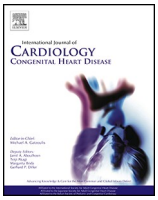
International Journal of Cardiology Congenital Heart Disease 19 (2025) 100561

Contents lists available at ScienceDirect

International Journal of Cardiology Congenital Heart Disease

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-congenital-heart-disease



Coarctation of the aorta and accelerated atherosclerosis: A contemporary review on the burden of atherosclerotic cardiovascular disease

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ARTICLE INFO

Keywords:
Arterial stiffness
Atherosclerosis
Coarctation of the aorta
Coronary artery calcium
Coronary artery disease
Endothelial dysfunction
Hypertension

ABSTRACT

Coarctation of the aorta (CoA) is one of the most common types of congenital heart disease. Unfortunately, there is a high prevalence of hypertension and late cardiovascular mortality in patients with CoA despite successful repair. The growing impact of acquired cardiovascular disease remains a significant concern as the adult congenital heart disease population continues to rapidly expand and age. This review aims to explore (1) the determinants of vascular health and atherosclerosis including endothelial dysfunction and vascular wall abnormalities, (2) the prevalence of atherosclerosis and associated sequelae in repaired CoA including coronary artery disease, coronary artery calcium, aortic calcium, stroke, and peripheral artery disease, and (3) the contributing factors specific to CoA. This review aims to guide optimization of long-term cardiovascular health to ultimately reduce mortality and morbidity in this young high-risk population.

1. Introduction

Coarctation of the aorta (CoA) is one of the most common types of congenital heart disease (CHD) accounting for up to 10 % of all defects [1]. While CoA may appear to be a simple lesion cured by surgery, it is far from benign [2]. Despite successful surgical or transcatheter repair, it is well known that many patients go on to develop hypertension early in life. Unfortunately, large cohort studies have demonstrated a high rate of late cardiovascular mortality in patients with repaired CoA with many deaths attributed to the accelerated effects of hypertension including premature coronary artery disease (CAD) [3–6]. The growing impact of acquired cardiovascular disease remains a significant concern as the adult congenital heart disease (ACHD) population continues to rapidly expand and age [7,8]. While atherosclerosis is the main risk factor for cardiovascular disease in the general population, little is known about its role in patients with repaired CoA.

This review aims to explore the determinants of vascular health and atherosclerosis, the prevalence of atherosclerosis and associated sequelae in repaired CoA, and the contributing factors such that we may aim to optimize long-term cardiovascular health in and reduce mortality and morbidity in adults with repaired CoA.

Abbreviations: ACHD, adult congenital heart disease; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CAD, coronary artery disease; cIMT, carotid intima-media thickness; CHD, congenital heart disease; CMR, cardiovascular magnetic resonance; CoA, coarctation of the aorta; CT, computerized tomography; HDL, high-density lipoprotein; IAA, interrupted aortic arch; IMT, intima-media thickness; LDL, low-density lipoprotein; PVD, peripheral vascular disease; TAC, thoracic aorta calcium; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

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https://doi.org/10.1016/j.ijcchd.2024.100561
Received 13 December 2024; Accepted 24 December 2024
Available online 25 December 2024

2. Determinants of vascular health and atherosclerosis

Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids, fibrous elements, and calcification within the large arteries. This process is initiated by endothelium activation, triggering a cascade of events resulting in low-density lipoprotein (LDL) infiltration, activation of inflammatory pathways, vessel narrowing, and ultimately leads to atheroma plaque formation. Therefore, alterations in endothelial function and intrinsic vascular wall abnormalities may predispose to atherosclerosis. Endothelial dysfunction precedes the development of atherosclerosis and has been shown to increase the risk of developing cardiovascular disease in as little as 5 years [9] as well as predict progression of vascular arterial disease [10]. Vascular abnormalities such as arterial stiffness are independent risk factors for cardiovascular events [11].

Significant endothelial dysfunction and vascular wall abnormalities have been demonstrated following CoA repair and often co-exist [12–20]. Endothelial function is significantly impaired in repaired CoA patients compared to healthy controls as measured by endothelial-dependent flow-mediated dilation, endothelial-independent dilatation to glyceryl trinitrate, reactive hyperemic index, and pulse amplitude tonometry ratio [12–14]. Disturbed laminar flow or turbulent flow reduces wall shear stress and promotes endothelial dysfunction and is a likely pathogenic mechanism in patients with repaired CoA. Distorted blood flow patterns in the descending aorta are common following CoA repair [21] and contributing factors in repaired CoA patients will be specifically explored in a subsequent section of this review.

