_____

*Review Article*
## Late Coarctation Presenters Suffer Chronic Hypertension Resisting to Medicine Treatment

Andreas C Petropoulos1-4*, Maria Moschovi2, Aynur Xudiyeva3,4, Fexreddin Qarayev3 and Ibrahim Isayev1

1 Department of Pediatrics, Azerbaijan Medical University, Educational and Therapeutically Hospital, Greece
2 Department of Pediatrics/University of Athens, Hematology- Oncology Unit/1st, Greece
3 Merkezi Klinika Hospital, Azerbaijan
4 Azerbaijan State Postgraduate Education Institute of Ministry of Health, Baku, Azerbaijan

## Abstract
Coarctation of the aorta (CoA) is a common Congenital Heart Disease (CHD) presenting with many symptoms and signs, in any age group. From its dramatic appearance as a part of Hypo plastic Left Heart Syndrome (HLHS), to early Congestive Heart Failure(CHF)in neonatal and early infantile age, to undetected Hypertension (HTN) in early or even late adulthood. The aim of this short review is to present this unique CHD, underline the presentation of late detected CoA, presenting with HTN and its impact in treating resistant HTN even after successful surgical treatment. Finally, the late onset HTN, following successful surgical treatment and its medicine management will be addressed. This difficult to control on mono or dual pharmacotherapy and the late complications of persistent uncontrolled HTN is the basic reason that these patients are a long-life follow-up population with important medical needs and increasing morbidity and mortality.

### Abriviations
CoA; Coarctation of the Aorta; re-CoA: Recoarctation; CHD: Congenital Heart Disease; HLHS: Hypoplastic Left Heart Syndrome; CHF: Congestive Heart Failure; HTN: Hypertension; DA: Ductus Arteriosus; IAA: Interrupted Aortic Arch; BP: Blood Pressure; BAov: Aortic Bicuspid valve; LVOT: Left Ventricular Outflow Tract; ECG: Electrocardiography; Echo-2D: Transthoracic Echocardiography-2D; LVPO or VO: Left Ventricular Pressure Overload or Volume Overload; VSD: Ventricular Septal defect; (c-MRI: cardiac Magnetic Resonance Imaging; cv-CT: cardiovascular Computer Tomography; CAD: coronary artery disease; BA: Balloon Angioplasty; LVH: Left Ventricular Hypertrophy; LV: Left Ventricular; b-Blockers: beta-blockers; ACE-I : ACE inhibitors; ARBs: Angiotensin Receptor Blockers

## Introduction
Coarctation of the aorta (CoA) is a common congenital heart defect (CHD) found in approximately1 per 2500 live births [1] and is the fifth most common type of CHD, with a favorable prevalent in males. This frequency underestimates delayed diagnosis, even in the pediatric population [2]. CoA is characterized by discrete narrowing of the thoracic aorta adjacent to the Ductus Arteriosus (DA). Importantly, CoA is an aortopathy, that lies clinical, within a spectrum of arch abnormalities ranging from a discrete narrowing to a long segment of arch hypoplasia and advancing towards the extreme form of Interrupted Aortic Arch (IAA) although these two entities, is believed today to have different mechanisms. Early histologic changes and presentation of intracranial aneurysms [4]. suggests that wall abnormalities are not confined to the aorta. The prognosis of untreated CoA was extremely poor during the presurgical era with median survival age of 31 years and a quarter of patients dying before the age of 20 years [5]. Since the first surgical repair performed in the 1940s, treatment of CoA has dramatically changed. In infancy treatment of

choice is surgical repair with excellent short-to-late term outcomes [6]. In older patients, trans- catheter management with endovascular stenting is preferable to surgery in many institutions, and provides relief of pressure gradients across the coarctation site [7]. However in both circumstances patients have significant longer term risk for the development of hypertension (HTN) [8]. HTN is associated with significant morbidity and early mortality and although early treatment appears to delay the onset of HTN [8]. Remarkably one third of CoA patients still become HTN by adolescence despite early and effective surgical repair [9]. Data beyond adolescence show increasing prevalence with age, and by 50–72 years 90% of patients, have documented HTN [10]. This suggests that hypertension may be an inevitable consequence of CoA, even when an effective anatomical repair has been achieved early in life. Although it is unclear why this may be the case, it is postulated that there is dysfunction of a variety of the normal control mechanisms regulating blood pressure (BP) during growth and development in patients with repaired CoA. Identifying and preventing such maladaptive processes in CoA presents a challenge that if successful, will provide more effective treatment in the future [8]. For this, these patients continue to require lifelong follow-up for management of associated problems including HTN, atherosclerotic disease, re-CoA, and aneurysm formationscomplex [3,5,8]. We review the current literature to question whether developmental consequences of CoA condemn individuals to lifelong HTN, and evaluate the efficacy of the current treatment strategies.

