Aortic coarctation: late complications and treatment strategies
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Chapter 16

Future perspectives
Advances in paediatric cardiovascular surgery and medicine have shifted mortality as a result of congenital heart disease (CHD) both in infancy and adulthood.\textsuperscript{1,2} Due to improved survival this population is steadily growing in number and age. Little is known about long term survival, but late complications occur frequently. Life expectancy in patients after coarctation repair (CoA) remains diminished despite early detection and both catheter-based and surgical interventions.

Part I
To date there is a wide variety of treatment options in CoA involving surgical approaches and percutaneous treatment modalities including balloon angioplasty and stent repair. Traditional treatment in CoA, consists of open surgical repair which is still the treatment of choice in infants and in children beyond the neonatal period. However due to the development of significant collateralisation through intercostal arteries these patients remain at increased surgical risk due to bleeding complications. Older patients remain at increased risk of paraplegia (0.1-5%), an increased peri-operative mortality and an increased long-term risk of residual or recurrent coarctation, aortic aneurysm formation and hypertension.\textsuperscript{3}

Catheter-based approaches have been developed in an effort to reduce the risk for surgical complications and to shorten procedural recovery times.\textsuperscript{6,7} Balloon angioplasty is the treatment of choice in children with recoarctation, and currently available immediate results in native coarctation are similar with regard to gradient reduction as compared to surgery.

Stent implantation has shown excellent short-term results in both children beyond infancy and in adults with native coarctation. Moreover, stent repair is currently the mainstay of percutaneous treatment in adults with native and recurrent coarctation, as it prevents vessel elastic recoil and reduces the need for reinterventions in the future.\textsuperscript{9} Covered stents are currently recommended as first line intervention in endovascular management of aortic coarctation in various clinical conditions such as; native aortic coarctation, stent fracture and recoarctation and aneurysm formation after both surgical and percutaneous procedures.

Data with regard to the periprocedural risks and the intermediate complications such as aneurysm formation and the need for reintervention are now available. However, data with regard to long-term outcome after percutaneous treatment strategies are scarce. Adequate clinical surveillance by CT or MRI is therefore necessary in all patients, both for the individual patient as for the overall assessment of long-term outcome after the various treatment modalities.

Future studies should focus on the long-term follow-up for aortic complications, morbidity and mortality after each of the available treatment strategies. Moreover, a recently published Cochrane review demonstrated that data from randomized trials were not available to compare surgery and stent repair, which emphasize the need for randomized data to compare different treatment strategies.\textsuperscript{7} Future advance in coarctation stenting might be the use of bioabsorbable stents a new promising technique in the setting of coarctation stenting.\textsuperscript{8} This revolutionary technique may enable the use of stent treatment in infants and still prevent the need for redilatation in a growing child.\textsuperscript{9,10}
Part II
Our understanding of CoA has significantly changed in the last decades. This discrete narrowing of the descending aorta was first perceived as a local abnormality, but appears to be a more complex lesion. The complexity comprises widespread vascular abnormalities, significant end-organ damage after repair, and accelerated atherosclerosis. As a consequence aortic aneurysm formation, systemic hypertension, stroke, sudden cardiac death and heart failure account for the majority of premature death even after successful repair.\(^1\)\(^2\) The care for coarctation patients remains challenging due to the wide variety of late morbidity and mortality. Given the complexity and the adverse outcome in CoA patients, new therapeutic strategies aiming at reducing global cardiovascular risk need to be investigated.

This thesis demonstrates for the first time that 3 year treatment with high dose statins did not affect CIMT progression and the risk for future cardiovascular events during follow-up, despite a decrease in total cholesterol and LDL levels. Although our study did not support a role for statin therapy in CoA, the increased prevalence of CAD as reported by Roifman et al. might suggest a possible role for statins as primary prevention. These data are supported by the fact that a recent study demonstrated that 4 weeks treatment with Atorvastatin significantly improved endothelial function and decreased levels of pro-inflammatory cytokines.\(^12\)\(^13\) Future studies are needed to assess the role of statin therapy as primary prevention in CoA.

