



ORIGINAL ARTICLE

## Long-term follow-up after aortic coarctation repair: The unsolved issue of exercise-induced hypertension



Ana Sofia Correia<sup>a,b,\*</sup>, Alexandra Gonçalves<sup>a,b</sup>, Mariana Paiva<sup>a,b</sup>, Alexandra Sousa<sup>a,b</sup>,  
Sílvia Marta Oliveira<sup>a,b</sup>, Ana Lebreiro<sup>a,b</sup>, Cristina Cruz<sup>a,b</sup>, Maria Júlia Maciel<sup>a,b</sup>

<sup>a</sup> Serviço de Cardiologia, Centro Hospitalar de São João, Porto, Portugal

<sup>b</sup> Faculdade de Medicina, Universidade do Porto, Porto, Portugal

Received 10 January 2013; accepted 4 February 2013

Available online 14 November 2013

### KEYWORDS

Aortic coarctation;  
Exercise-induced  
hypertension;  
Follow-up

### Abstract

**Introduction:** Despite successful repair of aortic coarctation (AC), systemic hypertension (HTN) can persist in a significant percentage of patients. Exercise-induced HTN is also common in these patients, although its clinical significance is still unclear. In this study we aimed to assess the prevalence of exercise-induced HTN in adult patients with repaired AC.

**Methods:** We retrospectively reviewed the clinical records of patients aged >18 years with repaired AC followed at an adult congenital heart disease outpatient clinic in a tertiary care center. Demographic and clinical data including age at intervention, blood pressure (BP) at rest and on exercise, transthoracic echocardiogram (TTE) and treadmill exercise test results were evaluated. Exercise-induced HTN was defined as peak systolic BP  $\geq 210$  mmHg for men and  $\geq 190$  mmHg for women.

**Results:** We analyzed 65 patients (40 [61.5%] male; mean age at follow-up  $30 \pm 8$  years). Median age at AC repair was 7 years (P25-P75: 4-20) and mean follow-up was  $20 \pm 7$  years. Only one patient had diabetes and 10 (15.4%) had dyslipidemia. The majority of patients had controlled BP at rest and only nine (18%) were under antihypertensive medication. Forty-nine patients performed a treadmill exercise test. The mean duration of exercise was  $10.7 \pm 3.1$  minutes and mean peak heart rate was  $166 \pm 18$  beats per minute. Eleven (22%) patients had a hypertensive response, among whom only three (33%) had uncontrolled BP at rest. In our study treatment with angiotensin-converting enzyme inhibitors (ACEI) (OR 4.0 [95% CI 1.9–18.1]) and the peak instantaneous gradient in the descending aorta by TTE (OR 8.2 [95% CI 1.8–37.0]) were predictors of a hypertensive response with exercise. Age at surgery and type of AC repair were not associated with a hypertensive response on exercise.

**Conclusions:** In this study we found a significant prevalence of exercise-induced HTN in adult patients after successful AC repair despite adequate BP control at rest. Exercise-induced HTN was significantly related to higher peak gradient in the descending aorta and treatment with ACEI. These results highlight the complexity of the adult AC population and show that, even

\* Corresponding author.

E-mail address: [sofiakorreia@gmail.com](mailto:sofiakorreia@gmail.com) (A.S. Correia).

**PALAVRAS-CHAVE**

Coartação da aorta;  
Hipertensão arterial,  
Exercício;  
Follow-up

after a good surgical result, several patients remain at high cardiovascular risk and require long-term follow-up.

© 2013 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L. All rights reserved.

### **Follow-up a longo prazo de doentes com coartação da aorta corrigida: a eterna problemática da resposta hipertensiva ao exercício**

**Resumo**

**Introdução:** Apesar de a correção bem-sucedida da coartação da aorta, a hipertensão arterial pode persistir numa percentagem significativa de doentes. A resposta hipertensiva ao esforço é também um achado comum nestes doentes, embora com significado clínico ainda pouco esclarecido. No presente estudo pretendemos avaliar a prevalência de hipertensão induzida pelo exercício numa população adulta com coartação da aorta corrigida.