## Pathogenesis of CoA

Studies have suggested that abnormalities of blood flow in early infancy, defective endothelial cell migration, and excessive deposition of aortic duct tissue at the aortic isthmus can result in CoA [5]. Histologic examination of localized CoA lesions has demonstrated the presence of a tissue ridge extending from the posterior aortic wall and protruding into aortic lumen. This ridge consists of DA tissue with in-folding of the aortic media [3]. In older patients, aortic intimal proliferation also contributes to the narrowing at the site of CoA. The cause of discrete CoA remains unclear, but it seems to be multifactorial. Prenatal environmental exposures have been associated with CoA and other left-sided lesions [3]. However, there is a growing body of literature that suggests a genetic basis for development of these lesions. Familial cases of CoA, have been reported. Also, genetic investigation in families with children suffering from hypoplastic left heart syndrome (HLHS), Bicuspid Aortic valve (BAov), Left Ventricular Outflow Tract (LVOT) abnormalities with aortic valve stenosis and CoA, suggest a strong genetic influence, with an estimated recurrence risk in a future pregnancy of greater than 30-fold [11]. Mutations in the NOTCH1 gene have been identified in individuals with LVOT malformations, including CoA [12]. Furthermore, embryonic studies in zebrafish have highlighted the importance of intracardiac hemodynamics in epigenetic control of distal chamber development [5].

## Associated cardiac & extracardiac lesions

CoA can be an isolated CHD. It is also, commonly found in other congenital syndromes and CHD. The most common malformation associated with CoA is BAov. Autopsy examinations showed 54%-85% of patients with CoA have a BAov [13]. The coexistence of BAov and CoA is important to consider, because it places the patient at a higher risk of aortic complications. In a study following 341 patients with BAov over a median of 7 years, patients with BAov in the presence of CoA had 7.5 times increased risk of ascending aortic complications, most commonly dilation of the ascending aorta [13]. The same group also found that among patients with CoA, the presence of a BAov was an independent risk factor for the development of aortic wall complications [5]. CoA can be found also in some common genetic syndromes. Specifically, CoA is found in 18% of patients with Turner syndrome [5]. Williams's syndrome, a congenital and multisystem genetic disorder, has been associated with supra-valvular aortic stenosis. Aortic arch abnormalities, including CoA, are present in 10% of patients

with William's syndrome [14]. Finally, CoA can also be present in congenital cardiovascular anomalies involving multiple left-sided lesions, including Shone's complex and HLHS [5].

Regarding the extracardiac lesions: the link between intracranial aneurysms and CoA was described well before the surgical era, accounting for 5% deaths in patients with CoA on autopsy review [5]. Today's MRI scans report a prevalence of intracranial aneurysms in patients with CoA approximately of 10% [15]. Which is five times more common than the average population. In one study, HTN was more common in the population of CoA patients with intracranial aneurysms [15]. Most of the aneurysms described are small, and have a low risk of rupture. Currently the benefits of routine screening for intracranial aneurysms in CoA remain unclear [5].

## Clinical presentation – diagnosis

The clinical presentation of CoA differs significantly by age. Infants with severe forms may present with signs and symptoms of CHF and cardiogenic shock as the DA closes, most adults with unrepaired CoA are generally asymptomatic. A common presentation of CoA is systemic arterial HTN. In young adults presenting with severe upper extremity HTN, CoA should be excluded. Older or late presenting patients with severe HTN may experience symptoms including angina, headache, epistaxis, and CHF. In physical examination, femoral arterial pulses are the gold standard finding. They are diminished or delayed. Rarely, claudication may be reported because of lower extremity ischemia. Auscultation of the left sternal border may demonstrate a harsh systolic murmur with radiation to the back. An associated thrill may be palpable in the suprasternal notch. The finding of a continuous murmur may suggest the presence of arterial collaterals in those with long-standing unrepaired disease.

When suspecting CoA, evaluation should involve measurement of BP in all four extremities. The upper extremity systolic BP is usually 20 mm Hg higher than the lower extremities in patients with significant CoA. In rare instances of CoA patients with concomitant anomalous subclavian artery origin distal to the site of CoA, systolic BP differences may not be detected between ipsilateral arm and legs [16].

A variety of diagnostic methods can be added to the medical history and clinical examination to prove the existence of CoA and quantify its severity. The less invasive, cheap and easy to provide in all levels of care, Electrocardiography (ECG) can demonstrate in late onset patients unexplained evidence of left ventricular hypertrophy (LVH), from chronic left ventricular pressure overload(LVPO). The chest x-ray, can show a "figure of three" sign formed by the aortic nob, the stenotic segment, and the dilated post-stenotic segment of the aorta suggesting CoA. The heart silhouette can be normal or mildly enlarged. Inferior rib notching can also be seen in the third to eighth ribs bilaterally caused by the presence of dilated intercostal collateral arteries [5]. Transthoracic Echocardiography-2D (Echo-2D) has become the most accessible for the practicing physician. A comprehensive Echo-2D is recommended in the initial evaluation of a patient with repaired or suspected CoA. The diagnosis of the CoA itself, must address the amount of LVPO or VO, LVH, size, and LV systolic and diastolic dysfunction. Attention is needed in identifying associated cardiac defects especially left-sided lesions and/or VSD's. The morphology of the aortic valve: BAov or normal, as well as evidence of any level of LVOT should be clarified. In late presenters, the dimensions of the aortic root and ascending aorta can be followed serially to assess for associated aortopathy. Visualization of the aortic arch, may demonstrate a focal area of narrowing of the thoracic aorta adjacent to the left subclavian artery with associated flow turbulence on color flow Doppler interrogation shows increased velocity across the site of CoA. By using the modified Bernoulli equation calculation of the peak instantaneous and mean gradient across the CoA, is feasible. In the absence of another or multiple left-sided lesions (e.g. stenotic BAov, LVOT) leading to an increased velocity before the CoA site, the expanded Bernoulli equation should be used to avoid wrong estimation of the peak gradient. In late presenters, significant collaterals may have developed thereby reducing the peak systolic

gradient. With continuous-wave Doppler, a saw-tooth continues paten, reflects the forward flow in diastole because of diastolic run-off. A pressure gradient that persists into diastole is an indicator of severe stenosis. Higher gradient across the CoA and longer duration of diastolic forward flow in the thoracic aorta suggest more significant disease. The Doppler examination of the abdominal aorta providing useful information in the presence of significant, late presenting CoA. In these cases, Doppler demonstrates a continuous antegrade flow signal without evidence of flow reversal [17].

