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Coarctation of the aorta: From fetal life to adulthood

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Abstract

Coarctation of the aorta was once viewed as a simple discrete narrowing of the aortic isthmus that could be 'cured' by surgical intervention. It is now clear that this condition may: (1) affect the aortic arch in a highly variable manner; (2) be associated with a host of other left sided heart lesions; (3) represent a wider vasculopathy within the pre-coarctation arterial tree, leading to significant prevalence of hypertension by adolescence, and subsequent risk of early morbidity and death. This review outlines the evaluation and treatment of this disease from pre-natal to adult life. (Cardiol J 2011; 18, 5: 487–495)

Key words: surgery, echocardiography, stenting, hypertension, vasculopathy

Introduction

Coarctation of the aorta (CoA) is the fifth most common congenital heart defect, accounting for 6–8% of live births with congenital heart disease, with an estimated incidence of 1 in 2,500 births [1–3]. It is likely that the incidence is higher in stillborn babies [4]. It affects more male babies than female, with a reported ratio in males of between 1.27:1 and 1.74:1 [5, 6]. It usually manifests as a discrete constriction of the aortic isthmus (Fig. 1). However, it is more likely to represent a spectrum of aortic narrowing from this discrete entity to tubular hypoplasia, with many variations seen in between these two extremes. Morphologists argue that tubular hypoplasia, although it may coexist with discrete coarctation, should be considered as a separate entity [1] although this has not been proven. The presence of associated arch hypoplasia is relevant to longer term risk for the development of hypertension.

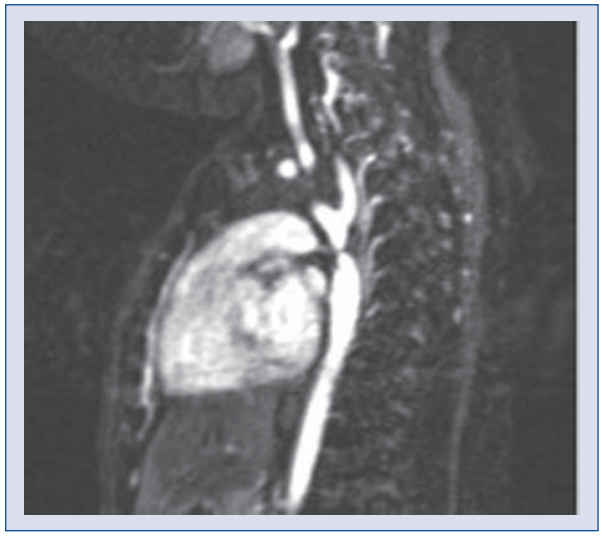

Figure 1. Magnetic resonance image of ten month-old male infant with discrete coarctation of the aorta.

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Etiology

The etiology of the discrete isthmic constriction of the aorta seen in patients with CoA remains very much in dispute. Although familial cases have been reported [7, 8] and association with various gene deletions described [9], there is no experimental evidence to support a unifying theory, something not helped by the absence of naturally occurring animal models.

Developmental theories have focused on abnormalities of blood flow [10], abnormal migration patterns of the developing aortic arch, and excessive distribution of arterial duct-like tissue around the aortic isthmus [11]. Such singular mechanistic views do not reflect the widespread changes seen both in left heart structures (mitral valve abnormalities, bicuspid aortic valve) and upper body vascular structure (cerebral aneurysms) so commonly associated with CoA. Peterson et al. [9] have demonstrated that changes induced by a gridlock mutation in the hey2 gene in the zebrafish lead to changes mimicking CoA in this species. Interestingly, inducing upregulation of vascular endothelial growth factor (VEGF) early in development is sufficient to suppress the gridlock phenotype and aortic abnormality in this model. VEGF plays a vital role in aortic development, acting as a chemo-attractant, stimulating angioblast migration toward the midline before formation of the aorta [12]. Indeed, targeted disruption of VEGF in mice leads to significant disruption of the developing aorta [13]. VEGF is also involved in stimulating generalized arterial differentiation through its effect on angioblast migration. Whether an initial mutation leads to secondary effects on VEGF or on other signaling systems involved in recruiting mural cells in fetuses, leading to CoA, is unknown.

