Advances in the management and surveillance of patients with aortic coarctation
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Chapter 1

Introduction and outline of the thesis

Adapted from:
Advances in the management and surveillance of patients with aortic coarctation

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Chapter 1

1. Outline of the thesis

Surgical repair has long been the only type of management available for coarctation of the aorta, since the first coarctectomy was performed in 1945. Balloon angioplasty was introduced as an alternative type of management for selected patients in the 1990s. The aim of this thesis was to evaluate the long-term results of invasive management of this condition by various techniques at various ages, in order to assess preoperative and peroperative predictors of long-term outcome and to subsequently compare these results between different techniques. The purpose thereof was to define the proper indication for these types of intervention. Long-term study findings indicated ongoing risk of arterial hypertension, recoarctation and aneurysm formation, despite initial success of management. To elucidate whether the clinical condition of these patients was associated with unfavourable vascular characteristics, aortic flow properties of such patients were compared by various techniques and compared to matched controls. The studies of this thesis, included in chapters 2 to 9, are introduced in this chapter. Chapter 10 summarizes all studies and discusses future perspectives of additional research.

2. Diagnosis, incidence and genetics of aortic coarctation

Coarctation of the aorta is defined as a hemodynamically significant narrowing of the descending thoracic aorta, usually just distal to the left subclavian artery where the ligamentum arteriosum originates. The local stenosis can be associated with isthmus hypoplasia, defined as isthmus diameter (portion of the aorta between the left subclavian artery and the patent ductus or ligamentum arteriosum) of less than 40% of the diameter of the ascending aorta and/or associated arch hypoplasia, defined as a proximal or distal transverse arch diameter less than 60% or 50% respectively of the diameter of the ascending aorta. Aortic hypoplasia will facilitate the diagnosis to be made in infancy, whereas the isolated type of coarctation can have an asymptomatic course and can be missed in hypertensive subjects. The incidence of coarctation is about 4/10,000 live births, constituting 7% of moderate and severe forms of congenital heart disease. Among other left ventricular outflow tract malformations, coarctation of the aorta has substantial evidence for a genetic component. The relative risk for first-degree relatives in this group was 36.9, with a heritability of 0.71-0.90. Data support a complex but most likely oligogenic pattern of inheritance.

3. Pathophysiology & role of exercise

The altered hemodynamics of coarctation are characterized by a disturbed cushioning function of the aorta and the upper body arteries, while the conduit function of the arterial system is preserved by collateral vessels. Unusually high-pressure fluctuations
are generated in the proximal aorta and upper body arteries by normal left ventricular ejection. Changes in the contour of the arterial pressure wave in aortic coarctation have been demonstrated in both experimental, acute coarctation  and patients. As a result of repeated high pulsatile stresses, degenerative changes are found in the aorta and proximal arteries. These changes are similar to those seen with aging and hypertension, but occur at a much earlier age. The arterial degeneration and cardiac hypertrophy that result from coarctation are therefore not explained on the basis of longstanding essential hypertension of equal severity. The presence of coarctation per se is now generally considered as an indication for invasive management, which is not influenced by coexisting hypertension. Although surgical repair and angioplasty are advocated and performed as soon as the diagnosis is made, arterial damage and dysfunction are found in long-term follow-up of patients in whom coarctation had been repaired at infancy. This finding led to the suggestion that coarctation may be a manifestation of a generalised vascular abnormality, constituting a diffuse cardiovascular disease. Exercise plays a crucial role in the assessment of patients with both native, uncorrected coarctation and with invasively managed coarctation. Aortic impedance was used to calculate that, with mild supine exercise in a 9-year-old-patient, a pressure wave with an amplitude of 135 mmHg and a peak systolic pressure of over 230 mmHg in the ascending aorta are generated. Taylor and Donald demonstrated dramatic increases in brachial artery pressure that occur during exercise in patients with aortic coarctation. In addition, these pressures exceed those seen in patients with severe essential hypertension, with values for which urgent therapy and restriction of activity would be considered. The same authors stress the usually asymptomatic, although potentially damaging, nature of these pressure changes, which occur with moderate exertion only. As was recently pointed at by Vriend et al., a hypertensive reaction on exercise is found in a considerable number of post-coarctectomy patients (20-35%) who are normotensive at rest. This finding could not be explained by significant residual aortic stenosis in several studies. Although attributed to abnormalities in aortic arch geometry, to primary baroreceptor alteration and to persistent structural and functional abnormalities of the arterial system proximal to the former coarctation, the exact mechanism of this phenomenon is not yet fully understood. Nevertheless, it seems clear that, whether determined by anatomy exclusively or influenced by neurohumoral factors also, clinical assessment and definition of a “successful” coarctation repair should take place in the context of both the patient’s resting studies and of functional exercise response, as has been advocated before. Blood pressure gradient between upper and lower extremities exceeding 20 mmHg has been a widely used indicator of recoarctation. However, it has been shown that after coarctation repair, the arm–leg blood pressure difference may not represent the hemodynamic significance of restenosis. Echocardiographic measurements have been investigated as indicators of restenosis subsequently. Although highly specific, the detection of angiographically significant recoarctation by a peak systolic gradient exceeding 40 mmHg, assessed echocardiographically, yields a
relatively low sensitivity in children.\textsuperscript{21} This figure could not be improved to more than 80\% by diastolic measurements, including peak diastolic gradient and maintenance of flow in diastole. Recently, MR criteria have been proposed as more accurate measures of recoarctation.\textsuperscript{21} The possible mechanisms in the process of recoarctation related to different surgical techniques consist of inadequate growth of the anastomosis, active fibrosis and narrowing at the anastomotic site, thrombosis at the suture line, and retention of abnormal, possibly ductal, tissue.\textsuperscript{24} Localised recoarctations following angioplasty, located at the site of the former coarctation ridge, may be caused by the impossibility to remove this material by this technique.