Cardiac catheterization was the golden standard for diagnosis of CoA before the era of new imaging techniques as cardiac Magnetic Resonance Imaging (c-MRI) and cardiovascular Computer Tomography (cv-CT). Today it remains essential in the interventional treatment management of patients with CoA. In older patients with potential concomitant coronary artery disease (CAD) who require operative intervention for CoA or aneurysm, coronary angiography should be performed before surgery and patient can benefit from both [5]. CMRI has become a valuable noninvasive modality to assess patients with mostly unrepaired and surgical repaired CoA. In late presenters with suboptimal Echo-2D views, c MRI can be used to characterize all the anatomical aspects previously discussed.

Along with gadolinium-enhanced MRI angiography and 3D reconstruction images, provides excellent resolution of cardiac anatomy and vascular structures. Using phase contrast flow analysis estimates the peak gradient of CoA [18]. Today, all measurements of diameters in vessels and gradients across the CoA area, as well as any additional stenosis in the cardiovascular system, calculated by c MRI, correlates with cardiac catheterizations findings [5]. These data can estimate future need for intervention. MRI angiography provides assessment of post-stenotic dilation or aneurysmal formation at the site of a previous repair. This estimation is better in surgical repairs as interventional repair with placement of stents carry the burden of artifacts. Most important, the lack of ionizing radiation provides an advantage of c MRI over cv CT, in

the serial evaluation of late complications after repair. The use of CV CT must be considered in selected patients, as those who carry pacemakers or implantable cardioverter defibrillators that are not c MRI compatible may benefit from surveillance with cardiovascular CT [19]. Other advantages of cv CT include, improved image resolution, shorter scan time, and greater availability across different institutions. CT angiography is also used to assess concomitant coronary anomalies that may not be so well visualized with c MRI. Considerable variations in measurements between the two techniques have been reported in the same patient, highlighting the importance of using one specific modality in serial assessment [20]. The users of cv CT assessing repaired CoA, adhering to radiation safety principles, must minimize radiation dose, as a regulatory requirement for all programs [5]. Recognizing the benefits of c MRI and cv CT the 2008 American College of Cardiology/American Heart Association Guidelines for the Management of Adults with Congenital Heart Disease recommend that patients with CoA have serial evaluation with CT or MRI at least every5 years [5].

**Therapeutically strategies**

Today, in all age group patients both interventional and surgical options of treatment are offered [5,21]. In patients with a native CoA or re-CoA, a measured peak-to-peak gradient greater or equal to 20 mm Hg by catheterization is an indication for treatment, either by Balloon Angioplasty (BA) or surgical approach. Patients with longstanding native CoA with significant collateral flow, have a lower measured gradient despite severe CoA. Therefore, patients with extensive collaterals should undergo intervention even in lower gradients. With many different options, deciding on the optimal treatment strategy for CoA can be complicated, as there is no comprehensive evidence-based standard of care or algorithm [21]. The 2008, Guidelines from the American College of Cardiology and the American Heart Association provide some insight, but the level of evidence supporting these recommendations is suboptimal [22]. In principle, management is based on the age of presentation, complexity of the anatomy, and whether the CoA represents a native vs recurrent

obstruction. For infants or young children presenting with native CoA, most centers prefer surgical repair due to the long-term risk of aneurysm following BA, the need for re-dilatation with stent placement in near future, and the limitations imposed by small arteries unable to accommodate larger sheath sizes [23]. However, BA can be considered as a palliative strategy in stabilizing critical ill neonates considered too sick for immediate surgical repair [24]. Surgical repair may also be more appropriate in patients with complex CoA anatomy, including those with transverse arch obstruction, tortuous segments of re-CoA, distortion of adjacent arterial branches, or when repair of associated cardiac defects is required [22]. In the older child ( with a body weight over 25 Kg), adolescent, or adult presenting with a simple, juxtaductal, native CoA, stent placement is considered a reasonable approach, offering a less invasive alternative to surgical intervention and good long-term outcomes [21]. Only stents expandable to an adult size should be used, to avoid later surgical intervention [24]. For recurrent CoA in the younger child, it is reasonable to consider initial BA, as aneurysm is less of a long-term concern than with native CoA [24]. BA is variably successful, and surgical reintervention may be required when there is incomplete relief of obstruction [21]. Stent placement can also be considered for recoarctation in older children and adolescents when the stent can be dilated to near adult size, avoiding the need for multiple redilations [24].

## Complications

May occur after all forms of treatment. The most important complications are: re-CoA, aneurysms of the ascending aorta or at the site of intervention, and arterial HTN. Further sequelae may develop due to CAD, BAov, and Mitral valve anomalies, infective endocarditis or cerebral aneurysms [25]. Cohen et al. report in their largest single-center study of postsurgical CoA repair, from patients of the Mayo Clinic survivorship was 84% at 20 years and 72% at 30 year's follow-ups. They conclude that four main points emerged in these patients: 1) age at the time of initial repair is the most important predictor of long-

term survival. Surgery should be offered to patients after age 1 year or sooner if hypertension is severe. 2) CAD is the most common cause of late death. 3) Age at the time of initial repair is the most important predictor of HTN. 4) Associated cardiovascular anomalies requiring subsequent surgery are common. Therefore, all patients need continuous lifelong follow-up after repair of CoA [26].