However, a more widespread vascular abnormality might be expected if this were so, and numerous studies have demonstrated normal lower limb vascular structure and function both before and after early coarctation repair [14–16]. The regional vasculopathy in patients with CoA is therefore more likely to be due to an effect of abnormal hemodynamics as a consequence of isthmic narrowing. But whether this is in response to reduced upper body flow dynamics or to increased intra-arterial pressure load is unclear. An increase in collagen and decrease in smooth muscle content of the pre-coarctation aorta in humans has been demonstrated in comparison to post-coarctation aorta or to proximal aorta of young transplant donors [17]. This is consistent with a rabbit model of CoA, where increased gene expression for collagen types I and III has been demonstrated in the aorta proximal to the coarctation site [18]. These investigators postulated that the mechanical stress associated with increased pressure load may initiate rapid gene expression for collagen production, leading to re-enforcement and reorganization of the vessel musculo-elastic fascicle, and thereby reducing the degree of pressure-induced aortic dilatation. However, a clear disadvantage of this is that the resultant stiffer vessel will lead to augmented central aortic systolic pressure and systolic hypertension [19], which is the major cause of longer term morbidity and mortality in these patients, even despite early repair.

Fetal diagnosis

CoA is notoriously difficult to diagnose in fetal life because the life-preserving presence of the arterial duct makes it difficult to detect isthmal narrowing. Recent reports have concentrated on serial measurements of isthmal *z* scores and isthmal-to-ductal ratios by fetal echocardiography which may be more sensitive indicators of fetal coarctation [20].

Abnormal isthmal flow patterns may also improve diagnostic specificity and may reduce false positives; however, confirmatory echocardiography is still necessary following birth, and coarctation in this setting cannot be ruled out completely until the arterial duct has closed. One early, but non-specific, finding on fetal echocardiography of potential aortic coarctation is an imbalance in ventricular size, with right ventricular dominance [21]. This is likely due to increased left ventricular diastolic pressures secondary to the coarctation, reduced right-to-left flow across the foramen ovale, and an increased volume load to the right ventricle. It is possible that these flow abnormalities may have a long-term effect on ventricular development and function. For example, in fetal sheep, an increase in the load on the heart leads to an increase in the number of binucleated myocardial cells [22], which unlike their mononuclear counterparts are not able to divide. Although this has implications for the total number of myocardial cells in the heart, it also may influence how the heart will respond to pressure load in the future [23]. Numerous studies have demonstrated increased ventricular mass in normotensive coarctectomy patients associated with changes in aortic arch morphology [24, 25]. A recent report showed that increased ventricular systolic stiffness, coupled with arterial stiffness, may

be implicated in hypertension in post-coarctectomy patients [26]. Thus, abnormalities in ventricular development may be important in the hypertensive response.

Presentation and management

The majority of patients affected present in infancy with varying degrees of heart failure which reflect predominantly the severity of the aortic narrowing. Ultimately, these patients require intervention; surgery is the treatment of choice in this age group, although balloon angioplasty has been used as a bridge to surgery in critically ill infants [27]. Early recognition is paramount, because rapid deterioration may occur with closure of the arterial duct and there is a trend towards less favorable outcomes in sicker pre-operative infants [28]. In either case, intensive management is required to ensure ventricular function is optimal prior to surgery. Various surgical approaches have been used, with the two commonest recent approaches being surgical excision of the coarctation with end-to-end anastomosis or augmentation of the coarcted aorta using the subclavian artery, the so-called 'subclavian flap repair' (SFR). Although reports are conflicting on the longer term outcomes of these two surgical approaches, most have concentrated on survival, the need for re-intervention and aneurysm formation [29, 30]. Aneurysm formation is a particular concern: untreated, it can lead to rates of rupture of up to 100% within 15 years [31]. Both aneurysm formation and restenosis are thought to be commoner with SFR [32], although surgical experience with the technique may be a factor. A recent report indicated that SFR may be associated with abnormal upper limb compliance and subsequent hypertension independent of recurrent narrowing [33]. Although this approach is less often performed in modern practice due to the reasons discussed above, this outcome is of significant importance in the longer term follow-up of these patients.