\section*{4. Invasive management by surgical repair or angioplasty}

Data on the natural history of coarctation have become scarce,\textsuperscript{25,26} since various types of management have become available and proved successful after Crafoord’s publication of surgical treatment of coarctation in 1945.\textsuperscript{27} The rationale of detection and early repair of coarctation is the significant mortality in untreated patients, in whom survival seems to be as low as 10\% at the age of 50 years.\textsuperscript{25} It has been recognised for many years however, that coarctation repair cannot prevent an increased risk of premature mortality. A mean life expectancy of only 38 years of age has been reported in patients who underwent repair in late childhood or young adult life.\textsuperscript{10,28} Nevertheless, even at older age treatment of coarctation seems to be beneficial by lowering blood pressure and probably reducing cardiovascular events.\textsuperscript{29-32} Surgical correction has been the only available treatment of coarctation until balloon angioplasty was introduced in 1982 by Lock et al.\textsuperscript{33} Surgery is widely accepted and applied for coarctation management at the current time, especially in neonates and small infants, since frequently associated arch and/or isthmus hypoplasia render these lesions less favourable for transcatheter interventions.\textsuperscript{34-37}

\subsection*{4.1. Surgical techniques}

Throughout the years several surgical techniques for the repair of coarctation have been applied. Literature on these techniques has focused on various early and late outcome variables following these techniques. These outcomes, discussed consecutively, comprise operative mortality, recoarctation, aneurysm formation and persistent systemic hypertension.

\textbf{Mortality}

Postoperative death is generally related to the presence of associated cardiac lesions.\textsuperscript{38-40} Reported actuarial survival probabilities at 5 years range from 80\% to 98\% in isolated coarctation, from 62\% to 94\% for patients with associated VSD and from 15\% to 60\% for those with associated complex cardiac anomalies.\textsuperscript{38-40} Different strategies have been advocated to reduce mortality in the latter group of patients. The one-stage
repair was reported to be a safe and effective approach in the preceding decade, \textsuperscript{38} but has not clearly been proven to be favourable by others.\textsuperscript{41}

