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Early vascular aging and arterial hypertension in children after correction of coarctation of the aorta

DOCTORAL DISSERTATION

Medicine and health sciences,
Medicine (M 001)

VILNIUS 2022

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Ankstyvas kraujagyslių senėjimas ir arterinė hipertenzija vaikams po sėkmingos aortos koarktacijos korekcijos

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ABBREVIATIONS

ABPM, ambulatory blood pressure monitoring
ACEi, angiotensin-converting enzyme Inhibitors
AH, arterial hypertension
ARB, angiotensin II receptor blockers
BB, β-adrenergic receptor blockers
BMI, body mass index
BP, blood pressure
BSA, body surface area
CCB, calcium channel blockers
cIMT, carotid intima media thickness
CHD, congenital heart disease
CPB, cardiopulmonary bypass
CoA, coarctation of the aorta
cSBP, central systolic blood pressure
CT, computed tomography
CWS, circumferential wall stress
DBP, mean diastolic blood pressure
DC, distensibility coefficient
DD, mean diastolic diameter of right carotid artery
EF, ejection fraction
Einc, incremental elastic modulus
EVA, early vascular ageing
fIMT, femoral intima media thickness
FMD, flow-mediated dilatation
IR, interquartile range
IVS, interventricular septum
LCCA, left common carotid artery
LSA, left subclavian arteries
LSVC, left superior vena cava
LV, left ventricle
LVH, left ventricular hypertrophy
LVID, LV internal diameter
LVMi, left ventricular mass index
LVPW, LV posterior wall thickness
MAP, mean arterial pressure
MH, masked hypertension
MRI, magnetic resonance imaging
PWA, pulse wave analysis

rcIMT, right carotid intima media thickness
RV, right ventricle
RWT, relative wall thickness
SBP, mean systolic blood pressure
SD, mean systolic diameter of right carotid artery
SDS, standard deviation scores
TTE, Transthoracic echocardiography
WCH, white coat hypertension
WCSA, cross-sectional wall area of carotid arteries

1. INTRODUCTION

1.1. Brief introduction

Coarctation of the aorta (CoA) is a congenital narrowing of the aortic arch with a disturbed structure in the aortic wall. CoA is currently no longer considered a simple localised abnormality of the descending aorta. It is now acknowledged as being an arteriopathy with life-long sequelae (1-3), and a remarkable increase in cardiovascular events in adult CoA patients (4). It accounts for 5-8% of all congenital heart defects and can occur at any age (5, 6). Critical CoA may present in neonates and be asymptomatic for a long time in children or adolescents until a murmur is heard or arterial hypertension (AH) is detected (7). Some patients do not have clinical presentation until late in life due to either less significant narrowing or rapid post-natal development of collateral circulation (8). Management depends on the age of presentation, complexity of CoA and whether it is a native obstruction or re-coarctation (7). A variety of surgical and interventional techniques has been described, each aiming to improve immediate results and long-term outcomes, especially focusing on AH. However, AH may still be present or develop de novo even after hemodynamically effective surgery or percutaneous intervention. It is reported that the prevalence of AH in patients after CoA correction ranges between 42–70% (9-12). AH in CoA patients is associated with significant morbidity and mortality. However, there are scarce data on the prevalence of AH, blood pressure (BP) phenotype and left ventricular hypertrophy (LVH) in children after different ways of CoA repair (13-16). Moreover, there are even fewer reports on the prevalence and BP phenotypes of AH using the current classification of AH according to 2016 European Society of Hypertension guidelines and the ambulatory blood pressure monitoring (ABPM) classification by the American Heart Association (17, 18).

Not only hypertensive but also normotensive patients, following CoA repair, present with premature arteriosclerosis and an increased risk of cardiovascular events (2). Correction of CoA does not resolve the inborn pathology of the prestenotic aortic vascular bed (19). Therefore, surrogate markers are being tested for diagnosis of subclinical cardiovascular disease and risk monitoring. There are studies showing that adult CoA patients have impaired endothelial function, increased carotid intima media thickness (cIMT) (20), decreased distensibility in the carotid arteries and increased levels of proinflammatory cytokines in comparison with healthy controls (4, 21). However, the data regarding early vascular ageing (EVA) in children following CoA repair are scarce.

The present work aims at a comprehensive description of BP status and phenotypes as well as the prevalence of LVH (22), and unravelling potential changes in arterial wall function and morphology in children following successful CoA repair with right arm BP not exceeding leg BP by ≥20 mmHg. The standardized nature of this analysis is expected to provide reliable evidence about the development and relevance of AH, antihypertensive therapy and arterial remodelling in children after successful CoA repair.

1.2. Aim and objectives

The aim is to evaluate EVA, late AH and LVH in children following successful CoA repair.

Objectives:

1. To determine the prevalence and hemodynamic phenotypes of late AH.
2. To determine the prevalence of LV geometry abnormalities among normotensive and hypertensive patients.
3. To evaluate the presence of EVA – assessed by markers of arterial wall structure, endothelial function, and central blood pressure.
4. To evaluate antihypertensive treatment of late AH and its adequacy.

1.3. Defended statements

1. AH is prevalent in children after successful CoA repair.
2. LVH is prevalent in children after successful CoA repair irrespective of BP control.
3. Children after successful CoA repair demonstrate signs of EVA evident by changes in arterial wall structure, endothelial dysfunction and increased central artery stiffness.
4. The treatment of late AH in children after successful CoA repair is inadequate.

1.4. Novelty of the study

Paediatric population after a successful CoA repair have not been previously thoroughly evaluated for the potential prevalence of AH and EVA preponderance. This multicentre cross-sectional study involved looking at data from a population at one specific point in time by using office BP and

ABPM devices approved for paediatric use and applying most recent paediatric AH guidelines. It showed that children following a successful CoA repair and even with a low BP gradient, had 56% prevalence of AH with dominant systolic hypertension and masked hypertension (23) phenotypes. This study also used EVA evaluation methods that were new and not routinely applicable in paediatric population. They demonstrated signs of EVA. Increased right cIMT (rcIMT) in children was associated with LVH, office BP difference between leg and right arm, re-coarctation in the past and interventional CoA correction. Increased local stiffness was associated with increased central systolic BP (cSBP) and pulse pressure. Decreased endothelial function was related to even a slight increase of peak and mean systolic gradient in the descending aorta. This study has also found a potential underdiagnosis and undertreatment of AH, especially the MH phenotype.

2. LITERATURE REVIEW

2.1. Definition and Epidemiology of CoA

CoA is a congenital narrowing of the aortic arch with a disturbed structure in the aortic wall (1-3). Native CoA has been defined as follows: resting systolic arm BP/leg BP >20 mmHg or mean Doppler systolic gradient across CoA region >20 mmHg; resting systolic arm BP/leg BP >10 mmHg or mean Doppler systolic gradient across CoA region >20 mmHg plus either decreased left ventricular (LV) systolic function or moderate to severe aortic regurgitation or additional collateral flow. However, all these definitions should be compliant with anatomic evidence of CoA, usually defined by advanced imaging techniques such as computed tomography (CT) or magnetic resonance imaging (24, 25). Nowadays CoA is no longer considered a simple localised abnormality of the descending aorta. It is now acknowledged as an arteriopathy with life-long sequelae (2, 3), and a remarkable increase in cardiovascular events in adult CoA patients (4). It accounts for 5-8% of all congenital heart defects and can present at any age (5, 6). CoA may be classified depending on combination of CoA anatomy and haemodynamic to infantile or ductus dependant (preductal) and adult type with collateral circulation not dependent upon ductus (post ductal). Critical infantile CoA may present in neonates, while adult type CoA may be asymptomatic for a long time in children or adolescents until a murmur is heard or AH is detected (7). Some patients do not have clinical presentation until later in life due to either less significant narrowing or rapid development of collateral circulation (8). Detailed CoA heterogeneity is described below.

2.2. Aortic arch and CoA anatomy

2.2.1. Normal left aortic arch anatomy

The first branch of the normal left aortic arch is the right brachiocephalic (innominate) artery, followed by the left common carotid (LCCA) and left subclavian arteries (LSA). This typical arch branching pattern occurs in 70–80% of patients. Normal “tapering” of the aorta is positioned towards isthmus. Isthmus segment is located between left subclavian artery and ductus/ ligamentum arteriosum. The aorta is an elastic artery while ductus arteriosus is a muscular artery. In normal hearts, the ductal extension should not exceed 50% of the aortic circumference (26, 27).

2.2.2. Aortic arch pathology, aetiology

The cause of innate aortic arch pathology lies within the roots of embryology (28). CoA may form due to the narrowing or maldevelopment of the aortic segments and may commonly present together with various degrees of transverse aortic arch hypoplasia, which was defined in different ways by various authors. A arch hypoplasia is mostly defined as the ratio of transverse arch to the ascending aorta <50%. But because of the decreased aortic blood flow, the size of the ascending aorta itself may be smaller than normally defined in a new-born presenting with CoA (29-31). Another way of the definition would be transverse arch diameter less than a patient's body weight in kg plus 1 (29-31). Lastly, the aortic arch is considered hypoplastic if the Z score value is ≤ -2. And if the proximal segment Z value is -4.5 to -6, it is too small to be adequately repaired through thoracotomy (32, 33).

In some cases missing embryology segments may even cause aortic interruption - a severe version of CoA (34). Disturbed right-left symmetry may lead to the formation of right aortic arch or mirror image branching for less than 0.1% of population and may be seen together with CoA (35). Persisting segments from embryology may indicate the formation of double aortic arch which has also been described together with CoA (36, 37).

2.2.3. CoA anatomy

There is a heterogeneity in the site of narrowing of the aorta as the site of constriction may be related to aortic segment or to ductus. In addition, there is a variation of constriction amount from a short segment, including an infolding wall, shelf, intimal ridge to a long segment involving tubular hypoplasia (arch, isthmus/descending aorta). Even though classical CoA is a focal discrete constricted aortic segment usually positioned in a juxta ductal location (38), there is a known anatomical heterogeneity. Preductal variant of CoA is described as locale infolding / restriction of isthmus region or tubular hypoplasia of B segment of aortic arch (between LCCA and LSA), or in most severe cases - isthmus absence. Paraductal CoA is rarely seen on its own and more often associated with hypoplastic left heart syndrome, with or without ductal tissue. While post ductal CoA functions with a present collateral vessels that connect arteries from the upper body to vessels below the level of CoA. Coexistence of several forms is common (e.g., tubular hypoplasia with local restriction and not always abnormal ductus tissue) (27, 39). All types of CoA can be found in each age group, however the preductal CoA is mostly

prevalent in children under 1 year of age, paraductal is most common in the 1-15 age group, while post ductal CoA type is most common above 15 years (40). Post ductal CoA may be asymptomatic in new-borns if collateral circulation is established from the subclavian, internal thoracic, transverse cervical, suprascapular, superior epigastric, intercostal, and lumbar arteries during the embryonic and foetal period. Whereas, with preductal CoA, collateral circulation does not develop as most of the oxygenated and nutrient-enriched blood from the placenta reaches the lower portion of the body via the ductus arteriosus. Thus, these new-borns typically develop poor perfusion of the lower body with prevalent differential cyanosis after birth when the ductus arteriosus closes. The clinical effects of CoA are variable and depend on the degree of narrowing (41).

2.3. Clinical heterogeneity of CoA

Clinically CoA is classified to infantile and adult CoA types. Infantile CoA is critical CoA form which present in neonates as it is ductal dependant, preductal or paraductal (7). Adult CoA type is ductal independent, post ductal CoA with a potential to be asymptomatic for a long time in children or adolescents until a murmur is heard or AH is detected (7). Some patients do not have clinical presentation until later in life due to either less significant narrowing or rapid post-natal development of collateral circulation (8).

2.4. Pathogenesis of CoA

There are several potential concepts of CoA pathogenesis that have been published. According to the ductus tissue or “Classical CoA” concept CoA results from the abnormal migration or extension of ductus arteriosus tissue into the foetal aortic wall. While narrowing of the aorta both prenatally and after ductal closure is associated with constriction of ductus tissue (42, 43).

In compliance with haemodynamic concept, CoA results from reduced foetal antegrade blood flow through the thoracic aorta (42). While as specified by the developmental concept CoA results from extensive remodelling of vasculature during embryology. A variable phenotype is determined by segments and cell populations involved in remodelling of the aorta during embryology stage (42, 43).

2.5. Anomalies associated with CoA

CoA might be diagnosed as isolated lesion or together with coexisting malformations. It is diagnosed with other complex cardiac defects for 1/3 of these patients (e.g. ventricular septal defects 39%, hypoplastic left heart syndrome 11%, double outlet right ventricle 6.7%, atrioventricular canal defects 4.4%, transposition of great arteries 7.7%, common ventricle 3.6%, tricuspid atresia 2.4%, pulmonary stenosis 1%, Tetralogy of Fallot 0.4%, mitral valve abnormality, including monochorda 4.9%) (44-47). Other patients are diagnosed with uncomplicated cardiac lesions such as: bicuspid aortic valve 20-85%, atrial septal defect or patent foramen ovale 20%, patent ductus arteriosus 43%, mild arch hypoplasia, mild mitral regurgitation or stenosis, mild aortic regurgitation, or stenosis (45-47). There are several recognized chromosomal / genetic abnormalities with higher known CoA prevalence among them 6.2% (e.g. Turner syndrome, Trisomy 21, Trisomy 18, DiGeorge syndrome) (45). At least 12.6% of girls diagnosed with CoA have karyotype-confirmed Turner syndrome (48).

2.6. CoA diagnostics

2.6.1. Prenatal diagnostics of CoA

Diagnosis timing and setting have an impact on preoperative condition, which influences a postoperative course and outcome of the disease. Prenatal diagnosis of CoA enables information provision and counselling, parental choice of the course of pregnancy, panning of delivery at a cardiac centre and postnatal management planning such as institution of prostaglandin infusion and surgery planning. Duct-dependent lesions diagnosed antenatally improve arterial pH and oxygenation, cause less myocardial dysfunction and end-organ damage, improve haemodynamic stability before surgery, causes no or little collapse and death (49-52). The diagnosis of CoA can be made as early as in the first trimester, however, prenatal CoA diagnosis remains a challenge as the determination of the diagnosis is dependent on the success of obstetric screening, and a comprehensive assessment is available only if mothers are referred for a foetal echocardiogram performed by a paediatric cardiologist trained to recognize congenital heart disease (CHD) (53, 54). The sensitivity of foetal diagnosis of isolated CoA ranges from 50 to 72% with still common delayed diagnosis (55) to high rates of a false negative and false positive diagnosis. The false negative diagnosis can lead to devastating outcomes,

while the false positive one lead to significant parental anxiety (56) and health care resource usage (repetitive foetal scans, impact on birth plan and delivery centre, delay in discharge home after birth, repetitive hospital visits). The main challenges of prenatal CoA diagnosis are the patency of ductus, which makes the anatomic narrowing less visible and limits the ability to detect any doppler gradients at CoA site (53). The common reasons for obstetrician referral for foetal echocardiography are: abnormal four-chamber view with ventricular disproportion (57), abnormal three-vessel view with the aorta and pulmonary artery disproportion or additional left superior vena cava (LSVC) (58-60). The main theories of LSVC association with CoA are the interference with inferior vena cava flow, then the flow through foramen ovale to left atrium; the obstruction to flow from left atrium to LV; however, multifactorial causes are most common (60).

The antenatal cardiovascular MRI may be adjunct to foetal echocardiography in diagnosis of CoA even though it is challenging due to a spontaneous, random foetal/maternal motion, thus slice re-planning for motion correction is needed (61, 62).

2.6.2. Postnatal diagnostics of CoA

If the prenatal suspicion of isolated CoA is not obvious after the first postnatal heart ultrasound and new-born pulse oximetry screening (63, 64), an early postnatal surveillance is needed until the duct closes with ongoing follow-up until <1 year of age (7, 65). If the diagnosis is not made prenatally, the timing of postnatal diagnosis of CoA differ depending on CoA type (65). Infantile CoA clinically manifests acutely with signs of poor feeding, dyspnoea, or signs of collapse, acute circulatory shock during the first weeks of life due to ductal narrowing and closure (9, 52, 66). On physical examination critical infants appear pale, experience various degrees of respiratory distress with common oliguria, anuria, general circulatory shock, and severe acidaemia (67, 68). The auscultation of a critical new-born or infant may reveal no cardiac murmur in half of such cases. A loud S3 gallop might be audible due to a progressive heart failure. Heart murmur may start to be audible after the start of prostaglandin infusion (9). Beyond the neonatal period, a cardiogenic shock is an unusual presentation but still a possibility during early infancy. The clinical finding characteristics of CoA in older paediatric patients is a systolic hypertension in arms, and low or unobtainable arterial BP in legs. Peripheral pulses are weak or delayed with the so-called brachial-femoral delay. However, the differences of pulses and BP between

limbs may not be present for a critical new-born until the beginning of prostaglandin infusion (68).

Transthoracic echocardiography (TTE) remains a mainstream of postnatal CoA diagnosis. Primarily used two-dimensional echocardiography and colour-flow Doppler studies from suprasternal and subcostal views assist with determination of CoA site, aortic arch anatomy, and helps to determine the severity (68, 69). The primary goal of 2D and 3D TTE CoA imaging is the identification of CoA location and the severity of aortic arch obstruction by measuring Z scores of each part of aortic arch and the narrowest part of the aorta as well as the gradient in the descending aorta. Z scores should be adjusted for body surface area for comparison with the general population normative values (31, 70). In addition, the determination of arch side (left or right) and branching pattern is important (69, 71). Nonetheless, it is crucial to perform complete TTE for the diagnosis of associated intracardiac anomalies listed above (68, 69).