Alterations in the vascular arterial structure and function of patients with CoA often persists even after successful surgical repair [12–20] and may create an environment that is more conducive to the development of atherosclerosis. Arterial stiffness has been demonstrated to be significantly increased in repaired CoA patients compared to healthy controls, as represented by increased pulse wave velocity, stiffness index, and augmentation index, and decreased distensibility, even in the absence of hypertension [12–20]. These abnormalities are thought to be acquired even prior to surgical repair as a likely consequence of the high-pressure load placed on the arterial walls leading to structural changes such as increased collagen and elastin deposition and reduced numbers of smooth muscle cells [22,23]. Therefore, CoA should be regarded as a condition of generalized vasculopathy rather than a simple isolated narrowing of the aorta.

3. Prevalence of atherosclerosis and associated sequelae

3.1. Mortality

There is a high rate of mortality in repaired CoA cohorts despite successful repair [3–6]. A historic cohort study published more than 3 decades ago suggested that >25 % of repaired CoA patients may die within 30 years from repair due to the effects of systemic hypertension [5]. An updated 2013 report of 819 patients from the same institution demonstrated a 20 % reduction in survival by three decades after repair (predominantly in early adulthood) compared with an age and gender matched population [4]. These findings have been confirmed in a separate cohort of 834 adults with repaired CoA with a median follow-up of 27 years where the mortality rate was demonstrated to be more than three times higher than that of a matched population [3]. More concerningly than reported in prior studies, a more obvious decline in survival was seen after only the third decade of life (not just after repair) with only 88 % and 66 % of patients surviving at 50 and 70 years of age, respectively [3]. Many causes of death were cardiovascular and potentially attributable to or exacerbated by systemic hypertension including left ventricular failure, myocardial infarction, and thoracic aortic aneurysm rupture or dissection. Other studies have reported coronary artery disease (CAD) to be the leading cause of death accounting for over 20 % of late deaths [6]. Therefore, the early identification and aggressive management of hypertension and other cardiovascular risk factors is particularly pertinent in this young high-risk population.

3.2. Coronary artery disease

It was long thought that premature CAD was an inevitable and unavoidable complication of CoA. Historical work dating back to 1968 on the post-mortem histology of coronary arteries of young male CoA patients (2–30 years of age) described severe changes in the intima due to excess collagen, striking thickening of the media layer, and even severe atherosclerotic lesions in young adult hearts compared to age- and gender-matched normal hearts [24]. Several large cohort studies have confirmed a clear association between CoA, premature CAD, and early cardiovascular mortality, but have also reported high rates of traditional cardiovascular risk factors [3–6].

The overall prevalence of CAD in the repaired CoA population has been reported to vary between 3.2 and 7.8 % depending on the study type and definition used [25–28]. To the best of our knowledge, there are only two studies, both retrospective in nature, which have directly investigated CAD prevalence in CoA with a comparison to matched control group. A Canadian study compared 756 mixed repaired/unrepaired CoA patients to 6481 patients with ventricular septal defect (VSD) at a mean age of 31 years [25], while the Mayo Clinic study compared 654 (mostly) repaired CoA patients to 876 patients with tetralogy of Fallot (TOF) or pulmonary stenosis at a mean age of 36 years [26]. Both studies reported significantly higher rates of traditional cardiovascular risk factors in CoA patients compared to controls including hypertension, hypercholesterolemia, stroke, and peripheral vascular disease (PVD) [25,26]. The overall prevalence of CAD in CoA was 4.9 % (vs VSD 3.5 %) in the Canadian study [25] and 7.8 % (vs TOF 6.3 %) in the Mayo Clinic study [26]. Additionally, the Mayo Clinic study reported the prevalence of premature CAD (before the age of 55 or 65 years in men and women, respectively) in CoA to be 4.4 % [26]. However, there was no significant difference in CAD prevalence compared to the matched control groups in either study including after adjustment for traditional cardiovascular risk factors. Conversely, a separate large United States population-based study investigating the impact of CoA on the age at myocardial infarction (MI) or coronary intervention (coronary artery bypass graft or percutaneous coronary intervention) in patients with and without CoA [29]. After adjustment for cardiovascular risk factors, patients with a history of CoA suffered MI at a slightly younger age than those without CoA (7.2 years younger) and underwent coronary intervention in the absence of MI at a significantly younger age (15.6 years younger) [29]. While it remains unclear if a (non-modifiable) diagnosis of CoA itself is a risk factor for CAD, there is clearly a concerning rate of premature CAD in repaired CoA which is strongly attributable to modifiable traditional cardiovascular risk factors. Consequently, premature CAD and associated mortality is likely preventable in the CoA population, further emphasizing the vital importance of aggressive cardiovascular risk factor modification in this high-risk population.