**Recoarctation**

The primary focus in most studies investigating risk factors for recurrent arch obstruction after early coarctation repair is the relationship between the technique of repair and recoarctation. The type of surgical repair may influence the prevalence of residual or recurrent coarctation by incomplete resection of ductal tissue, suture material and the width of the anastomosis. The possible mechanisms in the process of recoarctation related to these surgical factors consist of inadequate growth of the anastomosis, active fibrosis and narrowing at the anastomotic site, thrombosis at the suture line, and retention of abnormal, possibly ductal, tissue.\textsuperscript{24} In the absence of a large, randomized study, superiority of one technique over another is less likely to be demonstrated. On the whole, studies demonstrate no difference in recoarctation incidence between resection and end-to-end anastomosis and subclavian flap repair,\textsuperscript{39-40} although the probability of recoarctation appears to be higher after simple patch aortoplasty, when patch material was Dacron or is unspecified.\textsuperscript{41,42} To investigate the differences between surgical techniques more thoroughly, long-term results of polytetrafluoroethylene (PTFE) patch aortoplasty and end-to-end anastomosis for coarctation of the aorta in the Wilhelmina Children's Hospital were evaluated for a period up to 28-year of follow-up. Predictors of long-term outcome, including age at surgery, associated cardiac defects and type of surgical technique used, were focused on. The results are included in chapter 4.

A younger age has been suggested to predispose to recoarctation following PTFE patch repair.\textsuperscript{43} The age at operation has been found to be strongly related to the development of recoarctation.\textsuperscript{24,44} In contrast, the risk of persistent systemic hypertension seems to be related to age in an inverse manner. Brouwer and associates determined the optimal age for elective aortic coarctation repair, for the infant with isolated aortic coarctation who is symptom-free, to be 1.5 years.\textsuperscript{45} The risk for recoarctation drops rapidly and levels off at 1.5 years of age and the risk for late hypertension and premature death increases progressively after that age range.\textsuperscript{10,45} It has been pointed out that the age of 1.5 years may be rather conservative, since recoarctation rates drop below 5% in current surgical experience with repair performed at age < 1 year,\textsuperscript{46} and chronic hypertension developing in as much as 60% of patients thereafter in other studies.\textsuperscript{47} The combination of residual ductal tissue and diminished aortic wall compliance are responsible for the occurrence of late hypertension in this group. These phenomena may also play a role in recoarctation, in long-term follow-up. This may explain the disproportional hazards for recoarctation that were found after 5 years following different types of repair.

Several reports demonstrated that the anatomy of the aortic arch was a predictor of reintervention for recurrent obstruction after repair.\textsuperscript{14,45,48} The question can be raised how this finding should direct optimal surgical treatment. A conservative approach towards the hypoplastic arch seems to be justified in most cases, since Siewers et al. have suggested that when the ratio of transverse aortic arch to ascending aorta
exceeds 0.25, the arch can be expected to grow normally without obstruction and that extended resections should be reserved for those with ratios less than 0.25.49 Follow-up should consequently be directed towards early detection and management of recoarctation in these patients.

Aneurysm formation
Aneurysms have been encountered following all surgical techniques described. The interval from repair to aneurysm formation can vary from 2 to more than 30 years, thereby warranting a lifelong follow-up.50 The risk of aneurysm formation seems especially high following patch aortoplasty, incidence varying between 2% and 51%,51-53 both using Dacron54-55 and, to a lesser extent, PTFE-material.43 To illustrate these figures, a patient with an aortic aneurysm, detected 25 years after Dacron patch aortoplasty for native coarctation, is presented in chapter 6. In addition to the material being used, a factor of influence in performing patch aortoplasty seems to be excision of the coarctation ridge. This was associated with aneurysm formation in experimental and clinical series.54,56 The relation between age and development of aneurysms seem to be less strong than for recoarctation and appears to be inverse, as far as patch aortoplasty is concerned. Prosthetic patch aortoplasty is discouraged especially in adolescence and adulthood, because high incidence of aneurysm formation was found with advanced patients’ ages. Tubular interpositioning grafting and patch aortoplasty using autogenous arterial wall are proposed as viable alternatives.52,57,58 Arch hypoplasia is demonstrated to be another risk factor for aneurysm formation, although the surgical technique applied, may also play a role here. Bogaert et al. have identified transverse arch hypoplasia as a condition being highly related to aneurysm formation following patch aortoplasty.59 They suggest that narrowing of an aortic segment leads to blood flow acceleration and poststenotic turbulence, which may induce aneurysm development in the distal aortic segments. Since aneurysm formation has been encountered following resection and end-to-end anastomosis,60 in which the coarcted segment is fully resected and no “abnormal” patch material is present, wall abnormalities by themselves cannot be (solely) responsible for aneurysm formation, despite statements in several reports.52,56,60 Abnormal flow patterns originating in a concomitant hypoplastic arch may have a similar influence on resection and end-to-end anastomosis and patch aortoplasty.59