Additional advanced modalities for the evaluation of CoA are CT and MRI. These are used for the visualization of clearer anatomical aortic arch and CoA view. However, as both techniques involve a patient exposure to contrast and anaesthesia with CT using radiation, these imaging tools should be reserved for patients when imaging by echocardiography is not sufficient for the preoperative evaluation (69).

The most recent diagnostic tool used for CoA evaluation is a four-dimensional flow cardiac MRI which is even described as a potential alternative for a diagnostic cardiac intervention as obtained dynamic pressure profiles are shown to be similar between these methods (72, 73). Another new diagnostic modality under the development for CoA diagnostics is MRI based computational fluid dynamics. This is a computer simulation for the prediction of a fluid-flow phenomena. It allows a detailed spatio-temporal quantification of haemodynamic based on MRI and BP for the non-invasive rest pressure gradient evaluation in CoA region (74). Additionally, in some regions of the world, there are novel finite element model and 3D model printing techniques suitable for interventional and surgical treatment planning for the most complex cases (75, 76).

2.7. Treatment of CoA

2.7.1. Indications for the isolated CoA treatment

Infantile critical CoA must be corrected as soon as possible. Recommendations for adult type CoA correction were newly redefined in the

recent 2020 ESC Guidelines for the management of adult CHD (77) as follows. Repair of CoA or re-coarctation is indicated in hypertensive patients with BP in legs lower than BP in hands and with ≥20mmHg invasive peak-to-peak gradient in the descending aorta (Class I, Level C) or in hypertensive patients with ≥50% narrowing relative to aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is <20mmHg (Class IIa, Level C). For normotensive patients the repair of CoA should be considered with ≥ 20mmHg invasive peak-to-peak gradient in the descending aorta (Class IIa, Level C) or with ≥50% narrowing relative to aortic diameter at the diaphragm, even if the invasive peak-to-peak gradient is <20mmHg (Class IIb, Level C) (77). The only method recommended tor adult type CoA and re-coarctation correction in adults is interventional when feasible (77). However, the treatment of CoA in children is more complex, therefore it is discussed in more detail in paragraphs "Surgery of CoA" and "Interventional CoA treatment" below.

2.7.2. Surgery of CoA

The first surgical CoA repair was performed in 1944 (78). The surgical repair is preferred over the interventional treatment in neonates and infants <4 month-old (79), as it is associated with a lower risk of re-coarctation and perioperative mortality of infrequent occurrence of <1% (25, 80, 81), as well as low presence of significant complications for <6% of patients (82). For ≥4 month-old infants and for children weighing <20 kg, or for patients with complex CoA anatomy or underlying genetic disorder, the decision regarding the interventional treatment versus the surgical repair is determined by the expertise of centres and the underlying morphology of CoA on a case-by-case basis (79, 83, 84). Despite the proposed recommendations for the interventional treatment, the surgical repair continues to be the preferred approach in many centres worldwide for <5 year-old patients.

Nowadays, as surgical techniques continue to improve, it has resulted in the adjustment of tailored surgical planning under various scenarios. Isolated CoA repairs can be performed without cardiopulmonary bypass (CPB) via access through lateral thoracotomy. This approach is not suitable for CoA with hypoplastic aortic arch due to a limited access to the proximal part of the aortic arch, thus, the repair with CPB via median sternotomy is preferable in this case. Whereas, combined lesions repair sometimes needs to be corrected via staged and more complex procedures (32). There are several CPB options to be considered while repairing CoA, including deep hypothermic circulatory arrest with cool down to 18°C and switched off pump, where the safe interval

is ~45 min, and the advantage is a bloodless surgical field. Other CPB technique is selective antegrade cerebral perfusion which gives the continuous perfusion of the brain and upper part of the body, however, only a very limited 1/3 of the perfusion volume of kidneys and intestinal organs. Whereas the double arterial cannulation technique gives continuous perfusion of all organs and is most reliable in the majority of complex cases (32, 85).

After selecting the most appropriate CPB it is vital to prepare for surgical CoA correction itself by engaging all major technical principles (32). To consider the resection of the isthmus segment, the reconstruction with extended end to end anastomosis is recommended for the isolated CoA if the size of the proximal aortic arch is optimal (86). If the size of the proximal aortic arch is questionable with a cut off value of Z score -4.59, end to side anastomosis is preferable (87). Older techniques include patch aortoplasty and subclavian flap (88). Yet another challenge is the restoration of the aortic arch geometry. All these techniques are crucial to avoid early and late postoperative complications.

2.7.3. Early postoperative complications

Some of early postoperative complications include an aortic wall injury, dissection / intimal tear, aneurysm, atrial fibrillation, bleeding, respiratory failure, paradoxical hypertension, left recurrent laryngeal nerve paralysis, and phrenic nerve injury, or death (25, 89). Subclavian flap technique might cause a rare complication of subclavian steal (90). Paraplegia due to spinal cord ischemia and mesenteric arteritis with bowel infarction are very rare. An incomplete removal of the pathological tissue during surgical repair may lead to the development of aortic aneurysm, which is very rare after end-to-end anastomosis and highest after subclavian flap repair (91). According to the meta-analysis of nine studies, the gradient in CoA region was similar in patients treated with surgery compared with the balloon angioplasty with the risk of severe short-term complications greater after surgical CoA repair compared with balloon angioplasty. However, in mid- to long-term follow-up, the risk of aneurysm formation as well as the risk of re-coarctation was considerably lower with surgery (89).

2.7.4. Interventional CoA treatment

The first percutaneous balloon CoA angioplasty was performed in 1982 (92). The first stent implantation in CoA site was performed in 1991 (93, 94). After interventional techniques evolved it had replaced surgery for adults and

older children, who weigh >20 kg and have native isolated or long-segment CoA with stent placement more often preferred over balloon angioplasty alone (25, 83, 95-100). For smaller children, the decision regarding an interventional versus surgical treatment is made on case-by-case basis as described above in the surgical treatment section (79, 83, 84). The technical principles of interventional CoA assessment and correction have evolved with a few decades of practice.

Catheter intervention is performed via a femoral vascular access for most patients, while a carotid or axillary pathway is chosen for infants weighing <4kg (101). Multiple projection angiography is used for the evaluation of aortic arch and CoA segment for the most safe approach. Haemodynamic evaluation for peak-to-peak systolic pressure gradient recording across CoA assessment is performed prior to the final decision of CoA repair. The interventional indication to treat CoA is intracardiac peak-to-peak systolic pressure gradient across CoA higher than 20 mmHg (100). After the decision is made to correct, the next step is to select an appropriate balloon size for CoA treatment, which is recommended to be two or more times the size of the coarcted segment, but not larger than the size of the descending aorta at the level of the diaphragm and no larger than the size of aortic arch (102). Stent placement after the balloon angioplasty of CoA sustains hemodynamic benefit by improving luminal diameter, however, these children are more likely to result in a planned reintervention since the stent often needs to be dilated as the child grows (96, 103-105). Bare metal and covered stents are used in patients with CoA worldwide, while biodegradable stents are also under development with promising results (77, 106, 107).

The main complications of balloon angioplasty are a faster formation of re-coarctation for 5-25%, the development of aortic aneurysm for 5-7%, vascular access damage and thrombosis for up to 15%, while aortic dissection or rupture is rarely observed (24, 108-112). The advantages of stent implantation are: a less common vessel recoil, a less frequent vessel injury, and a lower risk of aortic aneurysm formation (103, 113, 114). The disadvantages of stenting include a need for a larger sheath, a risk of stent migration, a late stent embolization, a possible in-stent restenosis, and a failure to adapt and to grow. However, according to a recent systematic review with meta-analysis, the overall stenting achieves a better immediate relief of CoA with evidence of patients undergoing stenting experiencing fewer short-term severe complications compared with those undergoing balloon dilatation (115).

2.8. Long-term outcomes and major complications after CoA repair

Studies analysing earlier CoA correction experience from cohorts of 1946-1981 and 1914-2005 report a 30-year survival rate of 72-73% (116, 117).While a long-term follow-up study in a cohort of 273 patients published in 2016 reports a low mortality of 5.7% during the long-term follow-up of 31 years. The same study reports much higher survival rates estimated to be 94%, 91% and 80% at 20, 30, and 39 years following CoA correction, respectively (118). In addition, a multi-centre US study of larger cohort of 2,424 patients published in 2019 reported that postcoarctectomy presented an excellent 95.6% survival at 20 years (119). Even higher survival rates of 99%, 88% and 65% at 30, 50, and 70 years respectively are presented in another large retrospective study of 834 patients (120).

The significant technical improvement in the field of cardiovascular surgery as well as interventional cardiology has led to a growing population and excellent general survival rates of patients following a successful correction of CoA (10, 116, 118). However, the most recent study of 206 children reported event-free survival only of 74% at 5-year and 68% at 10-year follow-up (121).The care of these patients remains challenging due to a reported high prevalence of complications following CoA repair, including re-coarctation, systemic hypertension, aortic aneurysm formation, cerebrovascular complications, retinopathy, and premature coronary artery disease (10, 122-124). The contemporary cardiovascular event rate in CoA population, including myocardial infarction (125), is reported to be 11% in 10 years (126), and a 10% risk of developing intracranial aneurysms with increased risk of stroke (124), accounting for the majority of deaths at a relatively young age (4, 118). Small intracranial aneurysms in this population are thought to develop secondary to hypertension or as a part of vasculopathy(124). There is evidence of retinopathy only for hypertensive patients after CoA repair (122, 127-130). The retinal changes are matching those seen in patients with primary AH (122). Some studies have shown that CoA correction does not resolve the inborn pathology of the prestenotic part of the aorta and has shown a reduced prognosis even for individuals who had a successful repair (19, 131).

2.8.1. Re-coarctation

Re-coarctation is a common complication resulting from CoA repair. It is diagnosed for up to 30% of patients after surgical repair of CoA performed

in infancy (121, 132). Aortic re-coarctation has been defined the same as native CoA (25).

The factors predisposing to re-coarctation include: patient age at CoA repair <30 days (133) – under 3 months (121); the need of prostaglandin infusion prior to surgery (134); the hypoplasia of isthmus region (111); and CoA segment diameter of ≤3.5 mm prior to angioplasty or ≤ 6 mm after interventional treatment (133). The optimal CoA repair technique must be chosen individually to prevent the formation of residual obstruction and recurrent obstruction in the future. If the moderately hypoplastic proximal segment of aortic arch (Z score -2 to -5) is not enlarged adequately, it will not grow sufficiently for 1/3 of patients, thus resulting in residual obstruction (33, 135-137). However, there are data in literature showing that a proximal arch diameter below -4 Z score or below a patient's body weight in kg plus 1 does not predict re-coarctation (138, 139).

Clinical criteria such as signs of cardiac failure and haemodynamic criteria such as AH in upper limbs, post-procedural interventional peak pressure gradient of ≥20 mmHg, lower LV function are the main criteria for the reintervention and treatment of re-coarctation (25, 79, 84, 100). If a patient has a good clinical condition and the systolic BP in arms/legs is below 25mmHg, but there is a preserved LV function and high doppler velocity in CoA region without diastolic run-off, no invasive treatment is recommended only a follow-up.

The most common treatment option for re-coarctation is balloon angioplasty with stenting in selected patient groups, while at repeated surgery is uncommon. The balloon angioplasty is more often performed than stenting in small children ≤20 kg (140, 141). The immediate significant reduction of the gradient across CoA and the sufficiently increased diameter of aortic segment after balloon angioplasty are seen in over 80% of less than 6-year-old patients with re-coarctation. However, patients over 6 years of age gain more advantageous short and long-term outcomes after stent implantation than balloon angioplasty alone (1, 95-97, 100).

2.8.2. AH and LVH in young adults and children after CoA repair

A variety of surgical and interventional techniques has been described, each aiming to improve immediate results and long-term outcomes, especially focusing on AH. However, AH may still be present or develop *de novo* even after a hemodynamically effective surgery or percutaneous intervention. It is reported that the prevalence of AH in patients after CoA correction ranges between 42–70% (9-12). AH in CoA patients is associated with significant

morbidity and mortality. Paradoxical AH early after CoA repair is a well described complication with known pathophysiological mechanism which is set out below. While pathogenesis of the late AH in this population is the missing peace in the CoA puzzle. Similarly, the data also varies regarding LVH among hypertensive versus normotensive patients after CoA repair within the range of variation discussed in the paragraph below.

2.8.2.1. Paradoxical AH after CoA repair

Paradoxical AH is an early complication of CoA, which usually presents during the first 24 hours or 2 to 4 days after surgery if delayed (142). A few potential mechanisms for the development of paradoxical hypertension phenomenon have been described. The initial 24-hour phase of a direct postoperative hypertension mechanism is explained with sympathetic activation by higher baroreceptor set point due to a high preoperative BP (143). The initial phase may result in excessive bleeding and haemodynamic compromise. Another mechanism explains the possible few days delay of the manifestation of paradoxical hypertension due to the postoperatively reduced stretch of the baroreceptors causing an elevated sympathetic nervous activity demonstrated by higher epinephrine / norepinephrine levels. The last mechanism explains the second phase of the paradoxical hypertension by the activation of renin-angiotensin-aldosterone system with elevated plasma renin activity during the first week after surgery (142, 144). Systolic and diastolic hypertension during the second phase of paradoxical hypertension may cause mesenteric arteritis which has a potential to complicate with peritonitis if no effective antihypertensives are used for treatment (145). Even though the mechanism of paradoxical hypertension is well known, the uniform treatment strategy has not yet been published. No evidence supports one antihypertensive treatment strategy over the other in this case scenario. However, a couple of review articles have been published to describe the most used and effective antihypertensives targeting different pathways of paradoxical hypertension to prevent the development of potentially lethal complications (146, 147). The most commonly used medication during the initial phase is direct vasodilator Sodium Nitroprusside. It causes vascular smooth muscle relaxation by increasing cyclic guanosine monophosphate (148). β-adrenergic receptor blockers (BB) is the second most used antihypertensive group with esmolol, and labetalol described as the most effective in targeting two mechanisms of paradoxical hypertension, sympathetic activation, and renin release (149, 150). However, monotherapy with esmolol is often not sufficient (150). More than 30 years ago, the use of

prophylactic BB such as propranolol had been shown to be effective for the management of paradoxical hypertension, however, it did not find its way to the routine usage for early postoperative hypertension management in patients with CoA (151, 152). Alpha-agonists and Calcium channel blockers (CCB), especially nicardipine, have a potential for treatment of paradoxical hypertension, but these are not widely used (146, 153). The most commonly used antihypertensive for the second phase of the paradoxical hypertension are Angiotensin-Converting Enzyme Inhibitors (ACEi) due to their effect on renin stimulation. Today, the only available ACEi for the intravenous use is enalaprilat with a quite limited data on its use for paediatric hypertensive crisis (146, 148).

While evidence about paradoxical hypertension in this population is so abundant, there is yet a lot to be learned about the development of AH later in life after CoA repair.

2.8.2.2. Late AH after CoA repair

2.8.2.2.1. Prevalence of late AH after CoA repair

Late AH is the most significant complication of CoA (13-16), which appears despite a successful early CHD repair in children (117). While there is a clear definition of paradoxical AH after CoA repair (142), the time-related definition for late AH varies. Some studies use the term of *late AH* beyond the term of *paradoxical AH* (154) others apply *1 year after CoA repair* (155) or *from 4 to 5 years after CoA correction* (156). The prevalence of late AH postcoarctectomy in young adults is up to 68% according to various literature sources with higher reported prevalence in studies using office combined with ABPM monitoring (14, 157, 158). There are reports of high late systemic AH prevalence in children even in patients with a successful CoA repair with minimal or no residual gradient across the aorta (159, 160). However, the data on prevalence of AH in patients after CoA correction differ. This might be due to the different definitions used for diagnosis of AH, based on office or ABPM measurements, as well as the definition of a successful CoA correction. There are some studies describing an isolated systolic hypertension as the dominant phenotype after a successful CoA correction (17, 158, 161, 162). Another highly prevalent hemodynamic phenotype of hypertension after CoA repair is MH, which is diagnosed only for those patients who get an ABPM measurement (163). Exercise induced AH has been shown to be prevalent in

adult population after CoA repair, but not yet established in paediatric population (164).

2.8.2.2.2. Aetiology of late systemic AH after CoA repair

It is thought that aetiology of late systemic AH after CoA repair is multifactorial. However, the exact pathogenesis is still unclear (8, 165). There are some known and some hypothetical factors which can play a role in the pathogenesis of AH after CoA repair. Among the known factors there are those related with CoA itself such as the gothic arch type (155), the presence of re-coarctation (166), CoA correction type as well as timing, age at follow-up (167, 168), and the method used to measure BP (8, 14). Among the factors which are hypothetical and still under investigation, in addition to the inherent arteriopathy involving the narrowed segment of the aorta, is the increased arterial stiffness of the pre-coarctation part of the aorta induced by a chronic shear stress, and abnormal renal flow (157, 160, 169, 170). Below in this paragraph, known factors are discussed, while the detailed explanation of interdependent relationship of hypothetical factors, hypertension, and CoA are discussed in paragraphs covering arterial remodelling.