3.3. Coronary artery calcium

Coronary artery calcium (CAC) has been established as a validated non-invasive screening tool for atherosclerotic plaque burden and an independent predictor of future myocardial infarction and mortality in asymptomatic patients [30,31] as well as in younger adults [32–34] in the general population. CAC provides direct visual evidence of coronary atherosclerosis already present in an individual patient, even if subclinical. A recent Multi-Ethnic Study of Atherosclerosis (MESA) study of young adults (30–45 years) in the general population revealed the presence of any CAC (≥1) to be highly abnormal, particularly in males aged ≤35 years and females ≤45 years where any CAC places them in

the ≥90th percentile for age and gender and ultimately elevated atherosclerotic cardiovascular disease (ASCVD) risk [32].

There is only one known published study of CAC in CoA which retrospectively reviewed 131 repaired CoA patients with a CT coronary angiography (quantitative CAC assessment/score, n = 64) or CT chest for any indication (qualitative CAC assessment, n = 130) at a single center (mean age 46 years) and compared them to an age- and gender-matched control cohort of patients chosen from an emergency department database who received a CT coronary angiography for chest pain evaluation [35]. The overall prevalence of any qualitative CAC (≥1) in the CoA group was 28 %. Despite the matched control cohort being a chest pain symptomatic group, the CoA cohort had a significantly higher prevalence of high quantitative CAC score (≥400) compared with controls (8 % vs 2 %). While CAC was reported to be present in only a very small proportion (2 %) of patients aged <40 years at latest follow-up, this study did not review serial CT scans to determine the earliest age at which CAC may have been present which may therefore falsely underestimate the prevalence of CAC in a younger cohort.

We recently presented our retrospective review of serial CT chest scans in 93 patients with CoA or interrupted aortic arch (IAA) and compared them to a control group of repaired TOF patients, a condition with no known increased risk of ASCVD [36]. We demonstrated CoA/IAA patients were more likely to have CAC than TOF patients (22 % vs 12 %) and be younger at the time of diagnosis (median 46 years vs 54 years) despite TOF patients being older at time of latest CT scan. While our prevalence of CAC was only slightly lower than the aforementioned study [35], our cohort was much younger (mean 37 years of age at latest follow-up vs 46 years). In particular, we showed that males aged <35 years and females ≤45 years of age represented 44 % of CoA/IAA patients with CAC, highlighting that the burden of CAC in young CoA patients is potentially more prevalent than previously appreciated. We also demonstrated CoA/IAA patients with CAC were more likely to have hypertension and hypercholesterolemia than those without (78 % vs 48 %, and 28 % vs 0 %; respectively). Ultimately, further cross-sectional and/or prospective studies of CAC in repaired CoA patients are required to, firstly, confirm these findings, and, secondly, to determine if lipid-lowering therapy improves ASCVD outcomes in those with CAC.

3.4. Aortic calcification

Aortic calcification is increasingly recognized as a marker of atherosclerosis and has been shown to be associated with increased cardiovascular risk, PVD, stroke, and all-cause mortality, even beyond traditional risk factors and CAC [37–39]. There are no known published studies investigating aortic calcification in the repaired CoA population. In our recently presented retrospective review of serial CT chest scans in 93 patients with CoA or IAA, similar to our CAC findings as described above, we demonstrated CoA/IAA patients were more likely to have thoracic aortic calcium (TAC) than TOF patients (33 % vs 11 %) and be younger at the time of diagnosis (median 42 years vs 54 years) despite TOF patients being older at time of latest CT scan, with TAC also associated with both hypertension and hypercholesterolemia [36]. However, we demonstrated no difference in the prevalence of abdominal aortic calcium between CoA/IAA patients and TOF patients. Again, further cross-sectional and/or prospective studies of TAC in repaired CoA patients are required to confirm these findings.