The rate of recoarctation after surgical repair ranges between 3% and 15% in most studies and this is higher BA ranging from 7 to 20% [5,21]. Aneurysms of the ascending aorta or at the site of intervention has been reported to be between 3% and 46% [5]. Patients repaired with synthetic patch technique are at higher risk of late-term aneurysm development Patients with large aneurysm after CoA repair often require surgical management with use of an interposition graft. However, there have been several small case series of successful treatment of aneurysm using bare-metal and covered endovascular stents (27). Long-term studies are needed to determine the safety and durability of interventional repairs. Currently, COAST II -a randomized control study, initiatedin 2010- that aims to evaluate the efficacy and safety of covered endovascular stents for treatment of CoA with associated aortic wall injury, including aortic aneurysm and pseudo- aneurysm [27].

We will emphasize on HTN, as it is the most common lifelong complication, regardless of a successful surgical or interventional treatment strategy that exterminates any pressure gradient across the CoA. Furthermore, HTN is present from the early stages of the disease and is a common pathophysiological mechanism for CHF, accelerating atherosclerosis and as consequence CAD and finally provokes morbidity and mortality [5,21,26,28].

## Coarctation of the aorta and hypertension

Patients with CoA present early in life with CHF or later in life with HTN, followed from other complications such as rupture of cerebral aneurysms. Berry aneurysms of the circle of Willis or other vessels are believed to occur in as many as 10% of patients with CoA and HTN and may be multiple. Aneurysm size tends to increase with age, as does the risk of rupture.

**EURASIAN JOURNAL OF CLINICAL SCIENCES**

Uncontrolled HTN promotes the growth of the aneurysms and increases risk of rupture. Most patients are asymptomatic until rupture occurs, although some aneurysms may leak prior to rupture, resulting in warning symptoms of headache, photophobia, weakness and neurological signs. Rupture of a cerebral aneurysm is associated with high mortality rates and should prompt repair of both the aneurysm and CoA [28]. Studies continue to document that CoA is often missed in the first years of life, and the median age of referral to a pediatric cardiologist in one study was 5 years [29]. Even when HTN is diagnosed in a pediatric outpatient setting it is mostly suggested to be secondary to overweight, obesity or thought be essential HTN, more often. General pediatricians must increase their vigilance towards the diagnosis or the rule out of CoA in every case of newly diagnosed HTN [30]. Although early-to-mid-term outcomes of patients with CoA are excellent, with early mortality rates as low as 2%. However, significant longer term morbidity remains, particularly with respect to premature and persistent HTN. Early surgery may prevent or delay the onset of HTN. Approximately 30% of patients will be HTN by adolescence despite early surgery and more recent reports observe that about 60% of adults after correction of CoA in childhood are HTN [10,32]. These patients, as mentioned above are at risk of premature CAD, LV systolic as well as diastolic dysfunction, and rupture of aortic or cerebral aneurysms. Most studies report resting BP, but it is well established that a significant number of CoA repair patients with normal resting BP have an HTN response to exercise. to mechanisms responsible for longer term blood pressure control [8]. However, this theory does not explain the following:
i) lack of relationship between the degree of elevation of BP and the magnitude of obstruction, ii) the increased peripheral vascular resistance distal to the site of obstruction, iii) the delayed or lack of reduction of BP immediately following relief of obstruction. Early studies examining the impact of the renin-angiotensin system on HTN in CoA, concentrated on plasma renin levels with ambiguous results, mostly

The mechanism for development of HTN is not clearly understood. In a pathophysiological approach of understanding HTN in the setting of CoA, we must be aware that the initial point, is that the obstruction in any area of the ascending to descending aorta will impose significant afterload on the LV, which results in increased wall stress and compensatory LVH [28]. This becomes critical as the DA constricts and the LV afterload rapidly increases, with a resultant increase in LV pressures (systolic and diastolic). This causes elevation of the left atrial pressure, which may open the foramen ovale, causing left-to-right shunt and dilatation of the right atrium and right ventricle. If the foramen ovale does not open, pulmonary venous pressures and pulmonary artery pressures increase, and right ventricular dilatation develops. Because of that we have not only systematic HTN present, but also, secondary Pulmonary HTN because of the Left Heart obstruction. Cardiomegaly and LVH are related to the indirect effects of rapid development of severe obstruction. In milder cases of CoA, LV afterload may also gradually increase, allowing children to develop arterial collateral vessels that partially bypass the CoA. These children may be asymptomatic until HTN is detected or another complication develops [28]. Mechanical obstruction, renin-angiotensin–mediated humoral and endothelial dysfunction mechanisms, have been suggested. Regarding the mechanical obstruction mechanism, previously reported data have suggested increased aortic stiffness and alteration in autonomic cardiac balance in pre-operative neonates with CoA, suggesting an early maladaptive response

demonstrating no significant increases in these levels in CoA patients [8]. Subsequent studies have evaluated renin levels following alterations to resting homeostasis, such as fluid depletion or exercise [32]. Although Parker et al [32]. Demonstrated increased pre-operative plasma renin levels following significant volume depletion, the subjects studied were older children (5–16years) and the values were normalized post-operatively including in those who remained HTN, thereby making a causal link for sustained long-term hypertension unlikely. Currently most centers repair CoA in