Brown et al. identified the age of 9 years as a cut-off point towards a significantly higher risk of development of late AH at 5 to 15 years of follow-up (116). Choudhary et al. found that AH after CoA repair is associated with an initial repair after 6 years of age (12, 116). Higher incidence of re-coarctation, hence more AH is known to develop due to older surgical CoA correction methods such as the subclavian flap repair and others, where prosthetic material was used for aortic arch augmentation (167, 168). On the other hand, Kenny et al. concluded that 1/3 of CoA patients become hypertensive despite an early and effective surgical or interventional repair and the fact that AH is an inevitable consequence of CoA, even when anatomical repair was done in the first months of life (8).

Not only strictly determined re-coarctation plays a major role in the formation of AH. Reports of findings in cohorts of adults after CoA repair showed associations even of mild narrowing in the descending aorta with development of hypertension (118, 169). Also, there is data on persisting AH even after a successful interventional correction of re-coarctation (6, 166). One may assume that with time (i.e. age), the continuing of even a small elevation of systolic gradient in the aorta may aggravate the effect of a generalized disturbance of the aortic wall structure and increased stiffness and cause an isolated systolic hypertension (4, 171). Based on this data, Vriend et

al. suggested to adopt a lower threshold for reintervention for residual aortic narrowing than posed in current guidelines in order to improve long-term outcomes in these patients, however, no actual recommendations for hypertension screening following CoA repair exist to this day (169).

Even aortic arch morphology, especially the Gothic arch type, has been shown to potentially influence the development of AH in combination with changes in arterial structure and markers of vascular remodelling. Which might be explained by shear stresses occurring as blood moves through the acute angle of the Gothic arch (155).

2.8.2.2.3. Diagnostic challenges of AH in children after CoA repair

Currently, there are no unified guidelines or recommendations for the evaluation and management of AH in children after CoA repair. Thus, clinicians have to adopt the existing general paediatric hypertension guidelines of the European Society of Hypertension (17) or American Academy of Pediatrics (172), or American Heart Association (18) in combination with the American Heart Association and European Society of Cardiology guidelines for adult CHD (25, 77). The combination of these guidelines may give more insights on the peculiarities of measurement office BP, home BP, ABPM, and exercise BP. However, the decision on when to diagnose AH, when to start treatment, and what antihypertensives to use after a successful CoA repair remains the main challenge for the paediatric cardiologist.

The unanimous agreement of office BP measurement in diagnosis of CoA and re-coarctation is that BP must be measured in arms and in legs not only to detect AH in arms, but also to determine the systolic BP difference between arms and legs. In haemodynamically significant CoA and re-coarctation the brachial systolic BP is higher than systolic BP in legs ≥20mmHg.

One of the most important peculiarity in measuring of BP for patients after CoA repair is the selection of correct arm depending on the arch anatomy. For most patients, the right brachial BP is recommended as arch anatomy is confirmed as normal. However, right brachial BP is not informative, if there is anomalous arch anatomy with unusual origin or aberrance of the right subclavian artery or if right brachial artery was damaged during interventions. Additionally, left brachial BP measurement may also not be appropriate for the patients who underwent CoA correction by old-fashion Subclavian flap technique, where the left subclavian artery is usually sacrificed for CoA repair (173).

Screening for hypertension in previously normotensive patients after CoA repair is usually performed during annual check-ups by performing office BP measurements. When AH or re-coarctation is suspected, then more detailed BP assessment by ABPM and exercise BP evaluation is used in addition to diagnostic imaging tools (160). However, this is not enough as the high prevalence of MH in subjects after CoA repair is well known (163, 174, 175). Exercise induced AH has been shown predictive of later occurrence of AH in adult population (164). And AH is inadequately treated in up to 40% of patients after CoA repair (8, 157). These finding underlines the importance of ABPM in the routine management of patients after CoA repair and shows the need for specific guidelines and adapted BP percentile cut-off values for hypertension management in this specific population.

According to the European Society of Hypertension (17) and American Academy of Pediatrics (172) guidelines, the home BP monitoring has a great potential and superior reproducibility to office BP similar to that of ABPM (176). However, it is not recommended to be used for the initial diagnosis of AH, only for the follow-ups. The methods on how to perform home BP measurements and rough normative values for general paediatric population are given in European Society of Hypertension guidelines (17). However, there are no separate normative values for CoA population.

In CoA population, exercise induced AH has been shown to be predictive of later occurrence of AH related to increased arterial stiffness (164). However, the significance of isolated, exercise-induced hypertension is still a matter of a debate not only in paediatric population but also in adults (77). Even though the normative values for exercise stress testing in general paediatric population has been published (177), the use is limited only for older children and adults due to treadmill and bicycle technical requirements.

2.8.2.2.4. Treatment challenges of AH in children after CoA repair

The most important thing is to guarantee that CoA has been corrected successfully, without a presence of re-coarctation or a significant narrowing at any part of the aorta. If the residual narrowing of the aorta exists, a timely intervention and a relevant correction of the re-coarctation are necessary. And only then the non-pharmacological treatment and pharmacotherapy for the secondary AH may follow.

The general rules for the non-pharmacological treatment of AH are recommended to all hypertensive patients, including those following a successful CoA repair (17, 160, 172, 178). No physical activity restrictions are advised for subjects who are normotensive at rest and during physical

activities (77). However, patients with diagnosed AH are recommended to avoid heavy isometric exercises in proportion to the severity of their additional problems (77, 178).

Pharmacological treatment of arterial hypertension following successful CoA repair

There is a wide spectrum of antihypertensive medication recommended for treatment of AH in general paediatric population including diuretics, BB, CCB, ACEi, angiotensin II receptor blockers (ARB), alpha and β-adrenergic receptor blockers, central alpha-agonists, peripheral alpha-blockers and vasodilators. The latest paediatric hypertension recommendations thoroughly delineate the potential monotherapy as well as the combination therapy not only for primary AH, but also covers the treatment options for most of renal, endocrine, and cardiac causes of secondary hypertension (17, 172). However, there have been only a few clinical studies conducted on antihypertensive medication for the treatment of late AH following a successful isolated CoA repair in older children and young adult population.

Moltzer E. et al. compared the effect of candesartan (ARB) and metoprolol (BB) on BP, large artery stiffness, and neurohormonal status in an open-label, crossover study for adult hypertensive patients after CoA repair. This study concluded that metoprolol decreased the MAP more than candesartan did, while the large artery stiffness did not change with either of treatments. With metoprolol, plasma B-type natriuretic peptide increased, and plasma renin decreased. With candesartan, the plasma renin and noradrenaline levels increased, while aldosterone levels decreased. The neurohormonal outcome did not support a significant role for the renin-angiotensin system in the causative mechanism of late systemic hypertension after CoA (179).

G Di Salvo et al. compared atenolol (BB) and enalapril (ACEi) regarding the tolerability and efficacy on late systemic AH and left ventricular mass index (LVMi) in children and young adults after a successful CoA repair. This study concluded that even though both medications are similarly effective in reducing systolic 24-h BP, only enalapril demonstrated a significant reduction of LVMi, thus it should be recommended over atenolol not only for the antihypertensive effect, but also for the better reduction of cardiovascular mortality and morbidity (180). Moreover, Brili S et al. shown that ramipril (ACEi) has a potential to reverse the impaired endothelial function and decrease the expression of proinflammatory cytokine IL-6, sCD40L, and adhesion molecules even in normotensive young adults after a successful CoA repair (181).

Based on this limited data, the most appropriate agents for the late systemic hypertension after successful isolated CoA repair should be ACEi followed by BB and lastly ARB (181, 182). Additionally, a several review articles have provided an overview of the actual worldwide clinical practice of antihypertensive use in this population. Where vasodilators, thiazide diuretics, CCB are suggested in addition to the drugs evaluated by clinical trials mentioned above (160, 178).

However, there are still no unanimous guidelines for the antihypertensive treatment in this population due to the lack of randomized clinical trials. The most recent 2020 ESC Adult CHD guidelines recommend following the general rules of antihypertensive treatment provided in 2018 ESC/ESH guidelines (77, 183). Similarly, no individual pharmacological treatment opinions are provided in 2017 American Academy of Paediatrics guidelines (172). Whereas, 2016 Paediatric European Society of Hypertension guidelines are more specific by recommending BB, CCB and drugs affecting the renin–angiotensin–aldosterone system for patients after CoA repair (17). However, these recommendations are based only on a few very small sample size clinical studies (179, 184), with no separation made between medication groups for paradoxical and late AH following a successful CoA repair. Thus, the tough choice of antihypertensive drug still lies on the shoulders of a treating physician.

2.8.2.3. LVH in young adults and children after CoA repair

LVH is known to be a risk factor for adverse cardiac events. There is data suggesting that increased stiffness in the repaired aorta increases LV afterload leading to LV hypertrophy and diastolic filling abnormalities (185-187). Thus, LVH relationship to end-organ effects has been assessed using noninvasive techniques from echocardiography to cardiac MRI in CoA population (11, 154, 188). There are more data on the prevalence of LVH after CoA repair in adults compared with paediatric population after CoA repair with most of the studies containing mixed populations of older children and young adults (13-16). The prevalence of LVH in this study population waries between 25% and 50% partially due to the different LVH definitions and tools used to calculate LVH and relativelly due to contrasting targeted populations (different age groups, CoA repair techniques, timing of CoA repair etc.) (11, 154, 188-190)

Toro-Salazar O H et al. showed 46% prevalence of LVH by echocardiographically assessed LVMi in adults after a successful CoA repair with higher systolic BP being a single predictor of LVH ($p=0.01$) (10).

Additionally, Lee M G et al. noninvasively evaluated the end-end organ damage after a successful CoA repair in patients from 10 years of age with normal arches. They found a high prevalence of LVH (55%) with a trend towards statistical significance of a more pronounced LVH among hypertensive 31 of 49 (63%) compared with 13 of 31 (42%) with normotensive or patients in prehypertension (OR= 2.4; 95% CI (1.0 - 6.0); p = 0.06). This finding underlines the presence of an increased afterload in these patients. In addition, the researchers found a weak correlation between AH and LVH, abnormal cIMT, and retinal vasculature abnormalities. These findings indicate a possible neurohormonal origin of AH pathogenesis in repaired CoA patients with normal aortic transverse arches (11). Rinnström et al. conducted a large multi-centre register study including 506 adult patients with a previously repaired CoA. They discovered a little less than 1/4 of normotensive study population is bearing the burden of higher LV mass determined by echocardiography (190). They also revealed the LVH association with higher normal systolic BP even bellow the currently recommended target level (190). Whereas, Bocelli A et al. found a less pronounced LVH among successfully corrected young CoA patients from 23% to 38 %, with a considerable variation based on the criteria used to identify LV hypertrophy. This study also showed that older age at intervention is the most important predictor of the increased prevalence of LVH (154). Additionally, Quail M A et al. showed that LVMi obtained by cardiac MRI was significantly higher in successfully corrected adult CoA patients than controls (72 versus 59 g/m2, P<0.0005). The magnitude of the backward compression waves was independently associated with variation in LV mass (P=0.01), showing haemodynamically abnormal conduit vessel function after a successful CoA repair (188). Moreover, other studies have shown the relation between exercise-induced hypertension and LVH in this patient group (191).

2.8.3. Biomedical studies of arterial remodelling in young adults and children after CoA correction

Current evidence suggests that despite an early and successful CoA repair, the structural and functional alterations of the pre-coarctation aorta are still present with preserved post-coarctation arteries (192, 193). Consistent histological findings at the time of surgery in CoA patients show a disrupted arrangement of elastin within the tunica media, significantly more collagen and less smooth muscle mass in the aorta above than below CoA; thus, a more rigid pre-coarctation aortic wall (194). The studies published evidenced a

premature arteriosclerosis and an increased risk of cardiovascular events in young adulthood in both hypertensive and normotensive patients following CoA (2, 185, 195). An interdependent relationship between a vascular remodelling and hypertension in CoA patients are discussed in the paragraph below.

2.8.3.1. cIMT

cIMT was reported as being a useful tool for a cardiovascular risk assessment and prediction of end organ damage in adult CoA patients (4, 196, 197) with a recent estimation of cIMT exceeding 0.8 mm having a 15-fold higher cardiovascular risk (126). Dempsey et al. reported associations of increased peripheral BP with increased cIMT following CoA repair (198). However, this study included only 26 CoA patients, of whom only 12 were hypertensive, and did not classify those already treated with antihypertensives as hypertensive. In addition, in the Dempsey at al. study, cIMT was expressed in absolute but not standardised values (198). Other data attempting to explain the potential mechanisms of cIMT thickening in patients after CoA repair (160) have been published. cIMT is thought to increase in hypertensive CoA patients due to proliferation and hypertrophy of vascular smooth muscle or by the activation of synthesis of glycosaminoglycans due to activated gene expression by shear stress on endothelium (160, 198, 199). In addition, cIMT is reported to increase also in both normotensive and hypertensive patients after CoA repair via vascular dysfunction following CoA repair (4, 196). While mechanistically increased rcIMT in CoA patients may be explained by the exposure to greater pulse pressure, which is typical for CoA patients, even for those who had normal BP. Greater pulse pressure was found to be a predictor of cIMT in adolescents with primary hypertension as well (200). Along with that, Sarkola et al. reported that mechanistically patients after interventional CoA treatment with stents had greater rcIMT than those who were treated surgically (196).

On the other hand, considerations on potential mechanisms of increased cIMT effect on development of AH in patients after CoA repair (160) have been published. Increased cIMT is assumed to cause arterial stiffening which may increase afterload, LV wall stress and cause LVH, hence leading to the development of AH. Moreover, the increased cIMT is thought to directly build up the afterload and in yet unknown pathways lead to AH. Furthermore, the increased cIMT is expected to cause AH through a direct microvascular damage to kidneys or indirectly through increased reflection waves, which then cause microvascular kidneys injury (160).

Luijendijk P et al. evaluated the effect of high dose statins on the cIMT and cardiovascular risk in a multicentre, prospective, randomized, open label trial with blinded endpoint study for adults after a successful CoA repair. Following a three-year treatment with atorvastatin, it was concluded that this medication does not lead to a reduction of cIMT and the secondary outcome measures despite the decrease in total cholesterol and low-density lipoprotein levels. The authors recommended that the main focus to decrease the cardiovascular risk should be directed towards an antihypertensive medication (201, 202).

2.8.3.2. Arterial stiffness

Studies of adult CoA patients revealed not only structural changes of the carotid wall, but also a prevalent increased arterial stiffness resulting in the reduction of carotid distensibility (195, 196, 203).

There is published data indicating that the increased arterial stiffness in hypertensive patients was caused by altered proportions of collagen subtypes and the ratio of synthesis and degradation of collagen type-1 (204). There are articles aiming to explain the mechanisms of arterial stiffening in patients after CoA repair in hypertensive and normotensive patients (185, 193, 195, 196, 199, 204-209). The arterial stiffening is thought to develop in hypertensive CoA patients due to vascular dysfunction caused by shear stress on endothelium (205, 206) or because of the alteration of the proportions of collagen subtypes and degradation of collagen type-1 resulting from activated gene expression due to shear stress on endothelium (204, 207), or because of increased glycosaminoglycan production generated by activated gene expression due to shear stress on endothelium (199). Whereas the arterial stiffening is expected to develop in CoA patients despite the BP via vascular dysfunction following CoA repair (185, 193, 195, 196, 208, 209). The relationship between the arterial stiffness and AH is thought to be more complex and interdependent. An increased arterial stiffness is expected to influence the development of AH in patients after CoA repair via several mechanisms. The arterial stiffening may increase afterload, LV wall stress, and cause LVH, hence, leading to higher BP due to the arterial stiffening. The arterial stiffening is thought to influence the manifestation of AH through direct microvascular damage to kidneys or indirectly through increased reflection waves, which then cause microvascular kidneys injury (185, 193, 195, 196, 208, 209).

2.8.3.3. Endothelial dysfunction

Abnormal vascular reactivity measures are not consistently found in patients following CoA repair (156, 192, 210), and there is no reference for flow-mediated dilatation (FMD) data in children, thus there is no evidence on how different FMD values might be present in the population of healthy children. However, there have been attempts to explain the mechanisms of endothelial dysfunction in patients after CoA repair. One of the potential explanations is that endothelial dysfunction might be caused through shear stress on endothelium in hypertensive CoA patients (205). Additionally, endothelial dysfunction is also expected to be caused irrespective of BP in patients after CoA repair, as CoA is recognized as vasculopathy. However, the exact mechanisms, are unknown (160). Due to the potential interdependent mechanisms endothelial dysfunction may have an effect on the development of AH in patients after CoA repair by the contribution to the thickening of cIMT and arterial stiffening, which then may cause AH to evolve through the mechanisms mentioned above (156, 192, 210).

3. METHODS

3.1. Study design and setting

All the analyses were performed using data from a multicentre cross-sectional study named EVA in Children after CoA repair (EVA in CoA).

EVA in CoA recruited 110 children following CoA treatment from Lithuania, Latvia, and Poland within the period from January 2017 to May 2020 (Figure 1.).