3.5. Carotid artery disease

Carotid intima-media thickness (IMT) (cIMT) on ultrasound assessment is a well-validated surrogate marker of atherosclerosis and associated with endothelial dysfunction in the general population [10,40]. Increased cIMT, carotid plaques, and cardiovascular markers for vascular repair and apoptosis have been reported in patients with repaired CoA compared to controls, even in normotensive patients [14,16–18,27,41–43]. Increased cIMT can be seen even in children after CoA repair, suggesting that vascular changes and the increased risk of atherosclerosis is present early in life [18]. There is only one known study reporting an association between increased cIMT and cardiovascular events in 160 repaired CoA patients with a mean age of 31.7 years followed prospectively over a mean of 10 years [27]. While the overall prevalence of cardiovascular events in this young population was high (7 %), the absolute number was low (n = 11). Therefore, such statistical analyses should be interpreted with caution. Interestingly, a subsequent trial in the same group of 155 repaired CoA patients randomized to 3 years of high dose statin (n = 80) or placebo (n = 75) demonstrated no significant change in the primary endpoint of cIMT despite a significant reduction in serum cholesterol and LDL levels [44]. Conversely, baseline cIMT was significantly higher in hypertensive CoA patients compared to normotensive CoA patients, with hypertension found to be the greatest determinant for significant change in cIMT over time [44].

Furthermore, more recent studies have demonstrated that the mechanism leading to increased cIMT in repaired CoA patients appears to differ from the increased cIMT seen in non-CHD patients with CAD [42]. While concentric remodeling of the common carotid artery is seen in general CAD patients, CoA patients appeared to have increased common carotid artery lumen diameter, reduced carotid stiffness, and higher carotid strain, all of which is suggestive of eccentric remodeling [16,42]. It has been hypothesized that this differing mechanism may be due to an aorto-carotid stiffness gradient from increased aortic stiffness and decreased aortic distensibility leading to compliance mismatch at the CoA repair site and increased aortic forward flow into the common carotid artery and cerebral arteries [16]. Altered aorto-carotid stiffness gradient, with increased transmission of the aortic forward wave into the carotid artery and higher pulsatile energy in cerebral arteries, has been shown to be a predisposing factor for cerebral microvascular damage in older adults in the general population [45]. Together, these findings suggest that in repaired CoA, cIMT may not reflect an entirely atherosclerotic process but instead reflect altered hemodynamic function and/or intrinsic structural wall abnormalities and may be an unreliable marker for detecting atherosclerosis in this population.

3.6. Cerebrovascular disease and stroke

A diagnosis of CoA itself has been shown to be an independent risk factor for stroke [46–48]. The overall prevalence of stroke in the repaired CoA population has been reported to vary between 1.67 and 3.2 % depending on the study type and definition used [27,28,47]. A large Taiwanese population-based study of CHD patients aged <60 years demonstrated patients with a diagnosis of CoA to have a greater than five-fold increased risk of stroke compared to CHD patients without CoA [47]. While it is well known that there is an increased risk of intra-cranial aneurysms and hemorrhagic stroke in CoA patients, ischemic stroke remains by far the most common type of stroke suffered by CoA patients [46,47]. A recent meta-analysis demonstrated that the pooled estimated prevalence of intra-cranial aneurysms in patients with CoA to be only marginally higher than in the general population (3.8 % vs 3.2 %) and associated with hypertension [49]. A large United States population-based study of hospital admissions with a primary diagnosis of stroke showed that patients with a history of CoA suffered both ischemic and hemorrhagic strokes at a significantly younger age than stroke patients without CoA, even after accounting for traditional cardiovascular risk factors (ischemic stroke: 57 years vs 73 years, hemorrhagic stroke: 27 years vs 67 years; respectively) [46]. Unsurprisingly, hypertension is a strong independent risk factor for stroke in the CoA cohort conveying a greater than three-fold increased risk for this serious complication with potential for high morbidity and mortality [47].

3.7. Peripheral vascular disease

Few studies have investigated peripheral vascular (or arterial) disease (PVD) in repaired CoA patients. Severe atherosclerosis of the

internal mammary arteries has been reported in CoA patients particularly after late diagnosis and repair in adulthood [50]. Large retrospective cohort studies of CoA have reported a 5–13 % prevalence of PVD, significantly higher than their matched control populations (~2 %), though there was no clear definition of PVD provided [25,26]. To our knowledge, there are only two studies utilizing femoral artery ultrasound in repaired CoA cohorts with mixed results. One study demonstrated no significant difference in femoral IMT or plaques between repaired CoA patients and controls despite significantly increased carotid IMT and plaques [41]. The other study showed increased femoral and carotid IMT in repaired CoA patients compared to controls despite normal 24-h ambulatory blood pressure (ABPM) [17]. Age at repair appeared to be an independent predictor of femoral but not carotid IMT, suggesting that early repair has a greater effect on the preservation of the arterial wall in post-coarctation arteries than for pre-coarctation arteries [17]. Additionally, small aortic diameter has been associated with peripheral arterial occlusive disease in the general population [51] and it could be hypothesized that persistent arch reobstruction and hypoplasia in a repaired CoA population may further predispose to PVD. However, further research is required to determine the true prevalence and impact of PVD in the repaired CoA population.