**Métodos:** Análise retrospectiva de dados demográficos e clínicos de adultos operados a coartação da aorta, seguidos numa consulta de cardiopatias congénitas do adulto num centro terciário. Foram avaliados os dados correspondentes às características clínicas à data da cirurgia, perfil tensional atual, gradiente máximo residual na aorta descendente por ecocardiograma transtorácico (ETT) e parâmetros da prova de esforço. A resposta hipertensiva foi definida para uma pressão sistólica máxima no exercício  $\geq 210$  mmHg nos homens e  $\geq 190$  mmHg nas mulheres.

**Resultados:** Avaliamos 65 doentes [40 (61,5%) do sexo masculino; idade média  $30 \pm 8$  anos]. A idade mediana à data da cirurgia foi 7 anos [percentil 25 - percentil 75 (P25-75): 4-20 anos). O tempo médio de seguimento foi  $20 \pm 7$  anos. Apenas um doente tinha diabetes *mellitus* e 10 (15,4%) tinham dislipidemia. A maioria dos doentes tinha a pressão arterial controlada em repouso e apenas 9 (18%) doentes ainda estavam sob titulação da terapêutica anti-hipertensiva. Quarenta e nove doentes foram submetidos a prova de esforço, sendo a duração média da prova de  $10,7 \pm 3,1$  minutos e a frequência cardíaca máxima de  $166 \pm 18$  batimentos por minuto. Onze (22%) doentes tiveram uma resposta hipertensiva com o exercício e apenas 3 (7,2%) destes mantinham difícil controlo da pressão arterial em repouso. A terapêutica concomitante com inibidores da enzima de conversão da angiotensina (i-ECA) [OR 4,0 (95% IC 1,9 - 18,1)] e um gradiente máximo na aorta descendente obtido por ETT [OR 8,2 (95% IC 1,8 - 37,0)] associaram-se a resposta hipertensiva ao esforço. A idade à data da cirurgia ou o tipo de cirurgia não se correlacionaram com a resposta hipertensiva ao exercício.

**Conclusões:** Neste estudo encontramos uma prevalência significativa de resposta hipertensiva ao exercício, após a correção bem-sucedida da CoAo, e apesar de um adequado controlo da pressão arterial em repouso. A resposta hipertensiva ao exercício esteve significativamente associada a um maior gradiente máximo na aorta descendente obtido por ETT, bem como ao uso de i-ECA como antihipertensores. Estes resultados realçam a complexidade da população adulta com CoAo e o facto de que muitos doentes permanecem sob importante risco cardiovascular, apesar de uma prévia correção da CoAo bem-sucedida.

© 2013 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L. Todos os direitos reservados.

**Introduction**

Aortic coarctation (AC) was first described by Morgagni in 1760 and was characterized clinically in the early 20th century.<sup>1,2</sup> It is a common malformation, found in 5–8% of children with congenital heart defects.<sup>3,4</sup> It consists of a severe narrowing of the proximal descending aorta, creating a significant gradient in the descending aorta. If left untreated it is associated with poor prognosis and high mortality.<sup>5</sup> Development of surgical techniques and more recently percutaneous aortic angioplasty with stent implantation has significantly improved the prognosis of these patients.<sup>6–8</sup> However, AC cannot be considered a simple and easily corrected lesion. Even after successful repair, 20–40% of patients continue to have hypertension (HTN) at 10–20

years of follow-up and 20–35% have an abnormal blood pressure (BP) response to exercise despite being normotensive at rest.<sup>9–12</sup> The pathophysiology of this abnormal BP behavior is unclear and different mechanisms have been proposed. Exercise-induced HTN has been attributed to abnormalities in aortic arch geometry, primary baroreceptor alterations and persistent structural and functional abnormalities of the vascular wall of the aorta and large arteries proximal to the former coarctation site.<sup>9</sup> Moreover, life expectancy, although better than in untreated patients, is still less than in healthy subjects.<sup>13</sup>

There is ongoing controversy regarding the significance of abnormal exercise BP after AC repair.<sup>14</sup> In this study we aimed to assess the prevalence of exercise-induced HTN in adult patients with repaired AC.