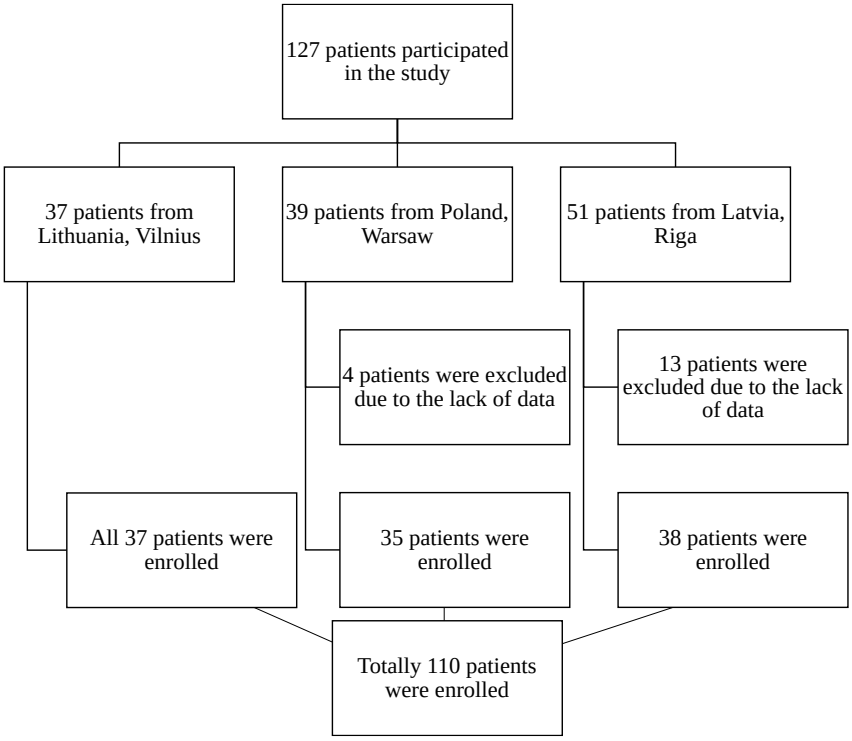


Figure 1. Enrolment of patients into the study.

The patients were included into the study according to the following enrolment criteria:

Inclusion criteria:

- Children aged 6-18 years.
- Isolated CoA.
- Right arm and leg BP difference <20mmHg after interventional or surgical CoA correction.

- Only hemodynamically insignificant shunt lesions (small ventricular or atrial septal defect) and bicuspid aortic valve with exclusively mild regurgitation or stenosis were permitted for enrolment.

Exclusion criteria:

- Diastolic tail in continuous wave doppler examination across the descending aorta in echocardiography.
- Any other chronic disease.
- Acute illness.
- Genetic syndrome.

3.2. Study organization

This was a multicentre cross-sectional study. After an international protocol was prepared, all study patients were examined in their centres according to the same protocol.

The study plan included clinical examinations and data collection, along with the comprehensive cardiovascular investigation that also included the measurements of office BP, ABPM, cardiac ultrasound, as well as the investigation of arterial wall structure, endothelial function, cSBP (described below). The training process for investigators was performed prior to the beginning of the study to ensure the identical approach to all predefined standard operating procedures (described below).

3.3. Ethical statements

The study was approved by local Ethics Committees of each participating centre. Lithuanian ethical committee permission number 158200-17-894-412. Latvian ethical committee permission number 1/18-03-12. Polish ethical committee permission number 41/KBE/2017. The study protocol corresponds to the 1975 Declaration of Helsinki revised in 2013. All patients and their parents or their legal representatives, as appropriate, gave written informed consent for the participation in the study.

3.4. Sample selection for the present analysis

The present analysis included all eligible patients from the EVA in CoA Study who met all inclusion criteria and none of the exclusion criteria.

3.5. Collected data

The following data was collected and was used for the present analysis within the same time frame of the study:

- Date of birth.
- Gender.
- Anthropometric data (height and weight).
- Type of CoA (Preductal/postductal).
- Correction of re-coarctation in patient history.
- Age at CoA correction (years).
- Years after CoA repair.
- Type of CoA correction (intervention or surgery).
- Years of follow-up after first CoA correction date.
- Years of follow-up after last CoA correction date.
- Aortic valve anatomy (bicuspid versus tricuspid).
- Antihypertensive treatment if AH was present before the enrolment to the study.
- Office BP and 24-hour ABPM (described below).
- Echocardiographic measurements (described below).
- Arterial wall structure, endothelial function, and non-invasive cSBP measurements (described below).

3.6. Data sources and measurements

3.6.1. Anthropometric data

Height and weight were measured by local investigators using calibrated scales and meters.

3.6.2. Office and ambulatory blood pressure measurement

Office BP measurements were performed on the right arm by an automatic oscillometric method after 5-minute rest in the supine position. Measurements were taken three times, and the mean was used. A SpaceLabs Monitor 90207 was used for ABPM on the right arm. Readings were taken every 20 minutes during daytime and every 30 minutes at night. Recordings

lasting ≥20h with ≥80% of successful readings were considered valid and were included in the analysis.

3.6.3. Echocardiography

TTE measurements were performed according to the recommendations for paediatric echocardiogram from the American Society of Echocardiography (211). Two-dimensional echocardiography and colour-flow Doppler studies from suprasternal and subcostal views were used for the determination of previous CoA site, aortic arch. The standard suprasternal position and continuous wave Doppler were used to measure the systolic gradient across the descending aorta (212). The left lateral decubitus position was used for the ventricular function assessment, LVH evaluation. LV dimensions (interventricular septum [IVS] and LV posterior wall [LVPW] thickness and LV internal diameter [LVID]) were measured in the long parasternal axis using M-mode images in end-diastole, at the height of papillary muscles. All measurements were performed by the same trained investigators.

3.6.4. Arterial wall structure, endothelial function, and central blood pressure measurements

Arteriopathy was evaluated by the measurements of the right carotid (c) and right and left femoral (f) IMT by an ultrasound system (Avante Health Solutions LOGIQ P5) equipped for two-dimensional imaging using a linear array transducer with a frequency of 12 MHz. The measurements were performed on the rcIMT due to haemodynamics related to CoA. Manual IMT measurements were taken, and the average of ten data point acquisitions was then calculated. Measurements were performed by the same trained physician in each centre for all patients. The doctoral student performed all measurements in Lithuania and Latvia.

Endothelial function was assessed by measuring the FMD of the right brachial artery according to the guidelines of the International Brachial Artery Reactivity Task Force (213). Subjects were positioned supine for imaging the right brachial artery above the antecubital fossa in the longitudinal plane (213).

Pulse wave analysis (PWA) was measured non-invasively with the oscillometric method, using a Vicorder® SMT Medical system device, previously validated in paediatric studies, although PWA function has not been previously validated for children use. PWA enables the calculation of

parameters describing the characteristics of the arterial system, including cSBP, augmentation pressure, augmentation index and central pulse pressure. The measurement was performed in the supine position after 5-minute rest, according to the published guidelines (23, 214). PWA was obtained from the right brachial artery.

3.7. Data definitions and transformations

CoA was classified into preductal and postductal.

Body mass index (BMI) was calculated using the following equation: $BMI = \frac{Weight\ (kg)}{Height\ (m)^2}$. BMI values for participants aged 6-18 years were further age and sex standardized to calculating standard deviation scores (SDS) by using CDC growth reference data (215).

AH was diagnosed according to the 2016 paediatric guidelines of the European Society of Hypertension (17). BP status was classified according to office BP and ABPM. In children >16 years of age, adult normative values were used for 24-hour systolic BP / diastolic BP (130/80 mmHg) (17). Further subclassification of BP phenotypes was performed according to the ABPM classification by the American Heart Association (18). White coat hypertension (WCH) was diagnosed when office BP levels were ≥95th percentile but normal ABPM results. Ambulatory pre-hypertension was defined when office BP and mean ABPM were within normal ranges, but ABPM load was increased to 25-50%. When office BP and mean ABPM was ≥95th percentile and ABPM load was 25–50% it was determined as ambulatory hypertension, while load >50% shifted the diagnosis to severe ambulatory hypertension. Patients who were normotensive according to office BP but had elevated mean ABPM ≥95th percentile were considered having MH. Patients receiving antihypertensive medications were considered hypertensive irrespective of their BP values. Patients on antihypertensive treatment with normal office BP and ABPM values were considered having controlled hypertension.

LVMi was calculated using the de Simone formula with LV dimensions measured in end-diastole: $\left(\frac{0.8\times\{1.04\times[(\mathrm{LVID}+\mathrm{LVPW}+\mathrm{IVS})^3-\mathrm{LVID}^3]\}+0.6}{Height\ (m)}\right)^{2.7}$

(216). LVMi values above the 95th percentile for age- and gender-based reference data were classified as LVH (217). For adolescents aged ≥16 years, LVH was defined as used in adults, indexed to the square metre of body surface area (17).

Relative wall thickness (RWT) was calculated by based on diastolic dimensions of IVS, LVPW and LVID, using the following equation: $RWT = \frac{IVS+LVPW}{LVID}$. Additionally, age-normalized RWT was calculated as proposed by de Simone et al. using the following equation: $normalized\ RWT = RWT - 0.005 \times (age - 10)$ and values above 95th percentile (0.38) considered indicative of concentric LV geometry [23]. LV geometry was classified according to LVMi and RWT to normal pattern (LVMi ≤95percentile, RWT ≤0.38), concentric remodelling (LVMi ≤95percentile, RWT >0.38), concentric LVH (LVMi >95percentile, RWT >0.38), and eccentric LVH (LVMi >95percentile, RWT ≤0.38).

Arterial wall structure, endothelial function, and cSBP transformations: the cross-sectional wall area of carotid arteries (WCSA), distensibility coefficient (DC), β stiffness index, incremental elastic modulus (Einc), and circumferential wall stress (CWS) were evaluated by derivative formulas: $WCSA = 3.14 \times \left(\frac{DD}{2} + rcIMT\right)^2 - 3.14 \times \left(\frac{DD}{2}\right)^2$;

$DC = 2 \times \frac{\left(\frac{(SD-DD)}{DD}\right)}{(SBP-DBP)\times 1.33} \times 1000$;

$\beta\ stiffness\ index = \frac{ln\left(\frac{SBP}{DBP}\right)}{\frac{(SD-DD)}{DD}}$;

$Einc = 3 \times \frac{\left(1+\frac{\frac{3.14\times DD^2}{4}}{WCSA}\right)}{DC}$;

$CWS = \frac{(MAP\times DD)}{2} \times rcIMT$, where DD is mean diastolic diameter of right carotid artery, SD is mean systolic diameter of right carotid artery, SBP is mean systolic blood pressure, DBP is mean diastolic blood pressure (218). cIMT, DC, Einc, and β stiffness index values were standardized to height-/age- and sex specific SDS using previously published normative values (21, 218). For FMD evaluation the main measured value was the percentage change in brachial artery diastolic diameter before and after cuff inflation. Values less than 10% were considered abnormal (213). The adult FMD cut-off values were used as there were no previously published age and sex specific normative values for children.

3.8. Statistical analysis

Normally distributed variables were presented as mean and standard deviation values; non-normally distributed variables were presented as

median and interquartile range (IR) values (25th and 75th quartile). The Shapiro–Wilk test was used to assess normality. Variances of normally distributed parameters were tested by an F-test. Means of continuous variables with a normal distribution and equal variances were compared using the Student's t-test for independent samples, and in cases of more than two testing groups, ANOVA was applied. Equality of means of normally distributed continuous variables but with unequal variances was tested using Welch's t-test. Continuous variables not satisfying normality assumptions were compared using the Wilcoxon test. The Pearson correlation was used for variables with normal distribution, and the Spearman's rank correlation was used for variables not satisfying the normality assumption. The Chi^2 test was used for testing relationships among categorical variables. Differences in AH prevalence among the different patient age groups at CoA correction and different re-coarctation status in anamnesis were also analysed using the Chi^2 test.

IMT values were presented as absolute, while SDS values were calculated according to the LMS method (21). Univariate binary logistic regression and odds ratio analysis were used to assess the associates with LVH and to evaluate the significance of age at CoA correction on the development of AH as well as the associates with increased cIMT and decreased FMD. Multivariable logistic regression analysis with stepwise forward-backward model building was performed to find the associates with AH and rcIMT SDS. Office BP SDS were calculated based on the 4th report (219).

Statistically significant test results were considered as those with p values ≤ 0.05, a trend towards significance with p values ≥ 0.05, but < 0.1. The G*Power 3.1.9.4 program was used to determine a sample size for all evaluated hypotheses to ensure the power of 0.95 to detect a desired effect size of 0.5 for all tests comparing the study population with general population, and 0.65 for the comparisons within various subgroups of the study population. Sample size varies from 20-30 up to 60-80 patients depending on selected analysis type and grouping requirement. Our sample size is 110 which is considered sufficient to derive reliable statistical estimates for all performed statistical tests. Statistical analysis was conducted with the R program. Supplementary analysis was performed using Microsoft Excel. Data was validated by using a standardized data validation plan to avoid including patients with missing data or data that falls outside the predefined plausibility ranges.

4. RESULTS

4.1. Characteristics of study participants

110 patients following CoA repair with a median age of 12.3 (8.9-15.7) years, including 69 males (62.7%), were included in the study (Table 1). A bicuspid aortic valve was found in 63 patients (57.3%). CoA was treated surgically in 73 (66.4%), while 37 (33.6%) patients underwent an interventional correction as the first treatment choice. Patients corrected surgically were younger at the time of procedure (median age 0.2 years (0.1-1.9)) compared with the interventional treatment group (median age 6.9 years (4.4-9.6), $p < 0.05$). Post ductal CoA was the dominant type diagnosed in 70 (63.6%) patients. Surgery was the first treatment choice for 36 (90%) of the preductal CoA type cases, whereas an almost equal preference for CoA correction modes was observed among those patients with the post ductal CoA type (33 patients of 70 treated by percutaneous intervention). Before enrolment in the study, 42 patients had undergone re-coarctation correction, with 41 (97.7%) cases corrected by an interventional approach – 20 were stented, 21 dilatated with a balloon alone. The median time of follow-up after the last re-coarctation correction was 6.7 (2.3-10.4) years.

Table 1. Patient demographics and basic data

Patient characteristics	**Values (mean and standard deviation or median and 25–75 IR)**
Number of subjects (males/females)	110 (69/41)
Age (years)	12.3 (8.9-15.7)
BMI	18.1 (16.5–22.3)
BMI – SDS	0.1±1.1
Age at the first CoA correction (years)	1.3 (0.1-6.5)
Years of follow-up after the first CoA correction date	8.9 ± 4.5
Years of follow-up after the last CoA correction date	6.7 (2.3-10.4)
Age at surgery (years) when surgery was the first CoA treatment choice	0.2 (0.1-1.9)
Age at intervention (years) when interventional treatment was the first CoA treatment choice	6.9 (4.4-9.6)
Peak systolic gradient across the aorta (mmHg)	27 (20-34)
Mean systolic gradient across the aorta (mmHg)	11 (9-15)

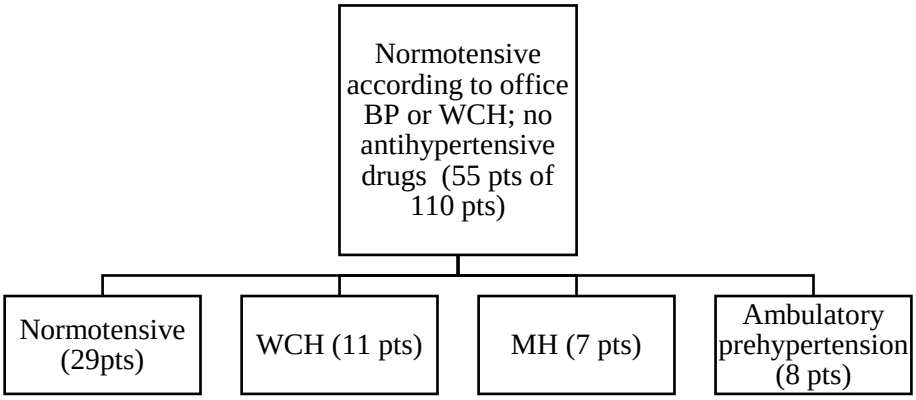
Patient characteristics	Values (mean and standard deviation or median and 25–75 IR)
Office systolic BP right arm (mmHg)	119±14
Office diastolic BP right arm (mmHg)	65±10
Office systolic BP SDS right arm	1.1±1.1
Office diastolic BP SDS right arm	0.2±0.9
Average 24-hour systolic ABPM (mmHg)	119±12
Average 24-hour diastolic ABPM (mmHg)	62±7
24-hour systolic ABPM SDS	0.77±1.3
Office BP difference between legs and right arm (mmHg)	2.0 (-7-12)
cSBP (mmHg)	110±11
24 ABPM MAP mmHg	82 (77-87)
24 ABPM MAP SDS	0.2 (-0.7-1.0)
Office pulse pressure in mmHg	54.3±14.1
24 ABPM pulse pressure in mmHg	56.5±12.3

Abbreviations: *ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; CoA, coarctation of the aorta; cSBP, central systolic blood pressure; IR, interquartile range; MAP, mean arterial blood pressure.*

4.2. Blood pressure status

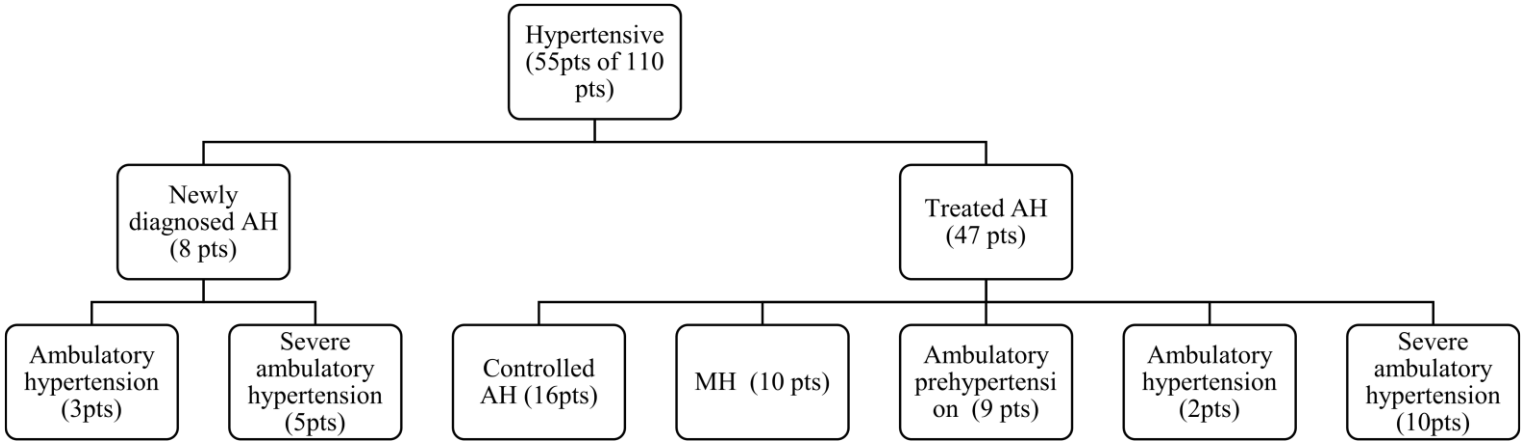
The prevalence of AH according to the office BP was 50% (55 of 110 patients). BP phenotypes after ABPM performance are summarized in Figure 2 and Figure 3. Isolated systolic hypertension phenotype was dominant HD phenotype. 30 out of 55 (54.5%) patients had uncontrolled or MH. 47 of the 110 (42.7%) patients were previously treated with antihypertensive drugs and were considered hypertensive. Of those 47, only 16 had ABPM values in the normotensive range, 9 had ambulatory prehypertension, 2 ambulatory hypertension, 10 severe ambulatory hypertension, and ten MH. A newly diagnosed hypertension was found in 8 of 110 patients, with 3 of them in the ambulatory hypertension range, and 5 in the severe ambulatory hypertension range. And additional 7 subjects were diagnosed with MH after performing ABPM for patients who have not been treated for AH before enrolment to the study and who were normotensive according to the office BP. Thus, the total prevalence of AH was 56% (62 of 110 patients) after evaluation of both office

BP and ABPM results. The AH prevalence was higher among those with a lower BP difference between legs and right arm (BP median difference among hypertensive patients 1 (-10–11) versus 4 (-2–13) mmHg among normotensives, $p<0.05$).