3.8. Retinal vasculature

Ocular fundoscopy allows examination of the fundus, the only location in the body where blood vessels can be directly visualized. Though not large arteries themselves, retinal vascular changes have been associated with cardiovascular mortality, acute coronary syndrome, stroke, and endothelial dysfunction in the general population independent of traditional cardiovascular risk factors [52–55]. Furthermore, the extent and severity of retinal vessel atherosclerosis has been shown to correlate strongly with the extent and severity of CAD [54]. Historical reports of the hallmark retinal changes of corkscrew-shaped retinal arterial and retinal venous tortuosity in CoA date back to the first half of the 20th century [56,57] and have been re-confirmed in the contemporary era [57–59]. In a prospective cross-sectional study of 60 patients with repaired CoA with a mean age of 42 years, almost all patients (98.3 %) had retinal arterial tortuosity and 75 % had retinal venous tortuosity, with greater tortuosity associated with adverse cardiovascular outcomes in those ≥45 years of age [58]. This study, like others [43,59], noted a surprising absence of classical retinal hypertensive changes despite the high prevalence of known hypertension in this population [43]. However, a large cross-sectional study of 70 repaired CoA patients demonstrated that patients with resting hypertension had smaller central retinal artery and central retinal vein dimensions compared with those without hypertension [43]. Retinal arterial narrowing is associated with an increased risk of adverse cardiovascular outcomes in the general population and may even precede the development of hypertension [52–55]. Further research is required to determine if retinal fundoscopy and imaging may detect subclinical hypertension and atherosclerosis in repaired CoA.

4. Optimizing long-term cardiovascular health in CoA

There are multiple potential intersecting factors predisposing to endothelial dysfunction, vascular abnormalities, and atherosclerosis in repaired CoA (Fig. 1). While little can be done about non-modifiable factors and treatment-related factors should be considered, it is likely that the key to minimizing long-term cardiovascular complications in this high-risk group lies in the optimization of all modifiable risk factors in all patients.

4.1. Non-modifiable factors

Unsurprisingly, similar to the general population, male sex and older age were associated with CAD in repaired CoA [26]. CoA can often be

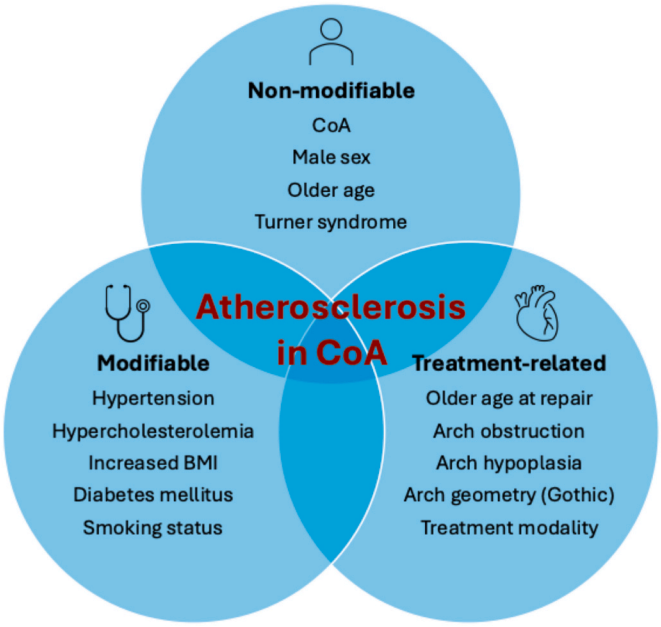

Fig. 1. Potential factors contributing to the development of atherosclerosis in repaired coarctation of the aorta.
BMI, body mass index; CoA, coarctation of the aorta.

associated with genetic syndromes which carry increased risk of ASCVD. At least 12 % of girls born with CoA have karyotype-confirmed Turner syndrome (XO) [60] and 7–15 % of patients with Turner syndrome have CoA [61,62]. There is a higher underlying predisposition to cardiometabolic disorders such as hypercholesterolemia, type II diabetes mellitus, and obesity in Turner syndrome [63]. Patients with Turner syndrome have a mortality rate three times higher than the general population mainly due to complications of cardiovascular disease [64]. Therefore, patients with CoA and Turner syndrome are at particularly high cardiovascular risk.