Persistent systemic hypertension
The occurrence of persistent systemic hypertension is strongly influenced by age at repair, varying between 10-60% depending on duration of follow-up, hypertension rates increasing at longer follow-up.10,28,45 Late hypertension can even occur despite early repair, as was demonstrated in patients repaired at age 2-3 months, of whom 28% was hypertensive at rest at 7-16 years of follow-up.13 Persistent systemic hypertension therefore cannot be prevented completely by early repair. It is neither explained satisfactorily by the presence of residual aortic arch gradients, which is only found in a minority of hypertensive patients.11 As was pointed out in the section on recoarctation before, the risk for recoarctation appears to drop rapidly
at or even below 1.5 years of age and the risk for late hypertension and premature
death increases progressively after that age range. Cure of hypertension (patients
no longer requiring any medication to treat hypertension) was reported in a review
of 6 series of adult patients in 13% to 76% (mean 64%). The one series with the
lowest cure rate (13%) was in a significantly older cohort of patients with a mean
age of 54 years. The type of repair could play an additional role in the occurrence of
postoperative hypertension. Patch aortoplasty involves less resection of ductal tissue,
compared to resection and end-to-end anastomosis, which may induce persistent
hypertension. On the other hand, circumferential anastomosis is not involved in this
type of surgery, which may be beneficial by preserving aortic wall compliance.

4.2. Angioplasty
Since 1982, balloon angioplasty for coarctation has been added as a viable alternative
to surgery for treatment of coarctation and is currently considered as a safe and effective
treatment. It was performed as the primary treatment of coarctation of the aorta
in 30 children, managed for this condition in during a period of 10 years from its
introduction in the Wilhelmina Children’s Hospital in 1990. Chapter 2 describes the
results. Angioplasty for coarctation has been used as treatment for both children and
adults. Successful stenting of native coarctation was first described in an infant with
hypoplastic left heart syndrome in 1993. Implantation of stents in older children
and adults in whom the aorta size has attained adult size is not problematic, but it
may be problematic in infants and children, whose aorta is not totally developed. In
practice, the indications for stent implantation are not clearly defined yet. Possible
indications are long segment coarctation and tortuous coarctation. Practically, two
possible mechanisms of recurrence include elastic recoil of tissue after angioplasty
and the presence of long segment narrowing. Stents provide support to recoil of the
dilated segment. In addition, the stents used for coarctation were designed to provide
a framework for endothelial cell growth and, perhaps, reduce the complication of
aneurysm formation. Although stenting may protect against immediate recoil, this
effect may be counterbalanced by intimal hyperplasia, leading to recurrence during
follow-up. In-stent restenosis due to intimal proliferation within the stent, stent
fracture, or stent recoil indeed was encountered in an intermediate follow-up study
of 578 patients from 17 institutions. Apart from the specific types of endovascular
or surgical complications, including wound infection and stent fracture, the most
important long-term complications overlap. These are reviewed subsequently.

Mortality and immediate success
Periprocedural mortality is seldom encountered in balloon angioplasty. Generally,
elective procedures are performed in the subgroup of patients with isolated coarctation,
without severe coexisting intracardiac defects. Patients of that category often are
managed by a simultaneous, surgical approach. Immediate success percentages
vary from 80 to 95% in procedures for isolated, discrete coarctation. As for
surgical repair, the question can be asked what exactly constitutes a successful result
of angioplasty. In general, a pressure gradient reduction to 20 mmHg or less is
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considered as such. Gradient reduction ranging from 31-35 mmHg in children63,64,71,72 and from 34-57 mmHg in adults65,73,74 have been reported for successful procedures. It should be noted that this pressure gradient reduction can underestimate a true relief, because of contributing collateral flow. Instead thereof, the angiographic result, although subject to interobserver variability, provides a collateral-independent result. Additional information is provided by the presence of a “waist” in the aortic contour, which is available instantaneously without catheter manipulation.