## Methods

### Population

We analyzed the demographic and clinical data of consecutive patients aged >18 years with repaired AC attending the adult congenital heart disease outpatient clinic at our tertiary care center. The surgical data included age and type of intervention. Resting BP, residual aortic coarctation by transthoracic echocardiography (TTE) and treadmill exercise test results were also evaluated. Exercise testing was performed according to the Bruce protocol and mean duration of exercise stress testing, mean peak heart rate and mean peak systolic BP were evaluated. BP was measured at rest and at 3-min intervals by manual measurement with conventional sphygmomanometry. Patients with a peak exercise systolic BP  $\geq 210$  mmHg for men and  $\geq 190$  mmHg for women were considered to have exercise-induced HTN.<sup>15</sup> All TTE studies were reviewed and left ventricular (LV) systolic function, LV mass and instantaneous peak gradient in the descending aorta were assessed according to the current guidelines. Mean follow-up was  $20 \pm 7$  years.

This retrospective observational study complies with the recommendations of our hospital's Ethics Committee.

### Statistical analysis

The statistical analysis was performed using the SPSS statistical software package for Windows, version 19.0. Continuous variables are summarized as mean  $\pm$  standard deviation (SD) or median (interquartile range), as appropriate. Categorical variables are presented as numbers and proportions (%). The chi-square or Fisher's exact test, as appropriate, were used to assess the effects of nominal variables on exercise-induced HTN. Additionally, the Student's t test or the Mann-Whitney U test, as appropriate, were used to evaluate the influence of quantitative variables on exercise-induced HTN. A p value  $< 0.05$  was considered statistically significant.

Predictors of exercise-induced HTN were identified using binomial logistic regression, and significant predictors were analyzed in a multivariate model to adjust for potential confounders.

### Results

We included 65 patients, 40 (61.5%) male, mean age  $30 \pm 8$  years (19–57). Ten (15.4%) had dyslipidemia and only one (1.5%) was diabetic. Fifty-eight (89%) patients were under antihypertensive therapy (54 [83.1%] with beta-blockers and 15 [23.1%] with angiotensin-converting enzyme inhibitors [ACEI]). Eleven (17%) patients were treated with more than one antihypertensive drug. The majority of patients had controlled BP at rest and only nine (18%) were still under antihypertensive medication. Mean systolic BP at rest was  $128 \pm 14$  mmHg and mean diastolic BP at rest was  $73 \pm 9$  mmHg.

An additional congenital heart defect was identified in 27 (42%) patients: bicuspid aortic valve (n=18), ventricular septal defect (n=4), patent ductus arteriosus (n=3), mitral valve

prolapse (n=1) and ostium secundum atrial septal defect (n=1).

Twenty-four (37%) patients had undergone AC repair within the first year of life and 40 (62%) later on (29 [45%] between one and 17 years old and 11 [17%] at 18 years or older). Mean follow-up was  $20 \pm 7$  years.

The majority of patients (32%) had undergone subclavian flap aortoplasty, 28% prosthetic patch aortoplasty and 19% had an end-to-end aortic anastomosis. Only 6% of patients had undergone balloon angioplasty. In 10 (15%) cases the type of surgery was not available.

Among these patients, eight (12.3%) were reoperated during the study follow-up and all patients were in New York Heart Association functional class I.