Catheter intervention

Some patients may not present with CoA until later childhood or adolescence, either due to less severe initial narrowing or to the development of collateral circulation bypassing the coarctation, or both. Most of these patients present with upper body hypertension. Non-surgical approaches to CoA in this population became popular with the advent of balloon angioplasty. Balloon angioplasty for coarctation was first reported in 1982, with use having become widespread over the past two decades [34]. Medium term outcome studies of balloon angioplasty have shown good initial relief of stenosis, but high rates of re-coarctation and aneurysm formation [35–38].

Hence, stent implantation is now the preferred intervention for coarctation in older children and adults, with persistent relief of stenosis and lower incidence of aneurysm formation compared to balloon angioplasty alone [39, 40] (Fig. 2). Recent guidelines have been published for transcatheter treatment of both primary and recurrent coarctation (Table 1). Ballooning and/or stenting are indicated when there is a transcoarctation gradient of > 20 mm Hg at the time of catheterization, although intervention may be warranted with less severe gradients if there is systemic hypertension with anatomic narrowing that may be contributing to the hypertension [41].

Stent technology has evolved in recent years and includes primarily balloon expanding, and occasionally self-expanding, stents in addition to expanded polytetrafluoroethylene covered stents. Covered stents have also been used to treat increasingly complex aortic arch obstructions and aneurysm formation [42, 43]. Covered stents offer the advantage of excluding any stretch-induced wall trauma from the endoluminal aspect of the aorta, particularly in the catastrophic event of aortic rupture which has been reported [44]. These stents are not currently approved for use in patients with CoA in the USA and therefore novel approaches of applying a Gore-Tex covering to a bare metal stent have been reported to counter this [45].

The short-term efficacy of stent implantation is well recognized but accurate long-term follow-up assessment is sparse. Recent reports have demonstrated potential physiological benefits following stenting, including mid-term left ventricular mass regression and long-axis function improvement, as well as amelioration in central aortic function with associated reduction of daytime ambulatory systolic blood pressure [46, 47]. Long-term evaluation of both stent and aortic wall integrity is essential to monitor potentially life-threatening complications. Follow-up with computed tomography examination suggests that the overall aneurysm rate is low [48] although other reports have had variable results [49, 50].

Outcomes: Don't forget the blood pressure!

Untreated CoA has significant early mortality, with one report identifying CoA in 17% of neonates