Recoarctation

As for surgical repair, recoarctation is the prevailing long-term complication after angioplasty. Especially in children and infants recoarctation rates after angioplasty may range from 15-30%.68,72 For this reason angioplasty is generally not performed in infants younger than 3 months, in whom the risk of recoarctation is unacceptably high. 63,68 In part, these adverse results may be caused by associated arch and/or isthmus hypoplasia in this infant population. The presence of aortic hypoplasia usually increases the left ventricular obstruction created by the coarctation, thus raising signs and symptoms before the age of 3 months in most patients. Consequently, the age minimum of 3 months overlaps with the exclusion of patients with aortic hypoplasia.

Recoarctation is less common in adults so that the risk of recoarctation decreases gradually with increasing age,63,72,75,76 probably secondary to the different build up of the vessel wall with decreasing elasticity. Excellent results for angioplasty in adults were reported by Fawzy et al. and they suggested that advanced age at dilatation could explain the low incidence of coarctation recurrence. 77 These different reports lead to the question whether the management of coarctation in children and adults should be different. The performance of angioplasty in different aged patients was therefore evaluated in chapter 3, including those of angioplasty for recoarctation.

Aneurysm formation

Aneurysm formation at the dilatation site has remained a long-term concern, although a gradual decrease in the incidence of aneurysm formation has been reported. Early studies noted a significant incidence of 50%,78 which decreased significantly, varying from 0-6% in later studies. 79-81 All age groups appear to have a comparable low incidence of aneurysm formation. This finding would coincide with Ritter et al., who postulate that the incidence of formation of aneurysms is similar in children and adults. 79 No indication exists that the natural history of aneurysms occurring after balloon dilatation of coarctation in adults is different from that in children. Media tearing and cystic medial necrosis have been postulated as a cause of aneurysm formation. 82 Sohn et al. demonstrated remodelling of dilated vessels. 80 It has been suggested that aneurysm development may be due to use of an overstressed balloon69 or to an inappropriate balloon size.64 This probably explains the decrease in aneurysm formation over time. The larger the balloon, the better the gradient relief, but the higher the probability of medial tear. The issue of acute and late aneurysm formation in this technique is addressed more extensively in chapter 7. The long-term results of
balloon angioplasty in adolescents and adults are discussed with reference to those of stenting of the aorta also.

**Persistent systemic hypertension**

Reduction in blood pressure might be expected to be smaller and take longer if the procedure is carried out at increasing age. In a review of 16 reports, endovascular treatment of coarctation led to a cure of hypertension (patients no longer requiring any medication to treat hypertension) in 18% to 88% (mean 61%), although four authors did not report their eventual effect on the patient’s blood pressure.

4.3. Comparison of management types

Several remarks should be made on comparing surgical repair to balloon angioplasty. First, as was pointed out by Hanley, a comparison cannot be directed towards a single ideal form of therapy, considering the complex physiologic and morphologic variability of this lesion. Instead, better defined indications for either surgery or angioplasty should be established. Secondly, individual studies span different time periods, focusing on particular age groups and particular morphologic subsets, which undermine a meaningful comparison between different techniques. Thirdly, controversy about an ideal type of surgical repair continues to exist, impairing comparison of balloon angioplasty with surgery in general. Therefore, variability in age and morphology has to be compensated for when comparing both management types. The number of studies comparing balloon angioplasty with surgical repair is limited. Shaddy et al. reported a prospective, randomized study including 36 patients in 1992. Long-term results were reported in 2005. A higher incidence of aneurysm formation and possibly a higher risk of restenosis after angioplasty were found in these studies. Johnson et al. presented a review of the literature on treatment of native coarctation in infants with both techniques in 1993. Although the early mortality rate was similar, balloon angioplasty revealed a much higher rate of recoarctation (57%) in infants as compared to those who underwent surgical repair (14%). Subsequent experience appears more favourable for angioplasty, recoarctation rates being comparable to surgical repair in more recent reports. Another review of the literature was provided by Carr in 2006. He concluded that results of primary angioplasty or stenting, performed at an average age of 22 years in the series reviewed, were similar, but they were not associated with less morbidity than surgical repair. Relief of hypertension was provided by both therapies with similar efficacy, at least in the short-term. Aneurysm formation is encountered after both balloon angioplasty and all types of surgical repair, not solely after endovascular intervention. Rates of aneurysm formation and recoarctation that have been encountered following surgical repair appeared to be comparable to endovascular treatment in reports before 2000. However, lower restenosis and recoarctation rates have been reported in more recently published surgical series. Except for those of Carr et al, these promising results were accomplished during intermediate-term follow-up, with a maximum of 5 years. Because the mechanism of recoarctation might differ between techniques, involving immediate recoil of the vessel
following angioplasty, additional long-term results are needed. Chapter 5 comprises a comparison of both modalities for the specific group of patients between 3 months to 16 years of age with an isolated, discrete type of coarctation. The follow-up in this study averaged 7.2 years following surgical repair and 5.4 years following balloon angioplasty. As was pointed out earlier, a caveat in comparing different management types is a different build up of patient groups. Primary balloon angioplasty may be performed more frequently at a higher age. Patients that are managed surgically have a long-segment coarctation or associated heart defects more frequently. A simultaneous surgical repair may be preferable. Angioplasty appears to be more favourable with respect to costs. Shaddy et al. calculated angioplasty to be 58% less costly than surgical repair. The length of hospital stay appears to be mainly responsible for this difference. An additional advantage of percutaneous management is of course its less invasive character. Besides cosmetic aspects, this may minimize the psychic and emotional aspect of this management for both the patient and parents. In conclusion, the relative advantages of the less invasive character and the shorter hospital stay might tip the balance in favour of balloon angioplasty in this patient category. However, a thorough and informative counselling of patients or their parents on this topic in this situation is obligatory to obtain informed consent.