According to the TTE evaluation at follow-up 64 (98.5%) patients had preserved LV systolic function. LV hypertrophy was identified in five (7.7%) patients and mean peak instantaneous gradient in the descending aorta was  $23.1 \pm 12.2$  mmHg.

The results of the symptom-limited treadmill exercise test, according to the Bruce protocol, were available in 49 (75%) patients (33 [67%] male). The mean duration of exercise stress testing was  $10.7 \pm 3.1$  minutes and the mean peak heart rate achieved at peak workload was  $166 \pm 18$  beats per minute. Mean peak systolic BP was  $181 \pm 37$  mmHg. Eleven (22%) patients had a hypertensive response to the exercise stress test. Of these, only three (33%) had uncontrolled BP at rest. There were no differences between the groups (exercise-induced HTN patients versus non-exercise-induced HTN patients) in gender, age at surgery, time since surgery or prevalence of uncontrolled BP at rest. There were also no differences in the presence of LV hypertrophy on TTE, exercise duration, peak heart rate at exercise, current treatment with beta-blockers or need for reoperation. However, current treatment with ACEI (OR 4.0 [95% CI 1.9–18.1]) and a higher peak instantaneous gradient in the descending aorta on TTE (OR 8.2 [95% CI 1.8–37.0]) were associated with exercise-induced HTN in our study population (Table 1).

### Discussion

Our results show that in long-term follow-up, HTN at rest and exercise-induced HTN are prevalent in a significant percentage of adult patients even after successful AC repair, which is in agreement with previous studies.<sup>9–12</sup> "Repair" may not be synonymous with "cure" in the case of cardiovascular abnormalities. Systemic HTN can occur late after AC repair and may be due to residual or recurrent coarctation, but even patients with a successful repair may develop systemic HTN due to anatomical and functional changes in the arterial wall.<sup>9</sup> Moreover, physiological abnormalities of large and small arteries in the pre-coarctation vascular bed may be an important contributor to exercise-related HTN and late morbidity or mortality.<sup>16</sup>

An abnormally high systolic BP on exercise was found in patients with adequate BP control at rest and in those under antihypertensive therapy with ACEI. The prognostic significance of exercise-induced HTN in patients with AC is still unknown, but there is ongoing interest in its potential predictive value for late systemic HTN. In this context, the exercise-induced HTN observed in these patients could

**Table 1** Exercise test response according to patient characteristics.

Variable	Hypertensive (n=11; 24%)	Non-hypertensive (n=34; 76%)	p
Gender (male; female), n (%)	8 (72.7%); 3 (27.3%)	21 (61.8%); 13 (38.2%)	0.766
Age at surgery (surgery after first year of life)	20 (73%)	8 (60%)	0.719
Age at surgery (years; mean $\pm$ SD)	6.2 $\pm$ 6.9	6.9 $\pm$ 8.2	0.812
Time since surgery (years; mean $\pm$ SD)	18.1 $\pm$ 6.3	20.2 $\pm$ 5.2	0.279
Uncontrolled blood pressure at rest, n (%)	3 (33%)	5 (15%)	0.336
Beta-blocker, n (%)	8 (72.2%)	32 (94.1%)	0.085
ACEI, n (%)	6 (54.5%)	4 (11.8%)	0.007
LV hypertrophy (by echo), n (%)	1 (9.1%)	1 (2.9%)	0.433
Peak gradient (mmHg; mean $\pm$ SD)	31.8 $\pm$ 12.4	23.1 $\pm$ 11.9	0.043
Exercise duration (minutes; mean $\pm$ SD)	10.83 $\pm$ 4.07	10.54 $\pm$ 2.91	0.800
Peak HR at exercise (bpm; mean $\pm$ SD)	166 $\pm$ 15	166 $\pm$ 19	0.963
Reoperation	1 (9.1%)	3 (8.8%)	1.000

ACEI: angiotensin-converting enzyme inhibitor; bpm: beats per minute; echo: echocardiography; HR: heart rate; LV: left ventricular; SD: standard deviation.

hypothetically identify higher-risk patients who could benefit from a different target for BP control.

