half of patients were lately diagnosed in our follow-up, which is in accordance with previous large population-based studies showing late diagnosis rates of over 62%.⁸

Whether late correction constitutes an independent risk factor for poor prognosis remains a matter of debate, with some suggesting a relationship of late correction with re-coarctation rates⁶ and others with long-term cardiovascular mortality. In our study, neither recoarctation nor clinical outcomes differed in a significant manner between age groups. Still, an earlier surgical treatment of comorbidities that are known to have an impact on cardiovascular mortality would presumably improve long-term survival. This hypothesis is supported by the absence of LV hypertrophy and cardiac symptoms in operated patients in our analysis.

It is of note that more than one third of patients remained hypertensive after surgical correction. This finding is in accordance with previous studies suggesting hypertension as the main late complication in operated patients, even in the absence of residual obstruction.^{9,11} Although the exact mechanism for this phenomenon

remains unclear, a role of arterial stiffness, endothelial dysfunction and altered autonomic cardiac modulation has been proposed.

In this matter, post-coarctectomy subjects have impaired endothelial function, which, in turn, increases peripheral vascular resistance, leading to increased blood pressure.¹⁰ Moreover, coarctation leads to deposition of collagen and depletion of smooth muscle in the aortic wall. This negatively affects aortic distensibility and the sensitivity of aortic arch baroreceptors, thereby impairing arterial compliance with substantial effects on blood pressure.^{15,16} Finally, it has been conjectured that hypertension results from compensatory sympathetic stimuli in response to acute unloading of the baroreceptors following surgery.¹⁰ Importantly, these features are not prevented by surgical correction, reinforcing that coarctation is a generalized vasculopathy far beyond the narrowing of the aortic arch.

Our study found a high prevalence of LV hypertrophy at baseline, which markedly decreased after surgical correction. Noteworthy, in coarctation, an increase in LV mass occurs in spite of elevated blood pressure, which may be explained by the “ventricular-arterial coupling” hypothesis, that postulates that aortic stiffness increases wave reflection pressure, leading to LV afterload.¹⁷ Importantly, such phenomenon leads to diastolic dysfunction and changes in LV morphology, which are partially reversed by surgery, as demonstrated in the present study and in previous ones.^{4,18-20} In fact, in our follow-up we found a significant reduction of indexed LV diameters, LV mass and posterior wall thickness in operated patients who did not manifest recoarctation.

Finally, pulmonary hypertension occurred in 12% of patients in our follow-up, which is in accordance with previous studies. Mechanistically, it is assumed that endothelial dysfunction and arterial stiffness are the most likely causes of pulmonary hypertension in these patients, though a role for vascular reactivity has been also proposed.²⁰ Moreover, BAV was the most common associated malformation in our analysis, which is in agreement with previous studies showing a common genetic mutation for both congenital heart diseases.²¹ Noteworthy, it has been proposed that such phenomenon would lead to greater hemodynamic changes, which could plausibly lead to worsen prognosis.²² In our study, patients with isolated and complex coarctation had comparable results, although larger studies are required to correctly address this issue.

Limitations

Our study has some limitations that are inherent to retrospective case series. Also, since we collected data from a tertiary care hospital, the possibility of a selection bias cannot be excluded, favoring those with more complex presentations of the disease. Finally, we did not register any hard endpoint, which weaken the capacity of identifying predictive risk factors for a worse prognosis.

Conclusions

Coarctectomy improves cardiac symptoms and LV hypertrophy, with a slight effect on the incidence of hypertension. Age at surgical repair and complex

malformations were not related to a worse prognosis. In our study, recoarctation had a negative impact on the benefit of surgery in one-third of patients, which reinforces the need for lifelong surveillance by echocardiography.