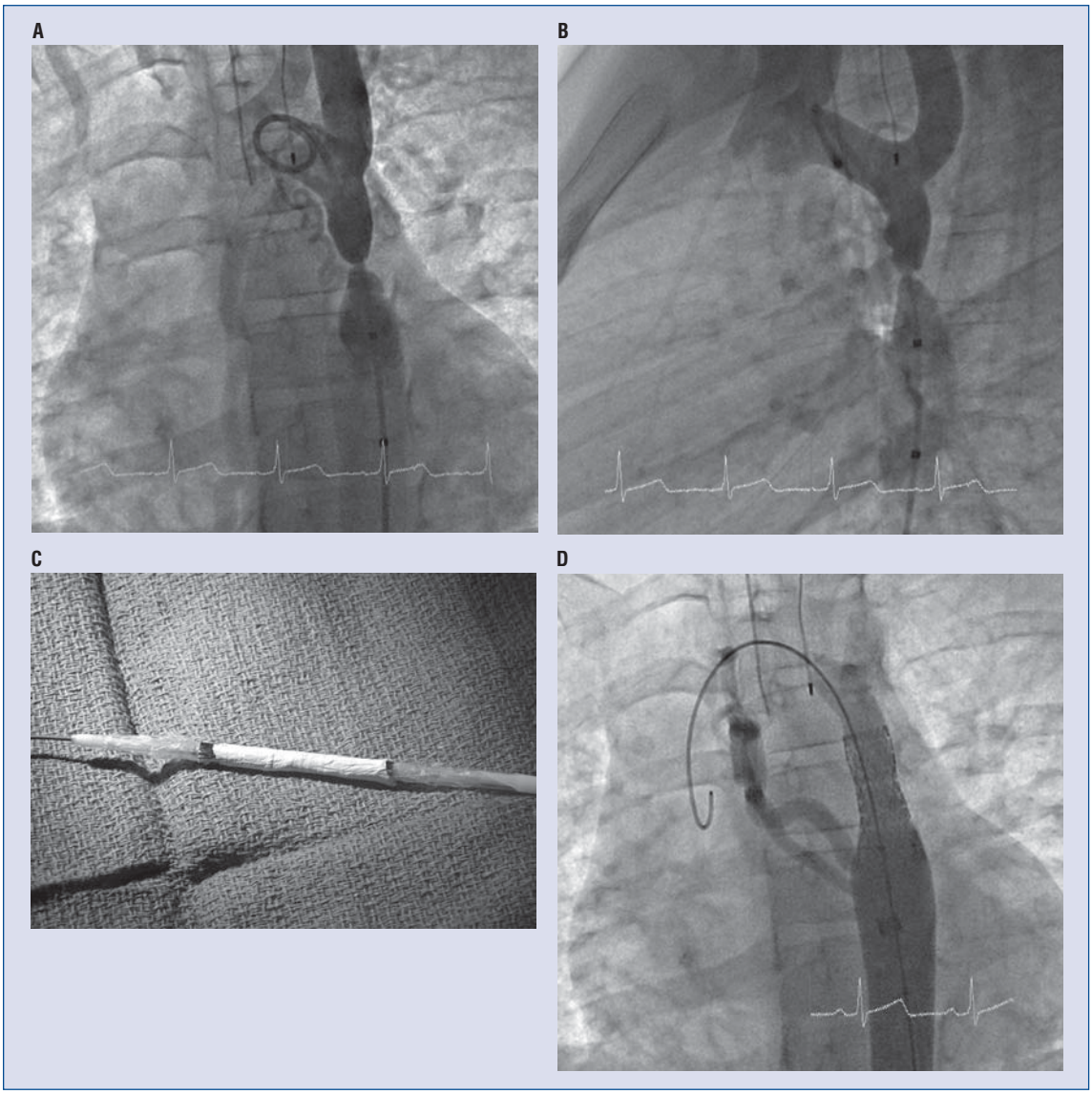

Figure 2. Series of images outlining stenting of a tight native coarctation with a self-fabricated covered stent in a nine year-old male; **A**, **B**. Demonstrate AP and lateral angiographic images of the tight native coarctation with multiple collateral arteries seen; **C**. Self-fabricated covered stent mounted on a balloon catheter as previously described [45]; **D**. Following implantation of the stent, there is no residual waist seen with no evidence of aneurysm formation. Large collateral arteries draining inferior to the stent are seen.

dying from congenital heart disease [51]. Most of those who survive infancy reach adulthood, but the mean age of death has been reported to be as low as 31 years for those surviving the first year without an operation [52]. Even in the treated population, there is significant early morbidity and mortality, with Cohen at al. [53] reporting estimated mortality of almost 30% at 30 years following repair, with an average age of death of 38 years (Fig. 3).

These outcomes are substantiated by other studies [54–56] with Clarkson et al. [54], reporting on 160 patients with 10–28 years of follow-up, observing that only 20% of patients were alive without complications and with a normal blood pressure at 25 years follow-up.

To some extent, these are historical reports. The identification and treatment outcomes of patients with congenital heart disease have improved significantly over the past two decades [57, 58], and early to mid-term outcomes for patients with CoA are excellent, with early mortality rates as low as 2% [59]. Significant longer-term morbidity remains however, with more recent reports observing less than 50% of patients with normal blood pressure

Table 1. American Heart Association guidelines for catheter intervention for coarctation of the aorta [41].

Recommendations for transcatheter balloon angioplasty of coarctation/recoarctation of the aorta

Class I

1. Transcatheter systolic coarctation gradient of > 20 mm Hg and suitable anatomy, irrespective of patient age (level of evidence: C).
2. Transcatheter systolic coarctation gradient of < 20 mm Hg in the presence of significant collateral vessels and suitable angiographic anatomy, irrespective of patient age, as well as in patients with univentricular heart or with significant ventricular dysfunction (level of evidence: C).

Class IIa

1. As a palliative measure to stabilize a patient when extenuating circumstances are present, such as severely depressed ventricular function, severe mitral regurgitation, low cardiac output, or systemic disease affected by the cardiac condition (level of evidence: C).

Class IIb

1. Beyond four to six months of age when associated with a transcatheter systolic coarctation gradient > 20 mm Hg and suitable anatomy (level of evidence: C).
2. Native or recurrent coarctation of the aorta in patients with complex coarctation anatomy or systemic conditions such as connective tissue disease or Turner syndrome but should be scrutinized on a case-by-case basis (level of evidence: C).