4.2. Treatment-related factors

4.2.1. Age at repair

Given that unrepaired CoA is likely to lead to altered aortic flow hemodynamics and structural wall changes as described above, it is unsurprising that older age at CoA repair is associated with greater endothelial and vascular dysfunction, and early repair appears to preserve arterial elasticity [13,17,18]. Older age at repair has been consistently demonstrated to be an independent risk factor for late mortality, particularly due to premature CAD [4–6]. However, these studies include only or predominantly a large proportion of patients operated in older eras, and CoA patients in the contemporary era are now offered repair much earlier in life due to advances in diagnostics and interventions. Nonetheless, despite early repair, endothelial dysfunction and vascular wall changes persist [13,17,18]. This suggests that CoA has a very early, possibly in utero, impact on the development of these abnormalities.

4.2.2. Arch geometry

Arch geometry, whether native or post-surgical, has been proposed as a contributor to hypertension and endothelial dysfunction. Studies with 4-dimensional cardiovascular magnetic resonance (CMR) imaging have demonstrated more abnormal helical flow in an angulated or Gothic arch compared to an ideal semicircular rounded Romanesque arch [21]. One center reported an association between a Gothic arch and hypertension as well as with endothelial dysfunction in repaired CoA patients [65,66]. However, others have not shown an association

between arch geometry, curvature, or torsion and hypertension or with endothelial function in repaired CoA patients and propose that aortic caliber may be more important for vascular load than shape or other geometric parameters [19,67]. Interestingly, aorta size mismatch between the ascending aorta and descending aorta on CMR imaging has been shown to be negatively correlated with VO2 max and exercise capacity [68].

4.2.3. Arch obstruction and arch hypoplasia

Arch obstruction, whether due to native CoA or recoarctation, and persistent arch hypoplasia may both cause a pressure gradient across the narrowed isthmus or arch, respectively. The increased pressure upstream not only contributes to systemic hypertension but also to turbulent flow and a reduction in wall shear stress on the vascular endothelium. Even a mild residual pressure gradient (>16 mmHg) across the previous CoA repair site has been shown to be associated with significantly more impaired endothelial function compared to patients without any pressure gradient [18]. Repaired CoA patients were twice as likely to develop late hypertension for every 1.0 m/s increase in maximum descending arch velocity on echocardiography compared to patients without an arch gradient [69].

It has been previously demonstrated that CoA patients with an associated hypoplastic arch treated with conventional CoA repair via thoracotomy had adequate growth of the hypoplastic distal transverse arch (between the left common carotid and left subclavian arteries) but the proximal transverse arch (between the brachiocephalic and left common carotid arteries) remained hypoplastic in a third of patients at long-term follow-up [70]. More extensive surgical techniques such as end-to-side anastomosis via sternotomy approach to adequately bypass and address arch hypoplasia have demonstrated low rates of hypertension after 20 years of follow-up [71].

Therefore, it is imperative to adequately address arch hypoplasia at the time of CoA repair and to maintain a low threshold to relieve any arch reobstruction during follow-up.

4.2.4. Treatment modality

Successful CoA repair is traditionally regarded as an optimal anatomical result with no residual arch obstruction and relief of hypertension. Endovascular stenting is increasingly utilized as the first treatment option for CoA in adults and older children [72,73]. However, it is well known that there is a high rate of arch reobstruction and need for reintervention following CoA stenting [74,75]. Arterial stent implantation can alter the compliance of the vessel [76]. While ascending aorta distensibility on CMR imaging increased following CoA stenting compared to pre-stenting [77], this may only be relative compared to other treatment modalities [78,79]. A multicenter cross-sectional study comparing vascular function in 75 CoA patients treated with surgery (n = 28), balloon dilatation (n = 23), or stenting (n = 24) demonstrated a significant difference in proximal aortic stiffness and distensibility on CMR imaging between treatment groups with stiffness highest and distensibility lowest in the stenting group and stiffness lowest and distensibility highest in the balloon dilatation group (surgical group being the intermediate), though no other significant differences including in endothelial function, aortic dimensions, or hypertension were reported [78]. However, other CMR imaging studies demonstrated no significant difference in aortic distensibility nor other similar parameters between CoA patients treated with surgery compared to stenting [79]. Further prospective long-term studies are required to determine the impact of different treatment modalities on anatomical and vascular outcomes.

4.3. Modifiable factors

Large retrospective cohort studies report significantly higher rates of traditional cardiovascular risk factors in repaired CoA patients compared to the general population and to other forms of CHD including hypertension, hypercholesterolemia, increased body mass index, diabetes mellitus, and smoking status [3,25,26,80]. A large population-based study of cardiovascular risk factors in 13,896 CHD patients demonstrated patients with a diagnosis of CoA to be associated with a higher overall risk factor burden compared to other forms of CHD with ≥1 risk factor seen in 70 % of CoA patients and ≥2 risk factors in 40 % of CoA patients after age- and gender adjustment [80]. We previously reported a significant increase in obesity in our Australian ACHD population within less than a decade such that over half of adults with repaired CoA were considered to be overweight or obese at latest follow-up [81].