Several other studies have demonstrated an exaggerated exercise systolic BP response in patients with repaired AC and questions have been raised over its relation to outcome and target organ damage. Some studies have shown that peak exercise systolic BP in patients with AC is strongly associated with mean daytime systolic BP on ambulatory monitoring.<sup>17</sup> A more recent prospective study showed that peak exercise systolic BP was a predictor of chronic HTN in patients with AC.<sup>18</sup> Furthermore, exercise-induced HTN is associated with increased intima-media thickness of the common carotid artery, which is a validated and reproducible surrogate endpoint for atherosclerosis.<sup>19,20</sup> Several investigators have suggested that patients with exercise-induced HTN might be amenable to antihypertensive therapy or limitation of strenuous physical activity.<sup>21</sup> In fact, exercise-induced HTN might become a therapeutic target if an unequivocal link with adverse outcome is demonstrated in this population.

In this study patients under beta-blocker therapy more frequently had a normal BP response to exercise, suggesting that these patients could be under more effective BP control. Moltzer et al. showed that in adult hypertensive patients after AC repair, metoprolol had a greater antihypertensive effect than candesartan. In their study the neurohormonal outcome did not support a significant role for the renin-angiotensin system in the causative mechanism of HTN after AC repair.<sup>22</sup> These findings may explain the association of ACEI and the exercise-induced HTN found in our study population. However, additional studies are needed to define the optimal antihypertensive treatment in patients after AC repair.

In contrast to other published studies,<sup>12,23</sup> we found no correlation between age at surgery and exercise-induced HTN. In our study the mean age at surgery was similar in both groups, with and without exercise-induced HTN, and exercise-induced HTN was not more prevalent in patients operated after the first year of life. However, the small sample size may explain this finding.

Similar to previous reports,<sup>17,24</sup> we found no significant relationship between LV hypertrophy and exercise BP variables.

By contrast, the correlation between exercise-induced HTN and a higher peak instantaneous gradient in the descending aorta by TTE was significant in our cohort. Exercise testing may be an efficient method for follow-up monitoring of these patients, identifying patients in need of further investigation, and for medical therapy optimization. In our population, patients with higher descending aorta gradients underwent additional investigation with cardiac magnetic resonance or cardiac catheterization. Those with confirmed recoarctation underwent surgical or interventional treatment. However, we found no significant correlation between reoperation and exercise-induced HTN. The small number of reinterventions in this population may explain this finding.

These results highlight the complexity of the adult AC population and the fact that, even with a good result after repair, several patients remain at high cardiovascular risk in the long term. Recent findings showing the predictive value of peak exercise systolic BP for the development of chronic HTN in these patients<sup>18</sup> focus attention on this parameter. Further studies will be needed to clarify the long-term consequences of exercise-induced HTN and the potential role of early antihypertensive treatment in this population.

## Conclusions

A considerable proportion of repaired AC adult patients have exercise-induced HTN. In our population, patients with a higher TTE peak instantaneous gradient in the descending aorta and patients under antihypertensive therapy with ACEI are at greater risk of exercise-induced HTN. Treadmill exercise testing can detect an abnormal BP response with exercise early during follow-up after AC repair and can be an efficient method of identifying patients at high cardiovascular risk, providing a screening tool for further investigation or therapy optimization.