neonatal life, and thus a prolonged period of renal hypo-perfusion is not normal with transductal flow ensuring adequate renal perfusion before birth. In patients with late presentation of CoA, there is often significant collateral circulation ensuring that renal perfusion is not significantly affected. However, HTN remains common suggesting that persistently elevated levels of renal renin or angiotensin are not the primary mechanism involved in the development of long-term HTN in these patients. It is less clear whether the upper body blood pressure increases, seen with developing CoA, induce changes in the overall number or sensitivity of angiotensin II type I receptors in the brain. Sangaleti et al [34]. have demonstrated that HTN due to CoA, in the rat is associated with hyperactivity of the brain renin-angiotensin system as indicated by increased expression of angiotensin II type I receptors mRNA in brainstem areas, known to participate in cardiovascular control. It is possible that these receptors are involved in the progression of HTN in post-coarctectomy patients involving the cardiac baroreceptors. This is more likely than a direct effect of angiotensin II on the arteriolar bed, as this would not explain the differential changes seen in the upper and lower body although it is possible that tissue angiotensin II production may be increased from vessels exposed to high-shear stress. Also, the expected effect of increased peripheral vascular resistance with angiotensin II is not typical of the systolic HTN seen in CoA [8,28]. Apart from reduced arterial compliance and blunted baroreceptor sensitivity, already mentioned above, other systems have been implicated in the early hypertensive response seen in post-operative CoA patients. Endothelial dysfunction, has been demonstrated in post-coarctectomy patients and has been suggested as a cause of HTN. Reduced vascular reactivity appears to be restricted to the pre-stenotic arterial tree [35] and subsequent studies have demonstrated that these changes do not appear to be related to timing of surgery suggesting early changes in control of vascular reactivity [8]. Whether this represents early programming is unclear, as this mechanism has not been studied in young pre-operative patients, and adult studies

generally recognize endothelial dysfunction therefore rather than a cause of HTN. Diffuse endothelial dysfunction is also likely to affect peripheral vascular resistance, which has the most profound effects on mean and diastolic BP values rather than systolic values and pulse pressure that are commonly raised in HTN CoA patients [8,32]. As highlighted above, we have for the time been, no clear understanding of the pathophysiological pathways that creates HTN in CoA patients, early or late after their successful treatment. To this condition more skepticism is added by the additional existing pathology of early CHF or commonly seen co-morbidities as the existence of a VSD, Left Heart obstructions or a BAov. It is known fact that up to 85% of CoA patients also carry BAov [36]. Histological abnormalities of the aortic wall in patients with BAov are well documented. Several groups of investigators have confirmed the presence of cystic media necrosis in patients with bicuspid aortic stenosis or regurgitation, which is characterized by vascular smooth muscle cell loss in the absence of inflammation, elastic fiber fragmentation and accumulation of basophilic ground substance within cell depleted areas of the aortic media [34]. Dilatation of the aortic root and proximal ascending aorta is one of the most common non-valvular findings in patients with BAov, with an incidence between 30% and 70% [34]. Importantly, cystic medial necrosis also is the underlying histological abnormality in ascending aortic dilatation and dissection in BAov carriers. High rates of vascular smooth muscle cell apoptosis and medial degeneration have been demonstrated even in non-dilated ascending aortas of BAov carriers independently from valvular hemodynamics or arterial HTN, lending support to the presence of an underlying systemic disorder. This final comment on involvement of additional anatomical lesions in provoking HTN in the setting of CoA, demonstrates the complexity of HTN. This is clearly understood when medicine treatment is needed to be applied to control HTN in these patients, in any age and condition pre or post-surgical/interventional, successful treatment.

## Discussion

CoA is the fifth most common defect,

accounting for 6–8% of live births with CHD. Most patients present in infancy, either acutely due to CHF following closure of the DA, or on routine screening due to absence of the femoral arterial pulse. Some patients will not present until later life due to either a less significant narrowing or rapid post-natal development of collateral circulation that maintains adequate blood supply to the lower body. Their presentation will be accidental diagnosis of HTN, cerebrovascular events or rarely intermittent claudication [8]. Early-to-mid-term outcomes of patients with CoA are excellent, with early mortality rates as low as 2%. However, significant longer-term morbidity remains, particularly with respect to premature systemic HTN (32).