Recommendations for stent placement in native coarctation and recoarctation of the aorta

Class I

1. Recurrent coarctation patients of sufficient size for safe stent placement, in whom the stent can be expanded to an adult size, and who have a transcatheter systolic coarctation gradient > 20 mm Hg (level of evidence: B).

Class IIa

1. Transcatheter systolic coarctation gradient of > 20 mm Hg (level of evidence: B).
   - Transcatheter systolic coarctation gradient of < 20 mm Hg but with systemic hypertension associated with an anatomic narrowing that explains the hypertension (level of evidence: C).
   - Long-segment coarctation with a transcatheter systolic coarctation gradient > 20 mm Hg (level of evidence: B).
2. When balloon angioplasty has failed, as long as a stent that can be expanded to an adult size can be implanted (level of evidence: B).

Class IIb

1. In infants and neonates when complex aortic arch obstruction exists despite surgical or catheter-mediated attempts to relieve this obstruction and when further surgery is regarded as high risk (level of evidence: C).
2. Transcoarctation gradient of < 20 mm Hg but with an elevated left ventricular end-diastolic pressure and an anatomic narrowing (level of evidence: C).
   - Transcoarctation gradient of < 20 mm Hg but in whom significant aortic collaterals exist, which results in an underestimation of the coarctation (level of evidence: C).

1–27 years following CoA repair [60]. The average age at operation of this cohort was nine years and there is emerging data to suggest that earlier age at surgery may be protective against the development of hypertension [61–63]. Although early surgery may prevent or delay the onset of hypertension, approximately 30% of children will be hypertensive by adolescence despite early surgery [62], and it is now arguable that hypertension is the single most important outcome variable in patients with repaired CoA. Most studies report resting blood pressure, and it is well accepted that a significant number of patients with normal resting blood pressure in the setting of CoA have an exaggerated blood pressure response to exercise which may predict the onset of established hypertension [65, 66].

The causes of hypertension in this cohort of patients are not fully understood, but malfunction in a number of individual systems have been implicated, including imbalance within the autonomic nervous system [17, 67], impaired vascular function [68, 69] and hyperactivation of the rennin–angiotensin system [70, 71]. It is likely that more than one of these systems is involved. The effect of abnormal arterial compliance on the arterial baroreceptors located in the aortic arch and the carotid arteries is of particular interest. Initial evidence for links between abnormal arterial structure and baroreceptor functioning was suggested by Sehested et al. [17]. They examined freshly resected coarctation tissue and demonstrated reduced isometric tension induced by potassium, noradrenaline and

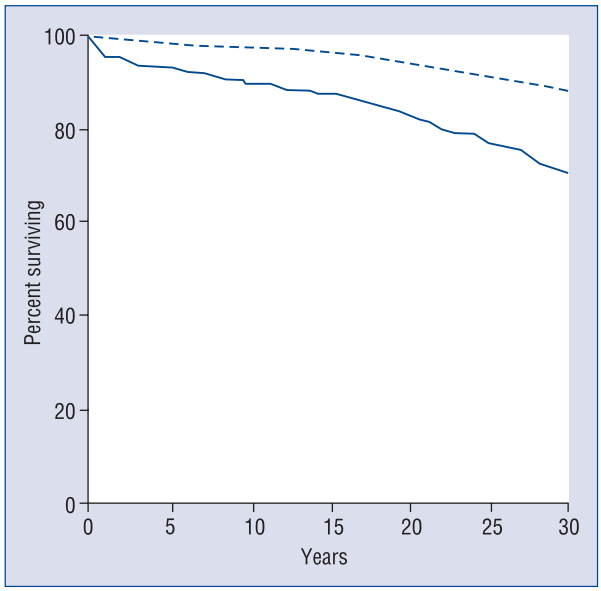

Figure 3. Taken from Cohen et al. [53]. Observed survival curves to 30 years of 588 surgically treated patients (solid line) and the expected survivorship of an age- and sex-matched population based on cohort life tables (dashed line).