Abbreviations: *ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CoA, coarctation of the aorta; MH, masked hypertension; WCH, white coat hypertension.*

Figure 2. BP phenotypes of office normotensive patients without antihypertensive treatment after CoA correction according to ABPM.



Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CoA, coarctation of the aorta; MH, masked hypertension.

Figure 3. BP phenotypes of hypertensive patients after CoA correction according to ABPM results.

Of 55 remaining patients who were considered normotensive according to office BP, 12.7% (7 of 55 patients) had MH, 14.5% (8 of 55 patients) ambulatory pre-hypertension, and 52.7% (29 of 55 patients) were normotensive in both office BP and ABPM (Figure 2). 20.0% (11 of 55) patients had elevated office and normal ABPM results and were diagnosed as having WCH. Of 47 patients already treated with antihypertensive drugs, normotension was achieved in 16 (34.0%). Among patients with uncontrolled hypertension (n=20) and MH (n=17) the dominant BP phenotype was isolated systolic hypertension (32 patients out of 37; 86.5%). Only 5 (13.5%) subjects had systolic-diastolic hypertension, 2 of which had severe ambulatory hypertension and 3 - MH.

4.3. Analysis of peak systolic gradient across the aorta

The average peak systolic gradient across the aorta was statistically significantly greater in hypertensive (32.0 (20.2-36.0) mmHg) patients compared with normotensive (25.0 (19.0-30.0) mmHg, p=0.02) counterparts, even though none of the patients showed a diastolic tail in continuous wave Doppler examination of the descending aorta and the difference between right arm and leg was <20mmHg in both groups. The peak gradient across the aorta was also significantly greater for patients who had had re-coarctation correction in the past (30 (22.3-36) mmHg) compared with patients who had not required re-coarctation repair (26 (19.0-32) mmHg; p=0.03). There was also a trend towards the significance of mean systolic gradient in the descending aorta among patients who had re-coarctation in the past (12.5±4.2 vs 11.2±3.5, p=0.1).

4.4. Effect of age at correction of CoA on subsequent AH

Surgical correction was performed at a younger age compared with percutaneous intervention (p<0.0001), and was predominant in the normotensive group of patients - 44 of 55 (80.0%) normotensive patients had surgical repair, versus 29 of 55 (52.7%) in the hypertensive group of patients (p=0.002; Chi^2=9.2; Table 2.). Most patients (56.6%) younger than 1 year of age at the time of CoA repair were currently in the normotensive BP range. However, after splitting the study group into three age groups (<12 months, between 12 months and 9 years, and ≥9 years), age at correction was not significantly associated with the development of AH (p=0.3) (Table 3). Mean gradient across the descending aorta was not significantly different among all

three age groups either (p=0.3). Additionally, univariate logistic regression analysis with age at CoA correction as a continuous variable was performed to evaluate the significance of age at CoA correction on the development of AH. Although not statistically significant, there was a tendency towards the significance of association between age at CoA correction and the development of hypertension (p=0.07).

Moreover, a multivariable logistic regression analysis was performed to find associates with AH. Initial dataset contained the following associates: age, age at CoA correction, gender, BMI SDS, CoA correction type, peak and mean systolic gradient across the aorta, re-coarctation in patient history. After performing a stepwise forward-backward model building, the analysis resulted in one significant associate and one towards the significance. Interventional CoA correction type was a significant associate with AH (β Interventional CoA correction type=1.1, p=0.009), while age was towards the significance (β age=0.1, p=0.08), pseudo-r2 McFadden's of this model 0.1.

Table 2. Characteristic of normotensive and hypertensive patients.

Variables	Normotensive 55 patients	Hypertensive 55 patients	p
Age (years)	**11.3 (8.5-14.1)**	**13.1 (10.0-16.2)**	**0.04**
Age at CoA correction (years)	0.6 (0.03-4.3)	2.8 (0.08-6.9)	0.05
BMI	**17.9 (15.8-20.6)**	**18.8 (17.2-20.6)**	**0.04**
BMI SDS	-0.01±1.1	0.2±1.2	0.31
CoA correction type (intervention/operation)	**11/44**	**26/29**	**0.002**
Office systolic BP right arm	**112.2±11.8**	**127.0±12.8**	**<0.0001**
Office systolic BP SDS right arm	**0.5±0.9**	**1.7±1.0**	**<0.0001**

Variables	Normotensive 55 patients	Hypertensive 55 patients	p
Office diastolic BP SDS right arm	0.2±0.9	0.2±0.8	0.44
Average 24 hour systolic ABPM	**113.5±10.4**	**125.1±11**	**<0.0001**
Average 24 hour diastolic ABPM	62.7±7.2	62.9±7.9	0.92
cSBP	**106.0 ± 10.3**	**114.3 ± 11.6**	**0.0002**
Peak systolic gradient across the aorta	**25.0 (19.0-30.0)**	**32 (20.2-36.0)**	**0.02**
Mean systolic gradient across the aorta	11.0 (9.0-13.0)	12.5 (9.25-15.8)	0.09
Years of follow-up after the first CoA correction date	8.9±4.2	8.9±4.8	1.0
Years of follow-up after the last CoA correction date	7.6 (2.9-10.0)	6.0 (1.8-11.2)	0.5
Correction of re-coarctation in patient history / no need for re-intervention on the descending aorta	17/38	25/30	0.1
LVH	15 of 55 (27.3%)	21 of 55 (38.2%)	0.2
LVMi g/m height 2.7	33.9 (30.7-40.6)	38.1 (33.3–42.7)	0.07

Abbreviations: *ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; CoA, coarctation of the aorta; cSBP, central systolic blood pressure; LVH, left ventricular hypertrophy, LVMi, left ventricular mass index.*

Table 3. AH prevalence in different patient age groups at CoA correction (Fisher's exact test).

BP status	I group (<12 months of age at CoA correction). N=53	II group (≥12 months-<9 years of age at CoA correction). N=42	III group (≥9 years of age at CoA correction). N=15	p value
Hypertensive patients	23 (43.4%)	22 (52.4%)	10 (66.7%)	0.3
Normotensive patients	30 (56.6%)	20 (47.6%)	5 (33.3%)	

Abbreviations: *AH, arterial hypertension; BP, blood pressure; CoA, coarctation of the aorta.*

4.5. Prevalence of LVH

LVH was diagnosed in 36 of 110 (32.7%) patients, without a significant difference between hypertensive (21 of 55 (38.2%)) and normotensive patients (15 of 55 (27.3%), p=0.22). The median LVMi value was 33.9 g/m height 2.7 (30.7-40.6) in 55 normotensive patients compared to 38.1 g/m height 2.7 (33.3–42.7) in hypertensive patients (p=0.07). Mean RWT (age normalized) was 0.4±0.07, without significant difference between hypertensive 0.4±0.08 and normotensive patients 0.4±0.06, p=0.70. When compared by LV geometry, 54 (49.1%) had normal LV geometry, 20 (18.1%) had concentric remodelling, 18 (16.4%) had concentric LVH and 18 (16.4%) exhibited eccentric LVH. Characteristics of patients within different LV geometry patterns are represented in Table 4. No differences of LV geometry patterns were found among hypertensive and normotensive patients (Table 5). Among patients who were considered normotensive according to office BP, LVH was found in 3 with MH, 1 with ambulatory pre-hypertension, and 6 true normotensive patients. In addition, 5 patients with WCH had LVH as well. A weak correlation was found between office pulse pressure and LVMi (r=0.2, p=0.02) as well as between ambulatory pulse pressure and LVMi (r=0.3, p=0.007).

The logistic regression analysis, which included age, age at the time of CoA repair, body surface area, BMI SDS, sex, office systolic BP, 24-hour systolic BP, mode of CoA correction, bicuspid aortic valve, previous re-coarctations, peak and mean systolic gradient across the descending aorta, aortic stenosis, and regurgitation, showed only BMI SDS as a significant

associate with LVH in the study population and body surface area (BSA), office systolic BP on right arm as well as ABPM systolic BP on right arm towards the significance. While BMI SDS and re-coarctation in the past were the only covariates associated with higher odds of concentric LV geometry (abnormally increased RWT) (Table 6). BMI SDS was highest in eccentric LVH group (p=0.0006) (Table 7).

Table 4. Characteristics of patients within different LV geometry patterns.

Variables	Normal LV geometry	Concentric remodeling	Concentric LVH	Eccentric LVH	Kruskal Wallis X^2	p
Age (years)	11.6(8.6-15.3)	12.2 (8.3-14.8)	13.0 (9.6-16.1)	13.5 (10.1-15.9)	1.7	0.64
Age at CoA correction (years)	2.5 (0.08-6.4)	0.1 (0.03-5.6)	0.6 (0.1-5.7)	1.2 (0.2-6.9)	2.7	0.45
BMI	**18.1 (16.6-21.1)**	**16.4 (15.4-18.6)**	**19.1 (17.6-22.5)**	**22.6 (18.2-24.8)**	**13.0**	**0.005**
BMI SDS	**0.1±1.0**	**-0.7±1.0**	**0.2±1.1**	**0.8±1.2**		**0.0006**
CoA correction type (intervention/operation)	16/38	8/12	7/11	6/12	1.0	0.80
Peak systolic gradient across the aorta	27.5 (24.0-35.3)	25.0 (16.5-33.3)	26.1 (20.3-33.5)	26.0 (19.3-31.0)	3.5	0.32
Mean systolic gradient across the aorta	13.0 (10.0-16.0)	11.0 (8.0-15.0)	11.8 (9.6-14.9)	11.5 (9.0-13.3)	3.3	0.35
Years of follow-up after the first CoA correction date	8.4±4.1	9.2±5.1	9.6±4.7	9.2±4.8		0.73
Years of follow-up after the last CoA correction date	6.8 (4.-10.7)	6.6 (1.-9.1)	2.7 (1.-8.2)	7.3 (1.-11.3)	4.5	0.22
cSBP	108.7±12.5	109.2±11.2	112.2±11.0	112.7±10.5		0.57
rcIMT	**0.5 (05.-0.52)**	**0.5 (0.5-0.6)**	**0.6 (05.-0.6)**	**0.5 (0.5–0.6)**	**19.4**	**0.0002**
rcIMT SDS	**2.6±1.4**	**3.3±1.2**	**4.4±1.4**	**3.1±1.4**		**0.0001**
rfIMT	0.3 (0.-0.3)	0.2 (0.-0.3)	0.3 (0.2-0.3)	0.3 (0.2-0.3)	4.1	0.26
rfIMT SDS	-1.8 (-3.0- -1.1)	-2.8 (-1.7- -1.9)	-1.5 (-2.7- -0.7)	-1.33 (-2.0- -0.7)	4.2	0.25
FMD	6.0 (3.4-8.0)	3.5 (2.3-5.0)	5.3 (2.5-7.9)	3.7 (2.9-6.0)	3.7	0.30
LV EF %	67.9 (64.0-73.0)	70.0 (66.9-73.4)	68.5 (64.4-72.3)	64.8 (61.0-70.3)	4.9	0.18

Abbreviations: *ABPM, ambulatory blood pressure monitoring; AH, arterial hypertension; BMI, body mass index; BP, blood pressure; CoA, coarctation of the aorta; cSBP, central systolic blood pressure; EF, ejection fraction; fIMT, femoral intima media thickness; FMD, flow-mediated dilatation; LV, left ventricle; rcIMT, right carotid intima media thickness.*

Table 5. LV geometry patterns among hypertensive versus normotensive patients.

LV geometry	Hypertension	Normotension	X^2	p
Normal	N=26	N=28	0.2	0.70
Concentric remodeling	N=8	N=12	1.0	0.32
Concentric LVH	N=9	N=9	0	1
Eccentric LVH	N=12	N=7	1.6	0.21

Abbreviations: *LV, left ventricle; LVH, left ventricular hypertrophy.*

Table 6. Univariable associates with LVH and concentric geometry in the study population

Variables	LVH OR	LVH 95% CI	LVH P Value	Concentric geometry OR	Concentric geometry 95% CI	Concentric geometry P value
Age at the time of CoA repair (years)	1.0	0.9-1.1	0.9	1.0	0.9-1.1	0.41
Age (years)	1.1	1.0-1.2	0.2	1.0	0.9-1.1	0.84
Male (gender)	0.6	0.3-1.4	0.3	0.9	0.4-1.9	0.73
Percutaneous intervention	1.2	0.5-2.7	0.7	3.3	0.7-15.2	0.12
Bicuspid Aortic valve	1.1	0.5-2.4	0.9	0.5	0.2-1.2	0.13
BSA	3.0	1.0-8.9	0.1	0.8	0.3-2.3	0.67
BMI SDS	**1.7**	**1.1-2.5**	**0.01**	**0.6**	**0.4-0.9**	**0.02**
Re-coarctation in the past	1.5	0.7-3.3	0.3	**3.0**	**1.3-6.8**	**0.01**
Mild aortic regurgitation	1.2	0.5-2.7	0.6	0.7	0.3-1.5	0.39
Mild Aortic stenosis	0.4	0.1-1.5	0.2	1.0	0.4-3.1	0.94
Systolic office BP on right arm	1.0	1.0- 1.1	0.1	1.0	0.9-1.0	0.80
Systolic average 24h ABPM on right arm	1.0	1.0-1.1	0.1	1.0	0.9-1.0	0.09

Variables	LVH OR	LVH 95% CI	LVH P Value	Concentric geometry OR	Concentric geometry 95% CI	Concentric geometry P value
Systolic office BP on right arm SDS	1.3	0.9-1.9	0.2	0.9	0.6-1.3	0.60
Peak systolic gradient across the descending aorta	1.0	0.9-1.0	0.3	1.0	0.9-1.0	0.35
Mean systolic gradient across the descending aorta	0.9	0.9-1.1	0.3	1.0	0.9-1.0	0.40

Abbreviations: *ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; BSA, body surface area; CoA, coarctation of the aorta; LVH, left ventricular hypertrophy.*

Table 7. Distribution of LV geometry and BMI SDS with different LV geometry patterns.

RWT	LVMi	
	≤95%	>95%
≤0.38	Normal geometry N=54 (49.1%) BMI SDS = 0.1±1.0	Eccentric LVH N=18 (16.4%) BMI SDS = 0.8±1.2
>0.38	Concentric remodeling N=20 (18.1%) BMI SDS = -0.7±1.0	Concentric LVH N=18 (16.4%) BMI SDS = 0.2±1.1

Abbreviations: *BMI, body mass index; LV, left ventricle; LVH, left ventricular hyper trophy; LVMi, left ventricular mass index; RWT, relative wall thickness.*

4.6. cIMT, local stiffness of carotid artery and FMD measurements

The mean rcIMT SDS was 3.1±1.5, rcIMT above 1.65 SDS was found in 91 of 110 (82.7%) patients. In addition, rcIMT was above 3 SDS in 46.4% (51 of 110 patients). The median of absolute values of rcIMT of patients following CoA repair was 0.51 (0.47-0.57). It was significantly greater than the median

of the 50th percentiles, being 0.38 (0.37-0.39), p< 0.05 and 95th percentiles, being 0.45 (0.44–0.46) of the same gender and age healthy children (p<0.05), and corresponded with values observed in young adults in the age range of 20–30 years (220).