This is associated with significant morbidity and early mortality and although early treatment appears to delay its onset, remarkably one third of CoA patients still become HTN by adolescence despite early and effective surgicalrepair [36]. Data beyond adolescence show increasing prevalence with age, and by 50–72 years 90% of patients have documented HTN. This suggests that HTN may be an inevitable consequence of CoA, even when an effective anatomical repair has been achieved early in life [8,10,28]. Although it is unclear why this may be the case, it is postulated that there is dysfunction of the normal control mechanisms regulating BP during growth and development in patients with repaired CoA [8,10]. As HTN is present as a symport in nearby all cases of CoA, the preoperative treatment can be effectively achieved by the using beta-blockers. The goal should be to reduce upper extremity HTN, but remember that vigorous attempts to achieve normal upper extremity BP may result in inadequate lower-body perfusion. Historically the first anti—HTN class of drugs used to treat pre or post CoA surgical and /or interventional obstruction were the beta-blockers (b-Blockers). These agents have been used for over 40 years in treating a variety of adult cardiac diseases. They inhibit chronotropic, inotropic, and vasodilatory responses to beta-adrenergic stimulation. B-blockers lower BP by antagonizing the beta 1 adrenergic receptor located on the myocardium to reduce heart rate and decrease contractility. However, beta blockers may also act on beta 2 adrenergic receptors on the smooth muscle of vasculature and the bronchi, increasing peripheral resistance and risk of bronchospasm [38]. The first drug which has been mainly used historically was propranolol. This is also a class II antiarrhythmic nonselective beta-adrenergic receptor blocker. Has membrane-stabilizing activity and decreases automaticity of contractions. It not suitable for emergency treatment of HTN. Atenolol, a near selectively blocks beta1-receptors with little or no effect on beta2-receptors has also been used for controlling pre-and post CoA, HTN.As the evolution of pharmacotherapy continues newer selective beta1-adrenergic receptor blocker that decreases automaticity of ectopic beats. Metoprolol is the leading drug of this sub-class. During IV administration, carefully monitor of BP, heart rate, and ECG are required. B-blocker therapy prior to surgery may reduce the severity of postoperative HTN, although most patients with preoperative HTN require at least transient postoperative therapy. Relieving the aortic obstruction promptly rather that attempting to treat HTN with antihypertensive medications must be the target strategy in treating HTN related to CoA [28].

Immediate postoperative HTN can be treated short-term with vasodilators, such as sodium nitroprusside, and intravenous b-blockers, such as esmolol. This, ultra–short-acting beta2-blocker can be useful in patients with labile arterial HTN, especially if surgery is planned, because it can be discontinued abruptly, if necessary, post-surgery.

May be useful in testing b-blocker safety and tolerance in patients with history of obstructive pulmonary disease who are at uncertain risk for bronchospasm from beta-blockers, due to his extremely short half-life, that is only nine minutes. Labetalol, that blocks alpha-adrenergic, beta1-adrenergic, and beta2-adrenergic receptor sites, is an alternatively option to control persisting BP. Guidelines regarding beta-adrenergic receptor blockers have been established [38]. From these, despite the historical use of propranolol and atenolol metoprolol is the only FDA approved b-blocker for pediatric HTN [38].

When longer-term anti-HTN therapy is

required, due to chronic HTN, following successful treatment of the CoA with no residual gradient, beta-blockers may be continued, ACE inhibitors (ACE-i) or angiotensin II antagonists. ACE-i target the renin-angiotensin-aldosterone system (RAAS). ACE converts angiotensin to angiotensin II (Ang II), a peptide that causes vasoconstriction and stimulates aldosterone production, itself a potent vasoconstrictor. ACE inhibitors lower blood pressure by decreasing ang and mitigating its downstream effects. In adults, ACE inhibitors are commonly used anti-HTN have the additional benefit of reducing cardiovascular and renal events. In pediatric populations, ACE inhibitors are the most commonly prescribed anti-HTN for both primary and secondary hypertension, including secondary to CoA, non-obstructive early or late HTN [37]. However, like in adult trials, pediatric trials provide evidence that some ACE inhibitors may be less efficacious in blacks. ACE-i approved for treatment of pediatric hypertension by the FDA include enalapril, fosinopril, benazepril and lisinopril [38]. Regarding captopril that was one of the earliest ACE-i approved for use in adults, there is a substantial body of clinical experience in children and adolescents and several trials have demonstrated clinical efficacy in treating HTN, despite its major disadvantage of captopril is the need for frequent dosing (3 times per day) [39]. Angiotensin receptor blockers (ARBs) target the Angiotensin II type 1 receptors located on the heart, kidney, blood vessels, and adrenal glands. By blocking the final step of the RAAS, ARBs inhibit vasoconstriction and lower blood pressure. Like ACE-i, ARBs is particularly beneficial in reducing LVH in adults with CHF. In adults and children, ARBs are effective at reducing proteinuria secondary to diabetes and may be particularly useful in patients with chronic kidney disease [41]. However, ARBs are generally less efficacious in African Americans. ARBs approved for the treatment of pediatric HTN include losartan, valsartan, candesartan, and olmesartan. Children tolerated ARBs well, and the side effects most frequently experienced were headache and dizziness [38]. In summary,

reviewing the existing literature the existing studies offer only limited data on the efficacy of different classes of anti-HTN medications in HTN -in primary stages of the disease-patients suffering from CoA or after successful repair. A study of 128 young-adult patients with hypertension following CoA repair reported better control of HTN with candesartan over metoprolol with fewer side effects [40]. However, in a small crossover study of 18 adult patients, metoprolol was found to be more effective than candesartan at lowering systolic blood pressure [10]. The 2008 American College of Cardiology/American Heart Association Guidelines for the Management of Adults with CHD recommend use of a b-blocker, ACE-i, or ARBs as first-line therapy, with a preference of one agent over another dependent on the presence of other coexisting lesions such as BAov with regurgitation or dilatation of the aortic root [10,41].