4.4. Management of long-term follow-up complications

Recoarctation
Satisfactory results have been reported on angioplasty for recoarctation in both children and adults. It has a low mortality, low morbidity, and good results at follow-up. Although some concern has existed concerning the possible increased risk in young children, the procedure does not carry a higher risk for those children below the age of 1 year. Furthermore, it seems to have the same rate of success in children below or above the age of one year. Associated cardiac malformations and transverse arch hypoplasia (defined as an arch dimension < 2 SD below the mean for age), both appear to be predictors of the need for reintervention following angioplasty for recoarctation. Since repeat angioplasty carries a low risk, this procedure may be a good alternative for surgical correction of recurrent recoarctation. This was demonstrated in 200 patients with a mean age of 7 years in a multicentre, prospective study. The decision on type of management will depend on individual preferences and specific patient characteristics. Since the adult aorta would be expected to have less elasticity than the growing aorta, the adult restenosis may have a stiff and fibrotic aortic wall. Nevertheless, no data are available that indicate a different result of angioplasty for recurrent coarctation at adult age.

Aneurysm formation
Conventional management of large thoracic aneurysms after aortic coarctation repair has been comparable to the surgical treatment of nonspecific aneurysms; however, hypothermic circulatory arrest has been more frequently required because of reoperations. Placement of endovascular stent grafts is a less invasive approach for
these patients, provided there is no residual coarctation or arch hypoplasia. Reported results are promising and mandate further investigation.94

**Persistent hypertension**
Drug therapy is indicated in children with secondary hypertension.95 In a report on transcatheter intervention in adults, 33% of patients showed persistent hypertension during long-term follow-up. Meticulous clinical follow-up is mandatory, including an exercise test to monitor eventual blood pressure increase and to assess effort tolerance.96 In adult post-coarctectomy patients, maximal exercise systolic blood pressure was found to be independently associated with mean daytime systolic blood pressure at ambulatory blood pressure monitoring by Vriend et al.97 In this study no independent predictive value of maximal exercise systolic blood pressure for left ventricular mass could be demonstrated.

5. **Surveillance following successful initial management**

Adult patients after surgical coarctation repair have impaired endothelial function in the forearm circulation, increased intima/media thickness, decreased distensibility in the carotid arteries and increased levels of proinflammatory cytokines and adhesion molecules in comparison with healthy controls.98 Although these alterations may have an important clinical impact and may precede major adverse outcomes, their detection requires sophisticated instruments and measurements. Consequently, routine follow-up shall be focused on the long-term complications discussed above. The follow-up routine generally includes clinical evaluation, blood pressure monitoring during rest and exercise, cardiac and angiographic MR, and echocardiographic Doppler ultrasound studies. In addition, invasive angiography and CT may be performed in specific patients. Applanation tonometry may be one of the more novel supplementary techniques that may be of value in the surveillance of the coarctation patient after initial management. The specific role in this surveillance and its contribution to the assessment of vascular function of the coarctation patient are discussed for some of the aforementioned imaging modalities.