Besides the limited effect of statin therapy on CIMT progression, this thesis demonstrates that hypertension is the strongest determinant for the change in CIMT over time. Therefore, treatment of hypertension seems the most important target to reduce cardiovascular risk in CoA patients in the future. Persistent or recurrent hypertension is one of the major concerns in CoA, as one of the most important contributing factors to the increased cardiovascular risk.\(^3\)\(^14\)\(^16\) Factors contributing to systemic hypertension are numerous such as a diminished arterial wall compliance, reduced baroreceptor sensitivity or residual aortic gradients which makes treatment challenging. Considering anti-hypertensive treatment strategies in CoA, literature assessing which of the various classes of anti-hypertensives offers the best blood pressure control in CoA remains scarce. The 2008 ESC guidelines recommend ß-blockers, angiotensin conversing enzyme inhibitors (ACE) and angiotensin II receptor blockers (ARBs) in patients with significant hypertension in CoA.\(^17\) Data comparing the effects of ß-blockers, ACE inhibitors and ARBs on blood pressure control are scarce in CoA.\(^38\) In recently published randomized crossover trial 4 weeks treatment with ramipril demonstrated a significant improvement of endothelial function and a reduction of the expression of the proinflammatory cytokines. Whether the use of anti-hypertensive agents such as ramipril should be initiated for normotensive patients needs to be addressed in larger trials.\(^19\) Future trials are needed to evaluate the effect of blood pressure lowering therapy on end organ damage and clinical outcome, as it seems the most important contributor for future cardiovascular risk in CoA.

Endovascular renal artery sympathetic denervation is a novel, minimally invasive therapy for patients with resistant hypertension.\(^20\) Recently one case-report has been published in which the effect of renal denervation was performed in a patient after coarctation repair with resistant hypertension. In this case-report a positive effect of renal denervation was observed.\(^21\) These results bare the hope that this minimally invasive technique might extend the currently very limited treatment options against hypertension in patients after successful coarctation repair in the future.
Early recognition of CoA patients at increased cardiovascular risk is very important. Proinflammatory cytokines and adhesion molecules which have been demonstrated to play an important role in atherogenesis might serve as an important clinical tool to identify patients at increased cardiovascular risk as well as a new therapeutic target in cardiovascular risk management. Increased levels of pro-inflammatory cytokines such as IL-6, and adhesion molecules (sVCAM-1 and sICAM-1) which cause endothelial dysfunction and play an important role in the development of atherogenesis have been found in CoA. Previous studies have shown that increase in levels of pro-inflammatory cytokines and adhesion molecules in CoA are caused by the dysfunctional vascular wall. Proinflammatory cytokines such as IL-1β and IL-6 activate the synthesis of acute-phase proteins such for example CRP in the liver and induce the up-regulation of the expression of adhesion molecules on the endothelial surface (such as VCAM-1). It is well known that the soluble forms of these adhesion molecules such as sVCAM-1 seem to have a predictive value in cardiovascular risk assessment. However the role of these pro-inflammatory cytokines and adhesion molecules as a tool to predict cardiovascular risk in CoA patients is unknown. Early identification is important to reduce long-term cardiovascular morbidity and mortality in CoA. Therefore, future studies are needed to evaluate the role of these biomarkers as tool for early identification of CoA patients at increased cardiovascular risk.

In the past few decades, genetic studies in humans have identified genes that are causative in various forms of inherited and sporadic congenital heart diseases. In CoA most cases are sporadic; however, there is a clear genetic component, with congenital heart disease occurring in almost 4% of offspring of women with CoA. Moreover there is a five-fold increased risk of bicuspid aortic valve (BAV) in first-degree relatives of children with left heart obstructive lesions such as CoA, aortic valve stenosis and hypoplastic left heart syndrome. Previous linkage analyses in 289 individuals in 43 families of children with left heart obstructive lesions have unravelled a genetic susceptibility locus on chromosomes 2p23, 10q21 and 16p12 which demonstrates that there might be a common genetic cause. Although genetic data are currently used as a research tool, it is inevitable that genetic studies will have an important role in determining prognosis in patients after coarctation repair. Genetic data will be important in determining the risk of future transmission of congenital heart disease to offspring of CoA patients. Moreover, these data might help to identify patients at increased risk for cardiovascular complications, which might enable individualized cardiovascular risk management in CoA patients in the future.
Reference List


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