## Summary

CoA was thought to be in past, a discrete LH obstructive lesion, easy to detect and treat. Today, it is not only the fifth most common CHD but can also be easily mist, despite the progress in imaging techniques (echo-2D, CT, c MRI), up to adulthood. Treatment strategies involve surgical and interventional procedures that have proven to have excellent early, mid and late term (up to 30 years), results. The most important morbidity is HTN. This can be seen early or late after even a successful surgical/interventional treatment. Further, 30% of them suffer from HTN by adolescence raising to about 60% in CoA repaired adults. This suggests that HTN may be an inevitable consequence of CoA, even when an effective anatomical repair has been achieved early in life. For this reason, late detected patients will suffer from chronic HTN. Despite the progress in pharmacotherapy the best medicine treatment is debatable and will include more than one class of anti-HTN drugs. Primary prevention to these Patients will be as soon as possible to detect and early operate before the age of one's year old [5]. The secondary prevention would aim to eradicate any residual stenosis in the lumen of the aortic arch and descending aorta and treat existing HTN if present with a b-blocker drug or

if not controlled on monotherapy to add an additional drug from the ACE-i or ARB's classes [38,39]. Finally, tertiary prevention would be treating lifelong HTN with a combination of two plus medications [39,41]. Patients with CoA who have undergone repair require lifelong surveillance. As this type of CHD is associated with many long-term complications, collaboration between pediatric and expertise in adult CHD, cardiologists is recommended. Further research into the mechanisms leading to HTN may identify therapies to target the vasculopathic changes seen in CoA and improve outcome [5,10,30].

**References**

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, et al. (2011) Birth Prevalence of Congenital Heart Disease Worldwide. J Am Coll Cardiol 58: 2241-2247. **Link:** https://goo.gl/VZYRFW

2. Strafford MA, Griffiths SP, Gersony WM (1982) Coarctation of the aorta: A study in delayed detection. Pediatrics 69: 159-163. **Link:** https://goo.gl/pxFXRL

3. Rudolf AM (2009) Congenital Diseases of the Heart-Clinical & Physiological Considerations. Wiley-Blackwell 3ed Edition. **Link:** https://goo.gl/3lK1nG

4. Connolly HM, Huston J, Brown RD Jr, Warnes CA, Ammash NM, et al. (2003) Intracranial aneurysms in patients with coarctation of theaorta: a prospective magnetic resonance angiographic study of 100 patients. Mayo Clin Proc 78: 1491-1499.**Link:** https://goo.gl/DQHDvZ

5. Nguyen L, Cook S (2015) Coarctation of the Aorta. Strategies of improving outcome. Cardiology Clinics 33: 521–530. **Link:** https://goo.gl/95bsIy

6. Kaushal S, Backer CL, Patel JN, Patel SK, Walker BL, et al. (2009) Coarctation of the aorta: midterm outcomes of resection with extended end-to-end Anastomosis. Ann Thorac Surg 88: 1932–1938. **Link:** https://goo.gl/AZ5hME

7. Hamdan MA, Maheshwari S, Fahey JT, Hellenbrand WE (2001) Endovascular stents for coarctation of the aorta: Initial results and intermediate-term follow-up. J Am Coll Cardiol 38: 1518–1523. **Link:** https://goo.gl/PQJQFG

8. Kenny D, Polson JW, Martin RP, Paton JF, Wolf AR (2011) Hypertension and coarctation of the aorta: an inevitable consequence of developmental pathophysiology Hypertension. Research 34: 543–547. **Link:**

9. https://goo.gl/by757D

10. O'Sullivan JJ, Derrick G, Darnell R (2002) Prevalence of hypertension in children after early repair of coarctation of the aorta: a cohort study using casual and 24h blood pressure measurement. Heart 88: 163–166. . **Link:** https://goo.gl/ZWH5u2

11. Hager A, Kanz S, Kaemmerer H, Schreiber C, Hess J (2007) Coarctation long-term assessment (COALA): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material. J Thorac Cardiovasc Surg 134: 738–745. **Link:** https://goo.gl/hCfMOY

12. McBride KL, Pignatelli R, Lewin M, Ho T, Fernbach S, et al. (2005) Inheritance Analysis of Congenital Left Ventricular Outflow Tract Obstruction Malformations: Segregation, Multiplex Relative Risk, and Heritability. American Journal of Medical Genetics 134: 180–186. **Link:** https://goo.gl/e18wcO

13. McBride KL, Riley MF, Zender GA, Fitzgerald-Butt SM, Towbin JA. Et al. (2008) NOTCH1 mutations in individuals with left ventricular outflow tract malformations reduce ligand-induced signaling. Journal Human Molecular Genetics 2886-2893. **Link:** https://goo.gl/6q9zw6

14. Oliver JM, Alonso-Gonzalez R, Gonzalez AE, Gallego P, Sanchez-Recalde A, et al. (2009) Risk of Aortic Root or Ascending Aorta Complications in Patients With Bicuspid Aortic Valve With and Without Coarctation of the Aorta. Am J Cardiol 104: 1001–1006. **Link:** https://goo.gl/F9s5ue

15. Pham PP, Moller JH, Hills C, Larson V, Pyles L (2009) Cardiac Catheterization and Operative Outcomes from a Multicenter Consortium for Children with Williams Syndrome. Pediatric Cardiology 30: 9–14. **Link:** https://goo.gl/O19s5R

16. Curtis SL, Bradley M, Wilde P, Aw J, Chakrabarti S, et al. (2012) Results of Screening for Intracranial Aneurysms in Patients with Coarctation of the Aorta. Am J Neuroradiol 33: 1182-1186. **Link:** https://goo.gl/ykNUHW

17. Allen HD, Gutgesell HP, Clark EB, Driscoll DJ (2001) "Moss and Adams", Heart Disease in Infants, Children and Adolescents, including the Fetus and Young Adult. 6th Ed. Lippincott Williams & Wilkins. **Link:**