5.1. **Blood-pressure monitoring**

Blood pressure gradients between upper and lower extremities equal to or more than 30 mmHg are considered to correspond with recoarctation requiring reintervention in practically all long-term follow-up studies and guidelines.99 Nevertheless, these gradients have lost much of their diagnostic value with respect to recoarctation with the advent of cardiac MR. Araoz et al. demonstrated poor correlation between blood pressure gradients and aortic diameter because collateral circulation obscured recoarctation in part of their patients.21 Besides recoarctation, ambulatory blood pressure monitoring has been described as a diagnostic tool to identify patients with elevated mean daytime blood pressure, independently associated with mild
residual descending aortic narrowing. These patients may benefit from adjunctive antihypertensive therapy and probably even require correction of residual aortic obstruction.

5.2. Ergometry
The mechanism for exercise systolic hypertension after a “good” surgical repair of coarctation of the aorta has been elaborated on extensively. This is justified by the finding that all successfully operated patients, who are normotensive at rest, are at risk for developing end organ damage due to incipient mild hypertension, documented by ambulatory blood pressure monitoring. Several factors have been implicated in the adverse exercise response, including an altered renin-angiotensin system, an augmented sympathetic discharge at peak exercise and poor compliance of the arterial tree proximal to the coarctation site. Studies on exercise blood pressure response have been undertaken only in patients following surgical repair. To our knowledge, no data have yet been established focussing on the follow-up after balloon angioplasty. The etiology of exercise-induced hypertension may, for a certain part, be independent of the preceding management strategy. Nevertheless, balloon angioplasty has several potential advantages, compared to surgical management in respect to development of exercise-induced hypertension. Aortic innervation and reactivity may be expected to be less impaired by the controlled tear within the aortic intima and media resulting from balloon angioplasty, compared to the resection and end-to-end anastomosis that involves a transvessel section. Additionally, the surgical anastomosis may result in inadequate growth of the anastomosis and narrowing at the anastomotic site in the growing aorta, despite a successful result immediately. This particular problem has not been encountered following successful balloon angioplasty. On the contrary, remodelling and normalization of the aorta after successful balloon angioplasty of aortic coarctation have been suggested to allow optimal growth of the aortic segments. The primary focus of most studies evaluating various surgical techniques and balloon angioplasty for aortic coarctation has been the development of long-term complications, including aneurysm formation and recoarctation. Few of these studies include exercise testing in regular follow-up evaluation. On the grounds mentioned above, we think that persistence of structural and functional abnormalities of vessels after repair of aortic coarctation should be investigated by monitoring systolic blood pressure during exercise or other high-cardiac output state, as was suggested before. If one limits assessment of structure and hemodynamics to resting studies alone, aortic arch abnormalities thought to be minor at rest, may be mistakenly underestimated as important hemodynamic determinants of hypertension during periods of increased cardiac output, e.g., exercise.

5.3. Echocardiography
Echocardiography plays a central role in the screening for recoarctation due to its low cost and widespread availability. When optimal imaging is feasible, as is the case in infants and children, the literature supports combined two-dimensional and Doppler colour flow echocardiography to image the aortic arch, isthmus, and coarctation site.
Echocardiography may be more sensitive and specific at lower patient’s ages, but even in the follow-up of an adult population, a sensitivity of 97% for recoarctation can be achieved echocardiographically.\textsuperscript{110} Local evaluation of the morphology and flow at the coarctation site can be assessed by Doppler echocardiography directly. Especially in the young patient population, echocardiography will be informative enough in deciding to perform reintervention for recoarctation. Furthermore, the contribution of collateral vasculature may be determined by combining echocardiography with arm/leg pressure gradients in these patients. On the other hand, echocardiography has been described to potentially fail in detecting recoarctation, tubular hypoplasia and aortic kinking in adult patients.\textsuperscript{111} Additionally, the coarctation diameter measured by two-dimensional echocardiography appears to be poorly predictive of the angiographic severity, as was demonstrated by Simpson et al. in a series of 15 children.\textsuperscript{112} These limitations apply to transthoracic, including suprasternal, echocardiographic imaging. Cross-sectional imaging of the coarctation seems possible with transesophageal investigation, presumably enhanced by biplane or 3D-imaging. Transesophageal echocardiography may play a limited but additional role in monitoring angioplasty procedures and appeared to be superior in detecting intimal dissection to computed tomography in this setting.\textsuperscript{113}