The clinical significance of exercise-induced HTN in patients late after AC repair is still a matter of debate. Further research is required in order to clearly define its additional cardiovascular risk and the potential protective role of antihypertensive treatment in these patients.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## References

- Morgagni JB. De Sedibus et Causis Morborum. Epist. 18, Article 6; 1760.
- Bonnet LM. Sur la lésion dite stenose congénitale de l'aorte dans la région de l'isthme. Rev Med (Paris). 1903;23:108.
- Hoffman JIE, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890–900.
- Towbin JA, Belmont J. Molecular determinants of left and right outflow tract obstruction. Am J Med Genet. 2000;97:297–303.
- Campbell M. Natural history of coarctation of the aorta. Br Heart J. 1970;32:633–40.
- Schuster SE, Gross RE. Surgery for coarctation of the aorta: a review of 500 cases. J Thorac Cardiovasc Surg. 1962;43:54–70.
- Vitullo DA, DeLeon SY, Graham LC, et al. Extended end-to-end repair and enlargement of the entire arch in complex coarctation. Ann Thorac Surg. 1999;67:528–31.
- Holzer R, Qureshi S, Ghasemi A, et al. Stenting of aortic coarctation: acute, intermediate, and long-term results of a prospective multi-institutional registry—Congenital Cardiovascular Interventional Study Consortium (CCISC). Catheter Cardiovasc Interv. 2010;76:553–63.
- Vriend JWJ, Mulde BJM. Late complications in patients after repair of aortic coarctation: implications for management. Int J Cardiol. 2005;101:399–406.
- Pelech AN, Kartodihardjo W, Balfe JA, et al. Exercise in children before and after coarctectomy: hemodynamic, echocardiographic, and biochemical assessment. Am Heart J. 1986;112:1263–70.
- Markel H, Rocchini AP, Beekman RH, et al. Exercise-induced hypertension after repair of coarctation of the aorta: arm versus leg exercise. J Am Coll Cardiol. 1986;8:165–71.
- Sigurdardottir LY, Helgason H. Exercise-induced hypertension after corrective surgery for coarctation of the aorta. Pediatr Cardiol. 1996;17:301–7.
- Cohen M, Fuster V, Steele PM, et al. Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction. Circulation. 1989;80:840–5.
- Swan L, Goyal S, Hsia C, Hechter S, Webb G, Catzoulis MA. Exercise systolic blood pressures are of questionable value in the assessment of the adult with a previous coarctation repair. Heart. 2003;89:189–92.
- Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass? The Framingham Heart study. Ann Int Med. 1992;116:203–10.
- Gardiner HM, Celermajer DS, Sorensen KE, et al. Arterial reactivity is significantly impaired in normotensive young adults after successful repair of aortic coarctation in childhood. Circulation. 1994;89:1745–50.
- Vriend JW, Van Montfrans GA, Romkes HH, et al. Relation between exercise-induced hypertension and sustained hypertension in adult patients after successful repair of aortic coarctation. J Hypertens. 2004;22:501–9.
- Luijendijk P, Bouma BJ, Vriend JWJ, et al. Usefulness of exercise-induced hypertension as predictor of chronic hypertension in adults after operative therapy for aortic isthmus coarctation in childhood. Am J Cardiol. 2011;108:435–9.
- Vriend JW, de Groot E, Bouma BJ, et al. Carotid intima-media thickness in post-coarctectomy patients with exercise induced hypertension. Heart. 2005;91:962–3.
- Vriend JW, de Groot E, de Waal TT, et al. Increased carotid and femoral intima-media thickness in patients after repair of aortic coarctation: influence of early repair. Am Heart J. 2006;151:242–7.
- Kavey RE, Cotton JL, Blackman MS. Atenolol therapy for exercise-induced hypertension after aortic coarctation repair. Am J Cardiol. 1990;66:1233–6.
- Moltzer E, Mattace Raso FUS, Karamermer Y, et al. Comparison of candesartan versus metoprolol for treatment of systemic hypertension after repaired aortic coarctation. Am J Cardiol. 2010;105:217–22.
- Daniels SR. Repair of coarctation of the aorta and hypertension: does age matter? Lancet. 2001;358:89.
- Tantengco MV, Ross RD, Humes RA, et al. Enhanced resting left ventricular filling in patients with successful coarctation repair and exercise-induced hypertension. Am Heart J. 1997;134:1082–8.