The mean of rcIMT SDS in patients with re-coarctation in the past was 3.6±1.4 compared with those without re-coarctation of 2.8±1.4, p<0.05 (Figure 4). This finding was also confirmed by logistic regression analysis (Table 8). A trend toward significance of increased rcIMT SDS in interventional correction mode compared with surgery was detected with logistic regression. rcIMT SDS differences between categorical subgroups of correction mode variable (balloon, stent and surgery correction mode) were observed, with a significantly greater mean rcIMT SDS in the stented CoA group (3.8±1.2) compared with the surgical correction (3.0±1.5), and those for whom balloon angioplasty was performed (2.7±1.5), p<0.05 (Figure 5). There was a moderate negative correlation of rcIMT SDS and BP difference between legs and right arm (Figure 6) (r=-0.4, p<0.05). rcIMT SDS was statistically significantly greater in the patients with LVH (3.7±1.6) than in the normal LVMi group (2.8±1.4, p<0.05) with a presence of a weak correlation (r=0.2, p<0.05). When compared rcIMT SDS within different LV geometry groups, the lowest rcIMT SDS was found in normal LV geometry group 2.6±1.4 in contrast with highest in concentric LVH 4.4±1.4 group, p=0.0001 (Table 11). rcIMT showed a weak positive correlation with RWT (r=0.31, p=0.001). There were no correlations between rcIMT SDS and age at the time of CoA repair, peak systolic gradient across the descending aorta, mean systolic gradient across the descending aorta, 24-hour ABPM systolic, diastolic BP SDS and mean arterial pressure (MAP) SDS, cSBP, fIMT SDS.

fIMT was equal to or lower than -1.65 SDS in 59 patients (53.6%). A significant correlation was found between fIMT and office pulse pressure (r=0.3, p<0.05) as well as 24-hour ABPM pulse pressure (r=0.3, p<0.05). The correlation between fIMT and BP difference between legs and right arm was insignificant.

All patients had a right carotid artery DC SDS below -1.65. The right carotid artery Einc was equal to or greater than 1.65 SDS for 93.6% (103 of 110), right β was within the normal range. Correlations of local stiffness of the carotid artery with peripheral and cSBP, office and ABPM pulse pressure, fIMT, LVMi, are shown in Table 9; a scatterplot of negative correlations between right DC SDS and cSBP (r=-0.5, p<0.05), age of CoA repair (r=-0.3, p<0.05), office pulse pressure (r=-0.4, p<0.05) and ABPM pulse pressure (r=-0.3, p<0.05) is shown in (Figures 7, 8, 9 and 10).

A right brachial artery FMD less than 10.0% was observed in 91 of 110 patients (82.7%). Re-coarctation in the past, BP difference between legs and right arm, and mean systolic gradient in the descending aorta were found to be statistically significant univariate associates with decreased FMD (Table 10). The median of the mean systolic gradient in the descending aorta was significantly greater in the group with FMD lower than 10% (12.0 (9.5-15.0) mmHg) versus the normal FMD group (7.0 (5.0-14.0) mmHg, $p<0.05$). A trend toward significance of decreased FMD in increased peak systolic gradient across the descending aorta group was observed (Table 10). The median of peak systolic gradient in the descending aorta was greater in the group with lower FMD (27.0 (21.0-34.0) mmHg) versus the normal FMD group (16.0 (12.0-33.0) mmHg, $p<0.05$) (Figure 11).

A multivariable logistic regression analysis was performed to determine associates with rcIMT SDS ≥3SDS. The initial dataset contained the following associates: age, age at CoA correction, gender, BMI SDS, CoA correction type, peak and mean systolic gradient across the aorta, re-coarctation in patient history, bicuspid aortic valve, mild aortic valve regurgitation or stenosis, AH, systolic office BP SDS on right arm, systolic 24-hour ABPM SDS on right arm, 24 ABPM MAP, 24 ABPM MAP SDS, office and 24 ABPM pulse pressure, office BP difference between the right leg and arm, cSBP, FMD, LVH. After performing a stepwise forward-backward model building, analysis resulted in two significant model associates with increased rcIMT - office BP difference between the right leg and arm (β for office BP difference between the right leg and arm =-0.04, $p<0.05$) and LVH (β for LVH =1.5, $p<0.05$). These two variables trended to predict rcIMT SDS elevation: MAP ($\beta=0.05$, $p=0.06$) and re-coarctation in anamnesis ($\beta=0.8$, $p=0.1$). McFadden's Pseudo-r2 of this model is 0.3. Additionally, rcIMT and rcIMT SDS were lowest in normal LV geometry group (Table 11).

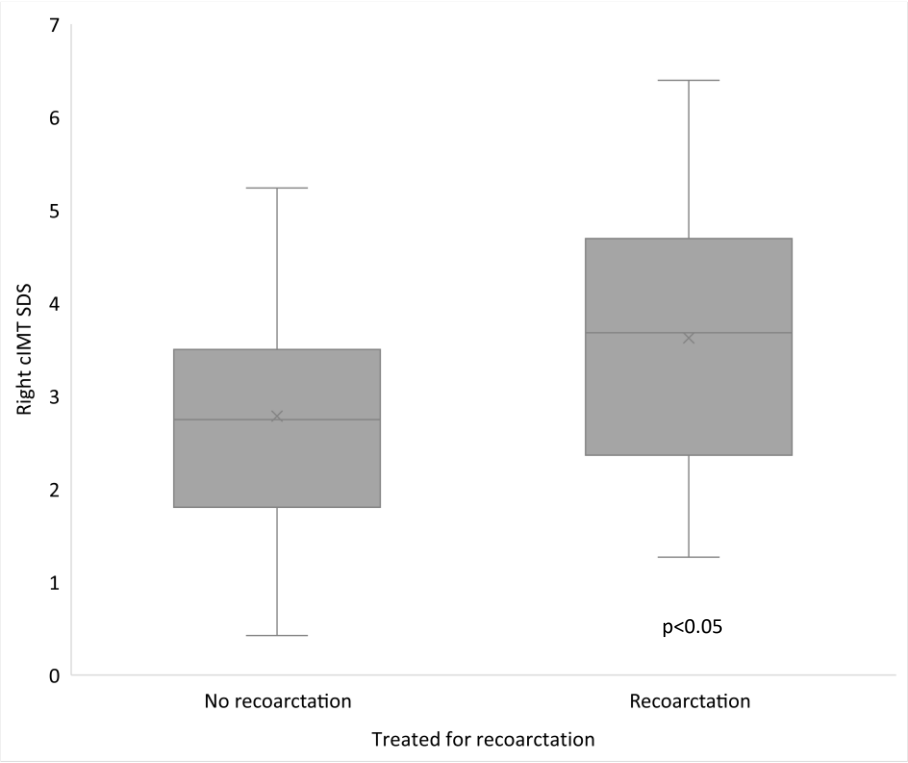


Figure 4. Comparison of right carotid intima media thickness (cIMT) SDS means between patients who did not have re-coarctation and patients who were treated for re-coarctation in the past.

Table 8. Univariable associates with increased rcIMT SDS in the study population.

Variables	**OR**	**95% CI**	**P Value**
Age at the time of CoA repair**	1.1	0.9-1.2	0.45
Patient age**	1.0	0.9-1.1	0.99
Gender (male)***	0.7	0.3-2.1	0.57
BMI SDS**	0.9	0.6-1.4	0.67
Percutaneous intervention***	3.2	0.9-11.7	0.08
Bicuspid aortic valve***	1.0	0.4-2.6	0.95
Re-coarctation in the past* **	**4.0**	**1.1-14.7**	**0.04**
Mild aortic regurgitation***	0.8	0.3-2.3	0.70
Mild aortic stenosis***	0.6	0.1-2.9	0.52
AH as factor***	1.9	0.7-5.3	0.21
Systolic office BP in right arm SDS*	0.9	0.6-1.4	0.65

Variables	OR	95% CI	P Value
Systolic 24h ABPM SDS in right arm*	1.4	1.0-2.0	0.09
cSBP*	1.0	1.0-1.1	0.43
FMD**	1.0	0.9-1.2	0.89
Peak systolic gradient across the descending aorta**	1.0	1.0-1.1	0.20
Mean systolic gradient across the descending aorta**	1.0	0.9-1.2	0.63
Office BP difference between leg and right arm in mmHg**	**1.0**	**0.9-1.0**	**0.04**
24 ABPM MAP mmHg**	1.0	0.9-1.0	0.32
24 ABPM MAP SDS**	1.1	0.8-1.5	0.44
Office pulse pressure in mmHg*	1.0	0.9-1.0	0.97
24 ABPM pulse pressure in mmHg*	1.0	0.9-1.1	0.09

Abbreviations: **Continuous normally distributed variables; **Continuous not normally distributed variables;***Categorical variables; ABPM, ambulatory blood pressure monitoring; AH, arterial hypertension; BMI, body mass index; BP, blood pressure; CoA, coarctation of the aorta; cSBP, central systolic blood pressure; FMD, flow-mediated dilatation; MAP, mean arterial blood pressure; rcIMT, right carotid intima media thickness.*

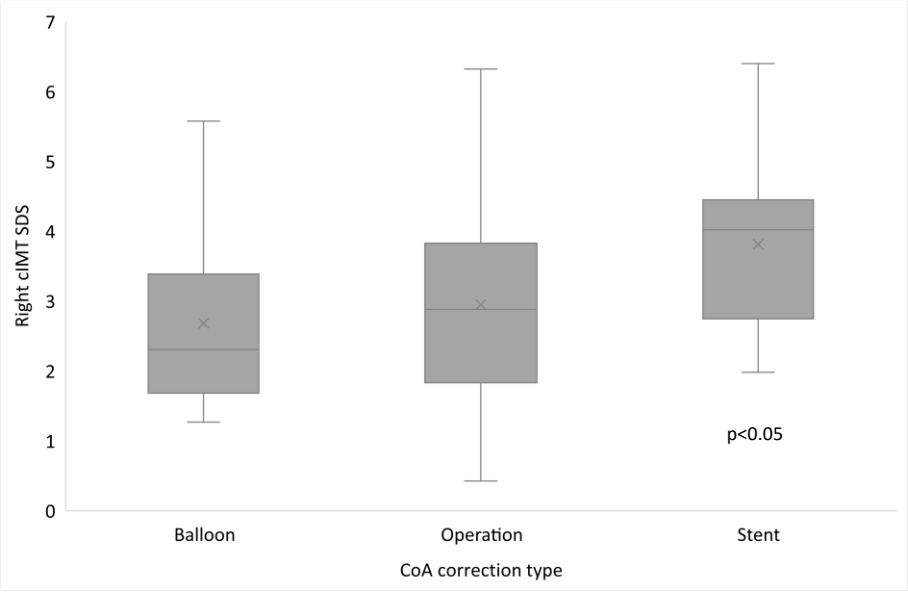


Figure 5. Comparison of right carotid intima media thickness (cIMT) SDS means between patients in whom coarctation of the aorta (CoA) was corrected by balloon angioplasty, surgery and stenting.

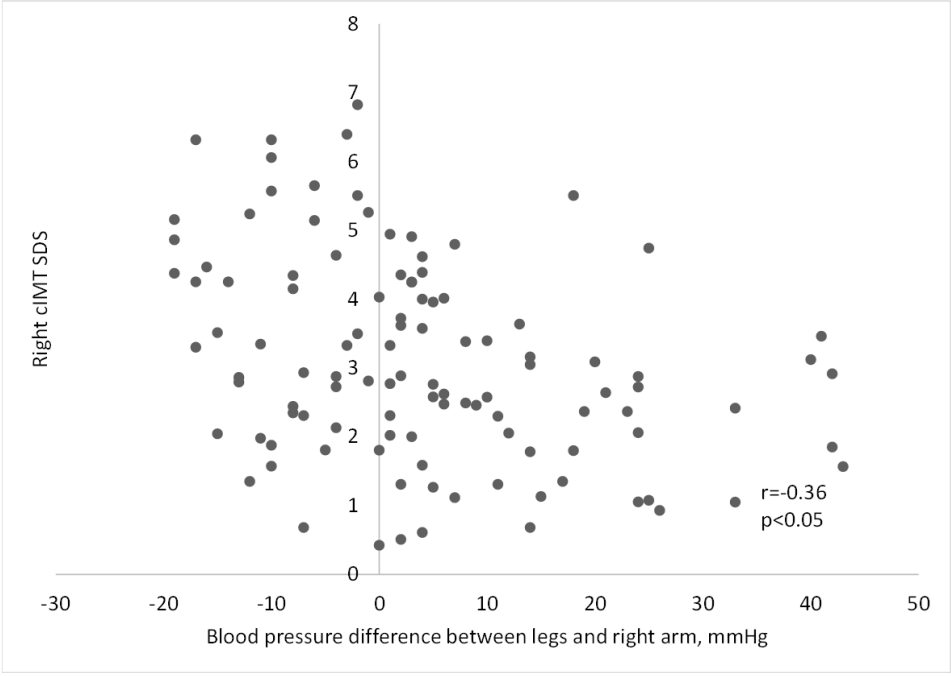


Figure 6. Scatter plot diagram of right carotid intima media thickness (cIMT) SDS and blood pressure difference between legs and right arm.

Table 9. Correlations of local stiffness of right carotid artery with BP, fIMT, LVMi, age at CoA repair, re-coarctation in the past.

Parame-ters of local stiffness of carotid	**Office systolic BP SDS**	**Systolic 24 ABPM SDS**	**cSBP**	**fIMT SDS**	**LVMi**	**Age at CoA repair**	**Office pulse pres-sure**	**24 ABPM pulse pressure**
DC right SDS	-0.2*	0.1*	**-0.5***	-0.2**	-0.03**	**-0.3****	**-0.4***	**-0.3***
	P=0.06	P=0.22	**P<0.05**	P=0.05	P=0.78	**P<0.05**	**P<0.05**	**P<0.05**
Einc right SDS	-0.1**	-0.1**	0.1**	-0.1**	0.1**	-0.1	-0.09**	-0.08**
	P=0.42	P=0.30	P=0.60	P=0.54	P=0.49	P= 0.62	P=0.37	P=0.42
β right SDS	-0.2**	-0.1**	-0.1**	0.04**	-0.1**	-0.02	-0.09**	-0.14**
	P=0.13	P=0.35	P=0.27	P=0.67	P=0.26	P=0.85	P=0.33	P=0.15

Abbreviations: **Pearson correlation at 0.05 (2-tailed); **Spearman rank correlation at 0.05 (2-tailed); ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CoA, coarctation of the aorta; cSBP, central systolic blood pressure; DC, distensibility coefficient; Einc, incremental elastic modulus; fIMT, femoral intima media thickness; LVMi, left ventricular mass index; β - stiffness index.*

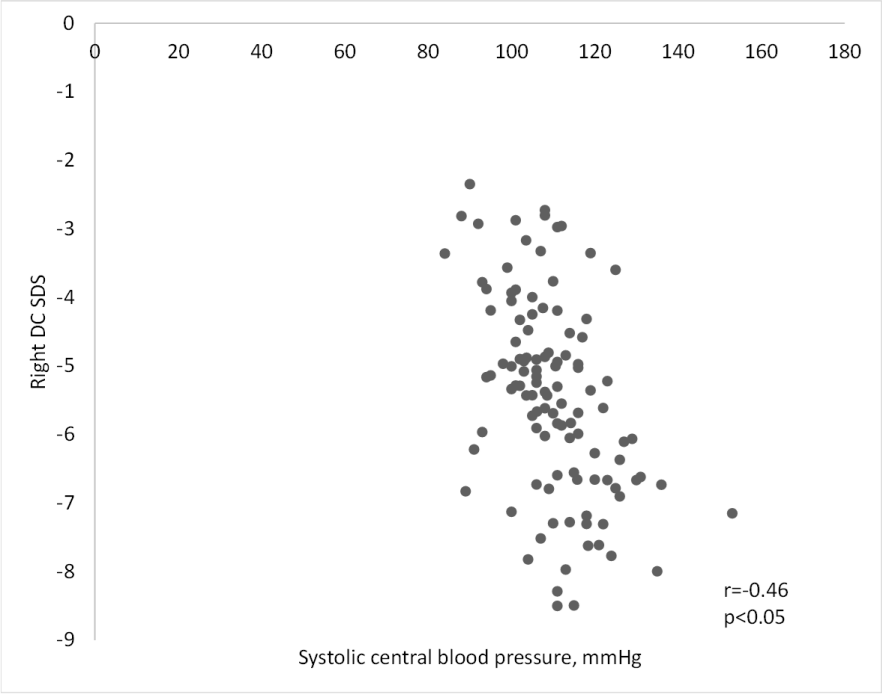


Figure 7. Scatterplot diagram of correlation between right distensibility coefficient (DC) SDS and central systolic blood pressure.