5.4. Magnetic Resonance Imaging

MR imaging has been advocated as a superior modality for both pre- and posttreatment evaluation of patients with aortic coarctation.\textsuperscript{111,114} Because it adequately provides detailed composite views of the aortic arch and coarctation, including patients with poor echocardiographic windows, it seems especially attractive for adolescents and adults, in whom sedation is not necessary to facilitate the procedure.\textsuperscript{111} Furthermore, MR imaging was identified as the most cost-effective follow-up procedure.\textsuperscript{110} Spin-echo MR, gradient-echo MR, velocity-encoded cine measurements and gadolinium-enhanced 3D angiography are the proposed components of an appropriate MR protocol.\textsuperscript{111,114} Spin-echo imaging can be used to effectively evaluate the morphology of the coarctation, depicting the location and degree of narrowing. Gradient echo pulse or balanced fast field echo sequences may be used to visualize the flow void immediately distal to the coarctation site, with which its severity can be estimated.\textsuperscript{112} Additionally, cardiac and valvular function can be assessed by this technique. Although coarctation severity may be estimated by peak jet velocity and peak flow measurements using velocity-encoded cine MR,\textsuperscript{115} yielding accurate estimates of pressure gradients across coarctation,\textsuperscript{116} more recently coarctation severity has been related to quantification of collateral blood flow.\textsuperscript{21,117} Today, 3D MRA is considered the technique of choice to visualize the malformation. It yields imaging with excellent correlation to conventional angiography and provides subtle details of the aortic wall that may be missed with reconstruction techniques such as maximum intensity projection (MIP).\textsuperscript{114,118} Integration of the subsequent parts of this protocol may result in new insights, as was demonstrated by Ou et al.\textsuperscript{119} They found a specific pattern of aortic geometry, the so-called Gothic-shaped, angular aortic arch, to be associated with increased systolic wave reflection, as well as increased central aortic stiffness and left
ventricular mass index in subjects after coarctation repair. These findings demonstrate that future surveillance of coarctation patients may be extended to modification of accelerated atherosclerosis of coarctation patients and not be limited to detection of major adverse outcomes such as recoarctation and aneurysm formation. To identify flow characteristics that may be responsible for premature vascular damage, encountered by adults after successful coarctation management, proximal and distal aortic properties were measured with magnetic resonance in these patients. This study has been described in chapter 9.

5.5. Applanation tonometry
Aortic pulse wave velocity, central blood pressure and augmentation pressure or index can be derived from the analysis of the aortic and/or peripheral arterial pulse waveform. These variables are associated with the presence of cardiovascular disease or risk factors. Pulse wave velocity and augmentation index predict cardiovascular outcome in general and various cardiovascular target populations. O’Rourke and Cartmill demonstrated that experimental coarctation caused characteristic alterations in invasively derived central aortic pressure pulse contour. That finding indicated impaired arterial function in the “cushioning” of pulsatile flow from the heart. Hemodynamic changes were demonstrated in the proximal aorta, and were held responsible for the different spectrum of complications and worse prognosis of this condition than simple hypertension of equal severity. The early return of the pressure wave reflection and augmented ascending aortic pressure wave were demonstrated in patients after coarctation repair, more than three decades later, by means of cardiac catheterization, echocardiography and MR imaging respectively. Applanation tonometry is an alternative, simple, non-invasive and generally available technique by which peripheral arterial pulse waveform can be recorded and mathematically transformed to approximate the aortic waveform. This technique thereby provides insight in structural and functional properties of the arterial tree. Although its use has not yet been described in the assessment of this specific patient group, the abnormalities in vascular function and structure of the aorta, including the precoarctation segment, may well be identified using applanation tonometry in patients with a successfully repaired aortic coarctation. Pulse waveforms of 11 patients following successful initial coarctation management were therefore analysed using applanation tonometry. Results were compared to those in 14 matched controls. Chapter 8 includes the methods and results of this study.
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Introduction and outline of the thesis