As we report above, these modifiable risk factors, particularly hypertension, have been implicated in the development of endothelial dysfunction, vascular wall abnormalities, and atherosclerosis. The European Society of Cardiology (ESC) Working Group on ACHD recently published a 2023 clinical consensus statement on acquired cardiovascular disease in adults with CHD including proposed screening and management [82]. The remainder of this review will focus on hypertension and hypercholesterolemia in repaired CoA.

4.3.1. Hypertension

It is well known that there is a high prevalence of late hypertension after CoA repair which has been closely linked to mortality at a young age [3,4]. Late hypertension has been reported in 8–75 % [19,83,84] of patients with repaired CoA using office blood pressure measurements and in 28–61 % of patients using 24-h ABPM [20,43,69,85–88]. The large variation in prevalence is likely due to the definition of hypertension utilized, the length of follow-up, and the age of the cohorts. However, while hypertension is often described as being late after repair, a concerning number of children and adolescents may develop hypertension [20,87]. A cross-sectional study of 41 children with CoA repair demonstrated half of patients had hypertension or pre-hypertension on 24-h ABPM and over 10 % had a peak exercise systolic blood pressure >200 mmHg [20].

The mechanism leading to the development of hypertension after CoA is likely multifactorial. While arch reobstruction is an important mechanistic risk factor for hypertension, only a third of patients with hypertension may have arch reobstruction [69], indicating that there must be other factors in its development. Neurohormonal factors such as increased muscle sympathetic nerve activity and impaired baroreflex blood pressure control, arterial wall abnormalities, endothelial dysfunction, and genetics have all been implicated in the development of hypertension in patients with repaired CoA [12,89]. Pulse wave velocity, a well-validated marker of arterial stiffness, has been reported to be significantly higher in CoA patients who were hypertensive on exercise-testing (>200 mmHg) compared to normotensive patients with a trend towards significance in patients who were hypertensive on 24-h ABPM [20]. These findings emphasize the vicious cycle of hypertension and vascular dysfunction in CoA patients, and ultimately predisposing this high-risk group to the development of atherosclerosis and associated sequelae.

Screening for hypertension should occur at least yearly with measurements on the right arm and lower extremity taken at every clinical visit. Patients should also be encouraged to self-measure right arm blood pressure at home. The latest 2018 American Heart Association (AHA)/American College of Cardiology (ACC) [72] and 2020 ESC ACHD guidelines [73] both recommend 24-h ABPM to detect or confirm arterial hypertension though only the ESC guideline provided a definition for this (24-h mean systolic >130 mmHg and/or diastolic >80 mmHg). Interestingly, poor inter-device reproducibility of 24-h ABPM devices between different manufacturers in repaired CoA patients have been reported suggesting that patients should undergo serial 24-h ABPM using the same manufacturer where possible, and device-specific reference values may be required to ensure reliable 24-h ABPM interpretation [90]. No additional blood pressure targets are specified in either the AHA/ACC or ESC guidelines with both recommending that medical

treatment should follow general guideline directed medical therapy. However, the more recently published 2023 ESC Working Group on ACHD clinical consensus provided a recommendation to consider a lower threshold for intervention to aim a blood pressure <120/80 mmHg in CoA [82]. However, the reasoning for this target was lowering aortic dilatation and rupture risk rather than for ASCVD and based on expert opinion rather than on evidence. Further research is required to determine the optimal blood pressure target and management in CoA.