prostaglandin in the prestenotic aortic tissue compared to the poststenotic area, indicating reduced contractility of the prestenotic aorta. This was associated with increased collagen and reduced smooth muscle content of the prestenotic aortic wall. The authors postulated that aortic arch baroreceptors in this prestenotic area may be activated less at a given pressure than receptors placed in a vessel with normal distensibility, thus allowing a higher pressure to be tolerated by the cardiac baroreflex. This inter-relationship between reduced arterial compliance and baroreceptor sensitivity has been evaluated in adolescents following early CoA repair with and without hypertension, with the reported finding that stiffer central arteries may be initially compensated for by increased baroreceptor sensitivity [72]. When this mechanism fails, hypertension becomes manifest; but a timing beyond which this outcome becomes inevitable has yet to be identified. Blunted baroreceptor sensitivity and reduced heart rate variability have been demonstrated in pre-operative neonates with CoA compared to controls, suggesting early maladaptive autonomic control of blood pressure [73].

Similar studies have been carried out in neonates looking at aortic compliance in order to examine the effects of CoA on fetal and early neonatal arterial stiffness. Vogt et al. [15] measured local arterial stiffness indices and distensibility in the ascending and descending aortas of pre- and post-operative CoA neonates, and compared these values to matched controls, demonstrating significantly reduced distensibility and increased stiffness indices in the ascending aortas of the pre- and post-operative group. There was no difference in the elastic properties of the descending aorta between the two groups. The same group was prospectively re-evaluated at three years of age and aortic elastic properties were measured in a similar fashion [16]. Persisting impairment of the local elastic properties of the ascending aorta was noted in the CoA group when compared to controls, although correlation between these findings and the longer term risk of hypertension was not possible.

The future

Although early outcomes are excellent, the potential for significant longer term morbidity in patients with CoA persists, irrespective of the initial treatment strategy. The first approach must be wider identification of the problem. Hypertension may be present in young children: this is often under-recognized or not treated aggressively enough [74]. More standardized protocols for the evaluation of blood pressure are required, with a consensus reached as to when to intervene and how to respond to exercise-induced hypertension which is not uncommon in adolescents and may be predictive of established hypertension. Follow-up imaging should be tailored towards early identification of re-stenosis and aggressive subsequent management. Magnetic resonance imaging has been identified as the most cost-effective means of follow-up in older patients [75] and offers detailed images of the aortic arch. Neuro-imaging to evaluate cerebral aneurysms, which have been reported in 10% of patients with CoA, may also be performed at the same time [76]. Current recommendations to intervene for re-coarctation are usually based on a systolic gradient of > 20 mm Hg at the time of catheterization, although less severe gradients may become more significant with provocation and it is not yet clear how to deal with these.

Ongoing attempts to delineate the exact type and timing of developmental maladaption that may be responsible for the development of hypertension are necessary to determine appropriate medical treatment. Much controversy exists regarding the best medical therapy for established hypertension in these patients. In many centers, beta-blockers are used and there is published data demonstrating

a beneficial effect of these agents on the early post-operative hypertensive response [77]. Recent data has also suggested that metoprolol is more effective than candesartan at reducing arterial blood pressure in patients with repaired CoA with varying impacts of these medications on neurohumoral activity and vascular stiffness [78]. A recent report demonstrated that ramipril decreases the expression of pro-inflammatory cytokines in normotensive patients with CoA [79]. Use of agents with anti-inflammatory effects may be prudent, as the endothelial dysfunction seen in patients with CoA may be a consequence of inflammation driven by abnormal flow dynamics at the repair site, or as a consequence of a more widespread vasculopathy as part of the 'syndrome' of CoA.

A more important question is whether the course of changes in blood pressure can be altered with early treatment. Early surgical intervention reduces the incidence of hypertension on follow-up, but whether or not this merely delays onset is not yet clear. It is conceivable that early 'prophylactic' treatment with targeted anti-hypertensive agents may prevent irreversible changes driving the hypertensive response from occurring, and thus improve the longer term outlook for these patients.

Conclusions

Although advances in the recognition and treatment of patients with CoA have taken place, much work still remains to be done to ensure that longer term morbidity, secondary to early onset hypertension, is minimized. CoA should be considered a lifelong disease affecting the entire pre-coarctation arterial tree, and regular follow-up with aggressive management of re-coarctation is vital. Consensus guidelines drafted from outcome data from multi-institutional networks may provide a more consolidated approach.

In the future, further research into the mechanisms driving the hypertensive response may identify therapies to target the vasculopathic changes seen with CoA and improve these outcomes.

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