18. Anthony N (2007) Echocardiography in Hurst's. The Heart 12th edition, McGraw Hill Medical, 443. **Link:**

19. Shepherd B, Abbas A, McParland P, Fitzsimmons S, Shambrook J, et al. (2015) MRI in adult patients with aortic coarctation: diagnosis and follow-up. Clin Radiol 70: 433–445. **Link:** https://goo.gl/pljMgE

20. Rosenthal E, Bell A (2010) Optimal imaging after coarctation stenting. Heart 96: 1169-1171. **Link**: https://goo.gl/sBhCno

21. Hager A, Kaemmerer H, Hess J (2005) Comparison of Helical CT Scanning and MRI in the Follow-up of Adults with Coarctation of the Aorta. Chest 127: 2296. **Link:** https://goo.gl/vK3rPg

22. Torok RD, Campbell MJ, Fleming GA, Hill KD (2015) Coarctation of the aorta: Management from infancy to Adulthood. World J Cardiol 7: 765-775. **Link:** https://goo.gl/ez57jE

23. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, et al. (2008) Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 118: 714-833. **Link:** https://goo.gl/Y4Y0EP

24. Cowley CG, Orsmond GS, Feola P, McQuillan L, Shaddy RE (2005) Long-term, randomized comparison of balloon angioplasty and surgery for native coarctation of the aorta in childhood.

27. Cohen M, Fuster V, Steele PM , Driscoll D, McGoon DC (1989) Coarctation of the Aorta Long-term Follow-up and Prediction of Outcome After Surgical Correction. Circulation 80: 840-845. **Link:** https://goo.gl/bbv2F8

28. Khavandi A, Bentham J, Marlais M, Martin RP, Morgan GJ, et al. (2013) Transcatheter and endovascular stent graft management of coarctation-related pseudoaneurysms. Heart 99: 1275-1281. **Link:** https://goo.gl/Ou2oPm

29. Patnana SR, Seib PM (2015) Coarctation of the Aorta. **Link:** medscape com/ article / 895502

30. Thoele DG, Muster AJ, Paul MH (1987) Recognition of coarctation of the aorta. A continuing challenge for the primary care physician Am J Dis Child 141: 1201-4. **Link:** https://goo.gl/kRadKr

31. Petropoulos A (2014) Hypertension in the Young An overgrowing concern in Pediatrics 2end BITS, Annual World Conference in Pediatrics, Abstract Book; Tayhan, China 24-26/10/2014 **Link:**

32. Bocelli A, Favilli S, Pollini I, Bini RM, Ballo P, et al. (2013) Prevalence and long-term predictors of left ventricular hypertrophy, late hypertension and hypertensive response to exercise after successful aortic coarctation repair . Pediatr Cardiol 34: 620–629. **Link:** https://goo.gl/EMbnoo

33. Mascherbauer J (2014) Mechanisms underlying arterial hypertension in contemporary patients with repaired aortic coarctation: do we know enough? Heart 0: 1–2. **Link:** https://goo.gl/xVG7mJ

34. Parker FB Jr, Farrell B, Streeten DH, Blackman MS, Sondheimer HM, et al. (1980) Hypertensive mechanisms in coarctation of the aorta—further-studies of the renin-angiotensin system. J Thorac Cardiovasc Surg 80: 568–573. **Link:** https://goo.gl/QpTUsp

35. Sangaleti CT, Crescenzi A, Michelini LC (2004) Endogenous angiotensin and pressure modulate brain angiotensinogen and at (1a) mRNA expression. Hypertension 43: 317–323. **Link:** https://goo.gl/1waobv

36. de Divitiis M, Pilla C, Kattenhorn M, Zadinello M, Donald A, et al. (2001) Vascular Dysfunction After Repair of Coarctation of the Aorta. Impact of Early Surgery. Circulation I-168. **Link:** https://goo.gl/aE5sjC

37. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, et al. (2010) ESC Guidelines for the management of grown-up congenital heart

Circulation 111: 3453-3456. **Link:** https://goo.gl/lwVKts

25. Feltes TF, Bacha E, Beekman RH 3rd, Cheatham JP, Feinstein JA, et al. (2011) Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation 123: 2607-2652. **Link:** https://goo.gl/t1B7yz

26. Suradi H, Hijazi ZM (2015) Current management of coarctation of the aorta. Global Cardiology Science and Practice: 44: 2-11. **Link:** https://goo.gl/5QlR6S disease (new version 2010). Eu Heart J 31: 2915–2957. **Link:** https://goo.gl/7E7ThC

38. Frobel AK, Hulpke-Wette M, Schmidt KG, Laer S (2009) Beta-blockers for congestive heart failure in children Cochrane Database. Syst Rev CD007037.

39. Chu PY, Campbell MJ, Miller SG, Hill KD (2014) Anti-hypertensive drugs in children and adolescents. World J Cardiol 6: 234-244. **Link:** https://goo.gl/zJb2ge

40. Flynn JT (2011) Management of hypertension in the young role of antihypertensive medications. J Cardiovasc Pharmacol 58: 111-120. **Link:** https://goo.gl/P8dSBg

41. Webb NJ, Lam C, Loeys T, Shahinfar S, Strehlau J, et al. (2010) Randomized, double-blind controlled study of losartan in children with proteinuria. Clin J Am Soc Nephrol 5: 417-424. **Link:** https://goo.gl/HWdTSl

42. Giordano U, Cifra B, Giannico S, Turchetta A, Calzolari A (2009) Mid-term results, and therapeutic management, for patients suffering hypertension after surgical repair of aortic coarctation. Cardiology in the Young 19: 451-455. **Link:** https://goo.gl/A4ie0f