4.3.2. *Hypercholesterolemia*

The association between abnormal lipid profile and the development of atherosclerosis is well known. Elevated LDL, low high-density lipoprotein (HDL), and, more recently, elevated lipoprotein(a) levels have been implicated in the development of atherosclerosis [91]. Large retrospective cohort studies of CoA have reported a 4–31 % prevalence of hypercholesterolemia and was significantly higher than their matched control populations (2.4–24 %) [25,26]. Despite a similar patient age across both studies (mean 31–36 years), the large variation in the reported prevalence is likely related to the lack of a clear definition of hypercholesterolemia provided in either study. The largest known study of 160 patients with repaired CoA involving measurement of lipid profile demonstrated elevated total cholesterol levels (≥5.18 mmol/L or 200.3 mg/dL) in 31 %, elevated LDL levels (≥3.0 mmol/L or 116 mg/dL) in 36 %, and decreased HDL levels (≤1.2 mmol/L or 46.4 mg/dL) in 71 % of patients at only a mean age of 31 years [27]. However, there is increasing evidence that optimal LDL levels should be lower than the cut-off used in this study, particularly in those with intermediate or greater ASCVD risk [92]. In a retrospective study investigating incidental CAC in repaired CoA patients with a mean age of 46 years, the median ASCVD 10-year predicted risk score using the 2013 ACC/AHA pooled risk equations in repaired CoA patients aged ≥40 years was 8 % and was higher than the 5 % reported in the control group consisting of patients presenting to an emergency department with chest pain [35]. Furthermore, the mean LDL level in the CoA group aged ≥40 years was 99.2 mg/dL (2.6 mmol/L). These results indicate that more than half of repaired CoA patients were at intermediate ASCVD risk (≥7.5 %) and individuals with an LDL level ≥70 mg/dL (1.8 mmol/L) may have warranted statin therapy [92]. Unfortunately, a repeated ASCVD risk score was not performed following the CAC results to understand the utility of CAC in re-stratifying ASCVD risk in CoA. However, given the high prevalence of reported CAC in the study (46 % in CoA patients aged ≥40 years), it seems intuitive that more CoA patients would be stratified up rather than down in risk. Furthermore, ASCVD risk was not able to be calculated in those <40 years of age at the time of the study with the since updated ACC/AHA calculator now incorporating age down to 20 years. While it may seem aggressive to initiate statin therapy for younger patients, such as those with repaired CoA, there is increasing understanding that low LDL throughout life will minimize lifetime risk of ASCVD [93]. Consequently, the latest 2021 ESC guidelines acknowledge that while 10-year ASCVD risk in relatively young (<50 years) apparently healthy people is generally low even in the presence of significant risk factors, the lifetime ASCVD risk in this scenario is very high [94]. Thus, these guidelines recommend 10-year ASCVD risk ≥7.5 % (using the ESC-created Systemic Coronary Risk Estimation 2 (SCORE2) risk calculator) to be considered very high risk (given high lifetime risk) and a risk of 2.5 to <7.5 % considered high risk in the young [94].

To date, neither the 2018 AHA/ACC nor 2020 ESC ACHD guidelines include any recommendations on lipid screening or management in CoA [72,73]. However, the 2023 ESC Working Group on ACHD clinical consensus on acquired heart disease in ACHD provide one expert consensus statement for CoA suggesting that they may benefit from stringent lipid control, and otherwise should follow the general screening and management recommendations provided for all ACHD patients [82]. Further large cross-sectional and prospective studies to determine the true impact of hypercholesterolemia in repaired CoA patients are warranted.

5. Conclusions

Patients born with coarctation of the aorta are at significantly increased risk for accelerated atherosclerosis and sequelae, affecting coronary, cerebrovascular, and peripheral arteries, even following successful repair. This increased risk is primarily driven by long-standing hypertension associated with endothelial dysfunction and abnormal vasculature as well as a high prevalence of other traditional cardiovascular risk factors. Further research is required to determine the markers and diagnostic tools most predictive for atherosclerosis and cardiovascular events in CoA in order to develop effective prevention and management strategies to reduce ASCVD burden and mortality in this high-risk population. Lifelong stringent surveillance and aggressive management of all modifiable risk factors are crucial in reducing the long-term impact of atherosclerosis and sequelae in CoA patients.

CRediT authorship contribution statement

Melissa G.Y. Lee: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft. **Phillip S. Naimo:** Data curation, Writing – review & editing. **Anoop N. Koshy:** Writing – review & editing. **Edward Buratto:** Writing – review & editing. **William M. Wilson:** Writing – review & editing. **Leeanne E. Grigg:** Writing – review & editing. **Subodh B. Joshi:** Writing – review & editing. **Katherine M. English:** Supervision, Writing – review & editing.

Disclosures

None.

Funding

Dr Melissa Lee is supported by a National Health and Medical Research Council (NHMRC) Medical Research Future Fund (MRFF) Investigator Grant (1197307), the 2024 RACP/Foundation for High Blood Pressure Research Establishment Fellowship (2024REF046), and an Avant Member Microgrant. Dr Anoop Koshy is supported by a NHMRC Investigator Grant.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Melissa G. Y. Lee reports financial support was provided by National Health and Medical Research Council. Melissa G. Y. Lee reports financial support was provided by The Royal Australasian College of Physicians. Melissa G. Y. Lee reports financial support was provided by Avant Mutual Group Ltd. Anoop N. Koshy reports financial support was provided by National Health and Medical Research Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

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