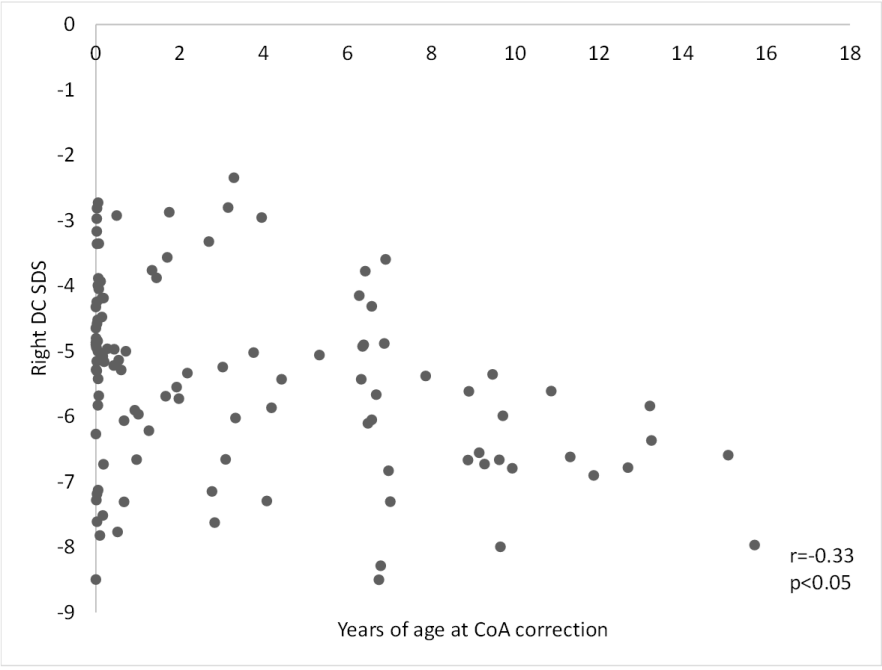


Figure 8. Scatterplot diagram of correlation between right distensibility coefficient (DC) SDS and age at CoA correction.

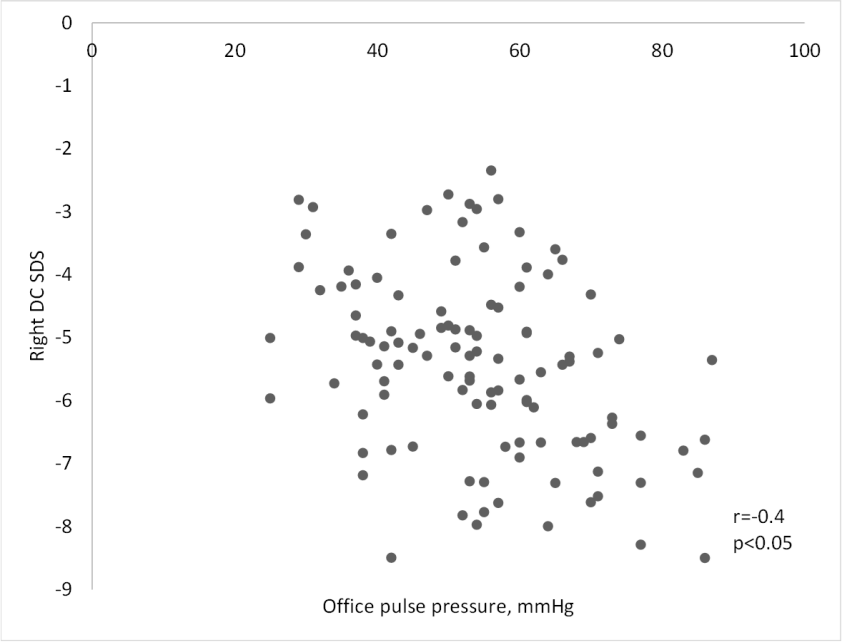


Figure 9. Scatterplot diagram of correlation between right distensibility coefficient (DC) SDS and office pulse pressure.

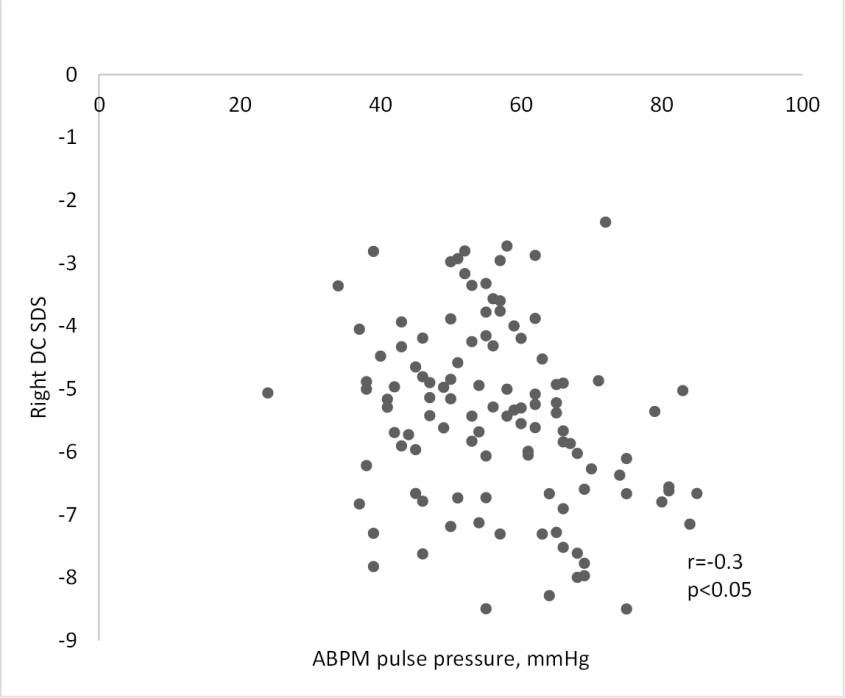


Figure 10. Scatterplot diagram of correlation between right distensibility coefficient (DC) SDS and ambulatory blood pressure (ABPM) pulse pressure.

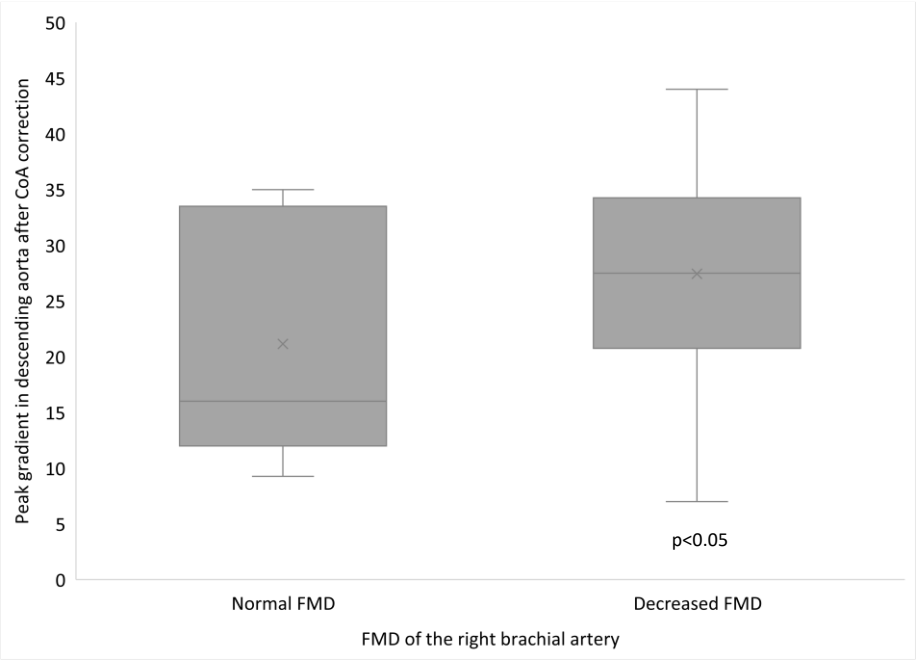


Figure 11. Median of peak systolic gradient in the descending aorta among normal and decreased flow-mediated dilatation (FMD) groups.

Table 10. Univariable associates with decreased FMD in the study population.

Variables	**OR**	**95% CI**	**P Value**
Age at the time of CoA repair**	1.0	0.8-1.2	0.85
Patient age**	1.0	0.8-1.2	0.58
Gender (male)***	0.8	0.2-3.6	0.81
BMI SDS**	0.7	0.4-1.4	0.32
Percutaneous intervention***	0.6	0.1-2.2	0.41
Bicuspid aortic valve***	1.0	0.3-3.9	0.97
Re-coarctation in the past* **	**0.2**	**0.03-0.8**	**<0.05**
Mild aortic regurgitation***	0.6	0.2-2.4	0.46
AH as factor***	0.4	0.1-1.8	0.25
Systolic office BP in right arm SDS*	1.2	0.6-2.2	0.66
Systolic 24h ABPM SDS in right arm*	1.1	0.6-1.8	0.81
cSBP*	1.0	0.9-1.0	0.49
rcIMT SDS*	1.0	0.6-1.6	0.99
Peak systolic gradient across the descending aorta**	1.1	1.0-1.2	0.05

Variables	OR	95% CI	P Value
Mean systolic gradient across the descending aorta**	**1.2**	**1.0-1.5**	**<0.05**
Office BP difference between leg and right arm in mmHg**	**0.9**	**0.9-1.0**	**<0.05**
24 ABPM MAP (mmHg)**	1.0	0.9-1.0	0.14
24 ABPM MAP SDS**	1.3	0.9-1.8	0.17
Office pulse pressure (mmHg)*	1.0	0.9-1.0	0.97
24 ABPM pulse pressure (mmHg)*	1.0	0.9-1.0	0.54

Abbreviations: **Continuous normally distributed variables*; **Continuous not normally distributed variables*; ****Categorical variables*; *ABPM, ambulatory blood pressure monitoring; AH, arterial hypertension; BMI, body mass index; BP, blood pressure; CoA, coarctation of the aorta; cSBP, central systolic blood pressure; FMD, flow-mediated dilatation; MAP, mean arterial blood pressure; rcIMT, right carotid intima media thickness.*

Table 11. Distribution of LV geometry and rcIMT SDS with different LV geometry patterns.

RWT	LVMi	
	≤95%	>95%
≤0.38	Normal geometry N=54 (49.1%) rcIMT SDS = 2.6 ± 1.4	Eccentric LVH N=18 (16.4%) rcIMT SDS = 3.1 ± 1.4
>0.38	Concentric remodeling N=20 (18.1%) rcIMT SDS = 3.3 ± 1.2	Concentric LVH N=18 (16.4%) rcIMT SDS = 4.4 ± 1.4

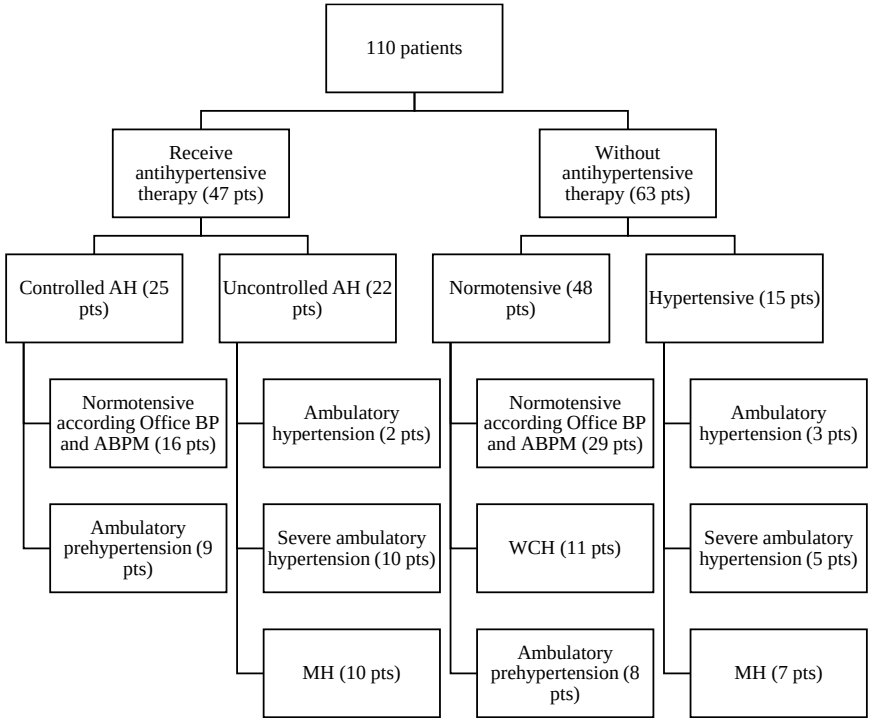
Abbreviations: *LV, left ventricle; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; rcIMT, right carotid intima media thickness; RWT, relative wall thickness.*

4.7. Antihypertensive treatment for late AH after CoA repair

4.7.1. Hemodynamic phenotypes of AH among treated and untreated patients for AH after CoA repair.

After performing office BP measurements and including 47 patients who already received antihypertensive therapy, a half of our study patients were considered hypertensive (55 out of 110). After 24h ABPM measurements, more than a half of our study patients became hypertensive (62 of 110 patients) due to newly discovered MH. Hemodynamic BP phenotypes among

treated and untreated patients for AH are summarized in Figure 12. Newly diagnosed AH was confirmed for 15 patients without antihypertensive therapy with 8 patients in Ambulatory or Severe ambulatory hypertension range and 7 patients with MH. While 48 patients without antihypertensive therapy were considered normotensive, meaning that they are normotensive according to office BP and ABPM (29 patients) or they are either in the ambulatory prehypertension (8 patients) or in WCH (11 patients) range.



Abbreviations: *ABPM, ambulatory blood pressure monitoring; AH, arterial hypertension; BP, blood pressure; CoA, coarctation of the aorta; MH, masked hypertension; WCH, white coat hypertension.*

Figure 12. Hemodynamic phenotypes of AH among treated and untreated patients for AH after CoA repair.

Real life antihypertensive therapy evaluation only for the patients who received AH treatment was analysed (47 of 110). They were categorized into controlled and uncontrolled AH groups (25 and 22 respectively). Patients within ambulatory (2 patients), severe ambulatory hypertension (10 patients) and MH (10 patients) range were included into the uncontrolled hypertension group. While controlled AH was considered if patient fell into the office and ABPM normotension (16 patients) or ambulatory prehypertension (9 patients).

Characteristics of patients who received antihypertensive therapy and were in either controlled AH or in uncontrolled hypertension range are listed in the Table 12. Uncontrolled AH group patients as expected had significantly higher average right arm 24-hour systolic ABPM as well as 24-hour systolic ABPM SDS (<0.01) and office systolic BP SDS was within ranges of tendency towards significance (p=0.08). Even though the median of peak gradient in the descending aorta was slightly higher in patients with uncontrolled AH (34.0 (26.3-37.8) vs 28.5 (15.8-34.0), p=0.02), the mean gradient in the descending aorta was without a significant difference among the groups. Uncontrolled hypertension group had lower median FMD compared with controlled AH group (4.5% (2.5-6.6) vs 6.0 (4.4-9.3); p=0.03). There were no significant differences in other vascular remodelling parameters among both groups (Table 12.)

Table 12. Characteristics of patients who received antihypertensive therapy and were in either Controlled AH or in uncontrolled hypertension range.

Variables	Controlled AH (25 pts)	Uncontrolled AH (22 pts)	p
CLINICAL CHARACTERISTICS			
Number of subjects (males/females)	17/8	14/8	0.75
Age (years)	13.2 (11.4-16.8)	12.3 (8.8-16.3)	0.52
BMI	18.6 (16.7-22.6)	20.5 (17.5-22.4)	0.46
BMI SDS	0.2 (-1.1-0.7)	0.6 (-0.3-1.3)	0.15
Age at the first CoA correction (years)	0.7 (0.1-6.9)	4.0 (2.0-9.1)	0.10
Years of follow-up after the first CoA correction date	7.2 (5.9-14.0)	6.5 (4.4-9.8)	0.92
Years of follow-up after the last	4.1 (1.4-12.8)	6.0 (2.0-7.8)	0.42

CoA correction date			
Office systolic BP right arm (mmHg)	124.0 (120.0-130.0)	126.5 (114.3-138.8)	0.32
Office diastolic BP right arm (mmHg)	68.0 (60.0-71.0)	60.0 (56.3-70.0)	0.93
Office systolic BP SDS right arm	1.5 (1.0-2.0)	1.9 (1.1-2.5)	0.08
Office diastolic BP SDS right arm	0.3 (-0.2-0.5)	-0.1 (-0.6-0.4)	0.21
Average 24-hour systolic ABPM (mmHg)	**118.0 (112.0-124.0)**	**132.0 (124.3-136.5)**	**< 0.01**
Average 24-hour diastolic ABPM (mmHg)	63.0 (56.0-66.0)	62.5 (58.0-64.8)	0.87
24-hour systolic ABPM SDS	**0.7 (0.3-1.0)**	**1.9 (1.6-2.3)**	**< 0.01**
Office BP difference between legs and right arm (mmHg)	3.0 (-1.0-13.0)	-5.5 (-13.8-9.3)	0.10
24 ABPM MAP mmHg	82.0 (77.0-87.6)	82.0 (75.3-85.8)	0.77
24 ABPM MAP SDS	0.1 (-1.2-0.7)	-0.1 (-0.7-0.7)	0.81
Office pulse pressure in mmHg	61.0 (53.0-66.0)	63.5 (55.3-73.3)	0.23
Correction of re-coarctation in patient history / no need for reintervention on the descending aorta	13/12	7/15	0.16

ECHOCARDIOGRAPHIC PARAMETERS			
LVMi	38.8±6.2	36.8±7.0	0.31
LV EF (Simpson BP %)	66.5 (62.3-72.3)	69.0 (67.0-72.0)	0.88
Peak systolic gradient across the aorta (mmHg)	**28.5 (15.8-34.0)**	**34.0 (26.3-37.8)**	**0.02**