Author contributions

Conception and design of the research: Barreto J, Roda J, Germano CW, Quinaglia T. Acquisition of data: Barreto J, Roda J, Germano CW, Damiano AP, Quinaglia T. Analysis and interpretation of the data: Barreto J, Quinaglia T. Statistical analysis: Barreto J, Quinaglia T. Writing of the manuscript: Barreto J, Quinaglia T. Critical revision of the manuscript for intellectual content: Barreto J, Roda J, Germano CW, Damiano AP, Quinaglia T.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Yokoyama U, Ichikawa Y, Minamisawa S, Ishikawa Y. Pathology and molecular mechanisms of coarctation of the aorta and its association with the ductus arteriosus. *J Physiol Sci.* 2017;67(2):259-70.
2. Lee MG, Allen SL, Kawasaki R, Kotevski A, Koleff J, Kowalski R, et al. High prevalence of hypertension and end-organ damage late after coarctation repair in normal arches. *Ann Thorac Surg.* 2015;100(2):647-53.
3. Quail MA, Short R, Pandya B, Steeden JA, Khushnood A, Taylor AM, et al. Abnormal wave reflections and left ventricular hypertrophy late after coarctation of the aorta repair. *Hypertension.* 2017;69(3):501-9.
4. Lombardi KC, Northrup V, McNamara RL, Sugeng L, Weismann CG. Aortic stiffness and left ventricular diastolic function in children following early repair of aortic coarctation. *Am J Cardiol.* 2013;112(11):1828-33.
5. Brown ML, Burkhart HM, Connolly HM, Dearani JA, Cetta F, Li Z, et al. Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. *J Am Coll Cardiol.* 2013;62(11):1020-5.
6. Choudhary P, Canniffe C, Jackson DJ, Tanous D, Walsh K, Celermajer DS. Late outcomes in adults with coarctation of the aorta. *Heart.* 2015;101(15):1190-5.
7. Farag ES, Kluin J, de Heer F, Ahmed Y, Sojak V, Koolbergen DR, et al. Aortic coarctation repair through left thoracotomy: results in the modern era. *Eur J Cardiothorac Surg.* 2019;55(2):331-7.
8. Peterson C, Ailes E, Riehle-Colarusso T, Oster ME, Olney RS, Cassell CH, et al. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using pulse oximetry. *JAMA Pediatr.* 2014;168(4):361-70.

9. Canniffe C, Ou P, Walsh K, Bonnet D, Celermajer D. Hypertension after repair of aortic coarctation—a systematic review. *Int J Cardiol.* 2013;167(6):2456-61.
10. Kenny D, Polson JW, Martin RP, Paton JF, Wolf AR. Hypertension and coarctation of the aorta: an inevitable consequence of developmental pathophysiology. *Hypertens Res.* 2011;34(5):543-7.
11. Rinnstrom D, Dellborg M, Thilen U, Sörensson P, Nielsen NE, Christersson C, et al. Hypertension in adults with repaired coarctation of the aorta. *Am Heart J.* 2016 Nov;181:10-5.
12. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. *J Am Soc Echocardiogr.* 2009;22(6):709-14.
13. Jaquiss RDB. Coarctation of the aorta: end-to-end anastomosis. *Oper Tech Thorac Cardiovasc Surg.* 2002;7(1):2-10.
14. Wright GE, Nowak CA, Goldberg CS, Ohye RG, Bove EL, Rocchini AP. Extended resection and end-to-end anastomosis for aortic coarctation in infants: results of a tailored surgical approach. *Ann Thorac Surg.* 2005;80(4):1453-9.
15. Kuhn A, Baumgartner D, Baumgartner C, Hörer J, Schreiber C, Hess J, et al. Impaired elastic properties of the ascending aorta persist within the first 3 years after neonatal coarctation repair. *Pediatr Cardiol.* 2009;30(1):46-51.
16. Kenny D, Polson JW, Martin RP, Caputo M, Wilson DG, Cockcroft JR, et al. Relationship of aortic pulse wave velocity and baroreceptor reflex sensitivity to blood pressure control in patients with repaired coarctation of the aorta. *Am Heart J.* 2011;162(2):398-404.
17. O'Sullivan J. Late hypertension in patients with repaired aortic coarctation. *Curr Hypertens Rep.* 2014;16(3):421.
18. Murakami T, Takeda A, Yamazawa H, Tateno S, Kawasoe Y, Niwa K. Aortic pressure wave reflection in patients after successful aortic arch repair in early infancy. *Hypertens Res.* 2013;36(7):603-7.
19. Menting ME, van Grootel RW, van den Bosch AE, Eindhoven JA, McGhie JS, Cuypers JA, et al. Quantitative assessment of systolic left ventricular function with speckle-tracking echocardiography in adult patients with repaired aortic coarctation. *Int J Cardiovasc Imaging.* 2016;32(5):777-87.
20. Oliver JM, Gallego P, Gonzalez AE, Sanchez-Recalde A, Bret M, Aroca A. Pulmonary hypertension in young adults with repaired coarctation of the aorta: an unrecognised factor associated with premature mortality and heart failure. *Int J Cardiol.* 2014;174(2):324-9.
21. Quintero-Rivera F, Xi QJ, Keppler-Noreuil KM, Lee JH, Higgins AW, Anchan RM, et al. MATR3 disruption in human and mouse associated with bicuspid aortic valve, aortic coarctation and patent ductus arteriosus. *Hum Mol Genet.* 2015;24(8):2375-89.
22. Abdulkareem N, Smelt J, Jahangiri M. Bicuspid aortic valve aortopathy: genetics, pathophysiology and medical therapy. *Interact Cardiovasc Thorac Surg.* 2013;17(3):554-9.