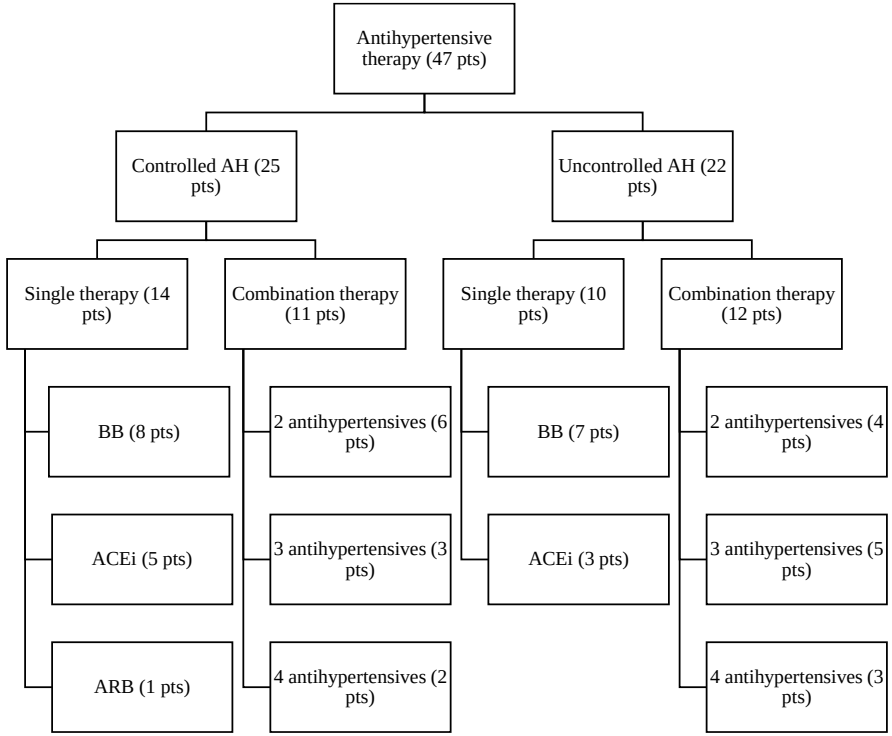
Mean systolic gradient across the aorta (mmHg)	12.0 (6.0-16.0)	14.0 (11.0-15.8)	0.16
Bicuspid aortic valve vs tricuspid	18/7	12/10	0.21
Presence of mild Aortic valve stenosis vs no stenosis	4/21	2/20	0.48
Presence of mild Aortic valve regurgitation vs no regurgitation	16/9	10/12	0.20
VASCULAR REMODELLING PARAMETERS			
cSBP (mmHg)	111.0 (106.0-118.0)	116.0 (109.5-124.0)	0.12
rcIMT SDS	2.8 (1.9-3.6)	2.9 (2.3-4.3)	0.44
Right fIMT SDS	-2.8 (-3.5- -1.7)	-2.3 (-4.1- -1.3)	0.34
FMD %	**6.0 (4.4-9.3)**	**4.5 (2.5-6.6)**	**0.03**
Right DC SDS	-5.5 (-6.6- -4.7)	-5.8 (-6.7- -4.9)	1.00
Right Einc SDS	3.4 (2.6-4.0)	4.1 (3.4-5.0)	0.98
Right β SDS	-0.8 (-1.8-0.1)	-0.5 (-0.9-0.3)	0.91

Abbreviations: *ABPM, ambulatory blood pressure monitoring; AH, arterial hypertension; BMI, body mass index; BP, blood pressure; CoA, coarctation of the aorta; cSBP, central systolic blood pressure; DC, distensibility coefficient; EF, ejection fraction; Einc, incremental elastic modulus; fIMT, femoral intima media thickness; FMD, flow-mediated dilatation; LV, left ventricle; LVMi, left ventricular mass index; MAP, mean arterial blood pressure; rcIMT, right carotid intima media thickness; β, stiffness index.*

4.7.2. Antihypertensive therapy

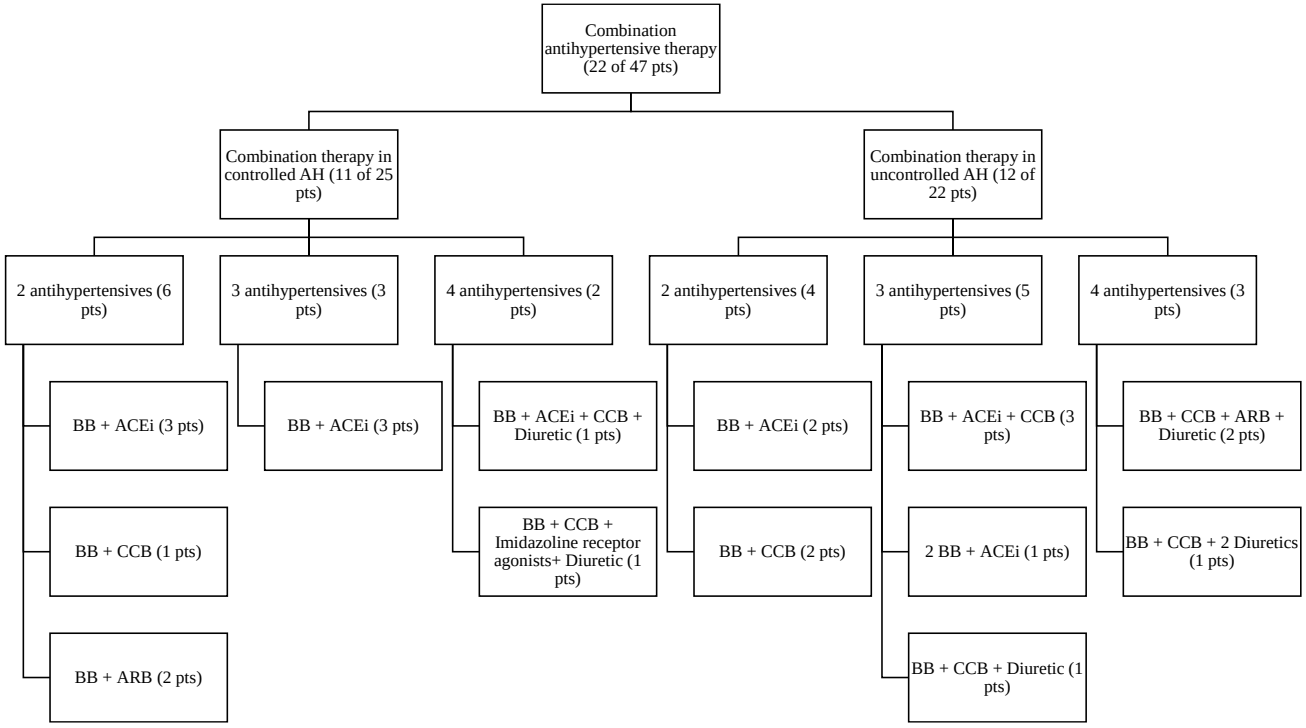
Real life antihypertensive therapy evaluation only for the patients who received AH treatment was analysed (47 of 110). They were categorized into controlled and uncontrolled AH groups (25 and 22 respectively). Antihypertensive therapy among patients after CoA repair with controlled AH and uncontrolled hypertension is summarized in Figure 13. Antihypertensive medication used for combination therapy among patients with Controlled AH and uncontrolled hypertension are listed in Figure 14. No differences were found between controlled AH and uncontrolled hypertension groups in regards of single or combination antihypertensive therapy (X^2=0.5, p=0.5). However, the uncontrolled group was not homogenic in regard to the single

and combination therapy among different hypertension phenotypes (Figure 15). Combination therapy was more prevalent among ambulatory and severe ambulatory hypertension patients, while single therapy was used more often among children with MH. BB were the most used antihypertensive group received by 80.1% of patients (38 of 47 patients). BB were the equally dominant antihypertensives among patients with controlled AH (8 of 14 patients) and uncontrolled BP (7 of 10 patients) receiving single therapy. BB were also included into all combination therapies among both groups. The first line BB was metoprolol (25 of 47 patients). The mean dose of metoprolol was significantly higher in uncontrolled hypertension group compared with controlled hypertension (0.8 mg/kg (0.6-1.0) versus 0.5 mg/kg (0.3-0.8), p=0.03). The second most used BB was nebivolol (12 of 47 patients), which was used only for combination therapy and mainly in the uncontrolled hypertension group (8 of 12 patients). The median dose of nebivolol was 0.07 mg/kg (0.04-0.1), it was higher in uncontrolled AH group with a trend towards significance (0.08 (0.06-0.1) versus 0.05 (0.04-0.06), p=0.08). ACEi was the second most used antihypertensive group received by 44.7% of patients (21 of 47 patients) for the single or combination therapy in both groups. Ramipril was the most popular, and 14 of 21 patients received it for a single or combination therapy with a median dose of 2.63 mg/m^2 (1.99-3.02). Enalapril was the second most used ACEi (7 of 21 patients) with a median dose of 0.17 mg/kg (0.12-0.19). ACEi were used in both groups without significant difference in agent or dose (Table 13). CCB amlodipine was more often used in uncontrolled AH group in combination with other drugs (p=0.04), however, the dose of amlodipine did not differ among groups (Table 13). The distribution of other medication was without significant differences among the groups. No superiority of specific drugs and drug combinations were noticed across the groups.



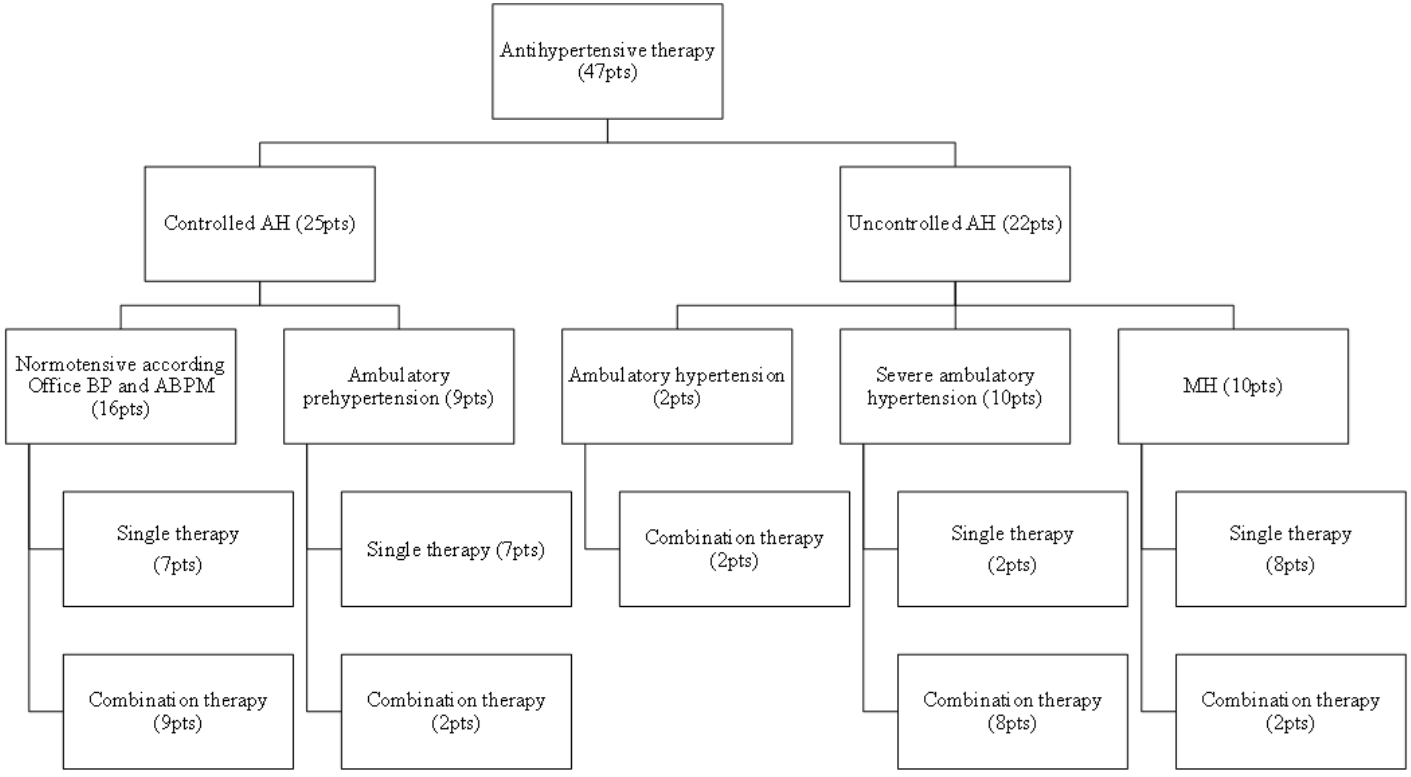
Abbreviations: *ACEi, Angiotensin-Converting Enzyme Inhibitors, AH, arterial hypertension; ARB, angiotensin II receptor blockers; BB, β-adrenergic receptor blockers; CoA, coarctation of the aorta.*

Figure 13. Antihypertensive therapy among patients after CoA repair with controlled AH and uncontrolled hypertension.



Abbreviations: *ACEi, Angiotensin-Converting Enzyme Inhibitors, AH, arterial hypertension; ARB, angiotensin II receptor blockers; BB, β-adrenergic receptor blockers; BP, blood pressure; CCB, Calcium channel blockers.*

Figure 14. Antihypertensive medication used for combination therapy among patients with controlled AH and uncontrolled hypertension.



Abbreviations: *ABPM, ambulatory blood pressure monitoring; AH, arterial hypertension; BP, blood pressure; MH, masked hypertension.*

Figure 15. Single and combination antihypertensive therapy distribution among different haemodynamic phenotypes of AH

Table 13. Antihypertensive therapy among treated controlled and uncontrolled AH patients

Variables	Controlled AH (25 pts)	Uncontrolled AH (22 pts)	p
ANTIHYPERTENSIVE THERAPY			
BB	19 (76.0%)	19 (86.4%)	0.47
ACEi	12 (48.0%)	9 (40.9%)	0.63
CCB	**3 (12.0%)**	**9 (40.9%)**	**0.04**
ARB	3 (12.0%)	0 (0%)	0.24
Diuretic	2 (8%)	4 (18.2%)	0.40
Doses of antihypertensive agents			
Metoprolol mg/kg	**0.5 (0.3-0.8)**	**0.8 (0.6-1.0)**	**0.03**
Nebivolol mg/kg	0.05 (0.04-0.06)	0.08 (0.06- 0.1)	0.08
Ramipril mg/m^2	2.38 (2.00- 2.97)	2.70 (2.01- 3.00)	0.90
Enalapril mg/kg	0.17 (0.16- 0.21)	0.13 (0.11- 0.15)	0.57
Amlodipine mg/kg	0.14 (0.12- 0.15)	0.10 (0.09- 0.13)	0.28

Abbreviations: *ACEi, Angiotensin-Converting Enzyme Inhibitors, AH, arterial hypertension; ARB, angiotensin II receptor blockers; BB, β-adrenergic receptor blockers; CCB, Calcium channel blockers.*

5. DISCUSSION

The significant technical improvement in the field of cardiovascular surgery as well as interventional cardiology has led to a growing population of patients following a successful correction of CoA (10, 116, 118). However, the care of these patients remains challenging due to a reported high prevalence of complications following CoA repair, including: systemic hypertension, aortic aneurysm formation, cerebrovascular complications and premature coronary artery disease (10). The contemporary cardiovascular event rate in CoA population, including myocardial infarction (125), is reported to be 11% in 10 years (126) and a 10% risk of developing intracranial aneurysms with increased risk of stroke (124), accounting for the majority of deaths at a relatively young age (4, 118). Some studies have shown that CoA correction does not resolve the inborn pathology of the prestenotic part of the aorta and have demonstrated a reduced prognosis even for individuals who had a successful repair (19, 131). Even though AH is the most significant complication of CoA (13-16), the data on prevalence of AH in patients after CoA correction differ. This is due to the different definitions used for diagnosis of AH, based on office BP or ABPM measurements, as well as the definition of a successful CoA correction (17, 158, 161-163). Moreover, there is only a scarce number of publications analyzing BP status in children after CoA repair according to the 2016 European Society of Hypertension guidelines and categorizing it into different BP phenotypes based on the interpretation of both office BP and ABPM results. Late AH is still a challenge for many adult and paediatric cardiologists even after hemodynamically effective CoA repair with reported prevalence up to 70% (9-16, 117, 157-160, 221). Our finding of a 56% prevalence of AH following a haemodynamically successful CoA repair is in the lower range (42-70%) compared to several other studies mainly from adult and adolescence populations (9-12). In contrast to other studies, our study group included only patients who met the criteria of the hemodynamically successful CoA correction and none of whom had re-coarctation at the time of enrolment. Our results indicate that even children with the hemodynamically successful correction present a high prevalence of AH. Also, we found MH in 12.7% of patients with office normotension without any antihypertensive therapy and in 18.2% of those who were already treated with antihypertensive drugs. In addition, we found that the dominant hemodynamic phenotype of hypertensive patients was isolated systolic hypertension detected in 86.5% of patients. Furthermore, hypertensive patients had a greater peak systolic flow gradient across the aorta

than normotensive patients (32.0 (20.2- 36.0) mmHg vs 25.0 (19.0-30.0); p = 0.02), however it was still below 40 mmHg. Moreover, the peak gradient was also significantly greater for those patients who had been treated for re-coarctation in the past. However, the role of even a small mean systolic gradient in the development of AH after CoA repair was not confirmed by our results of multivariable regression analysis. According to these results we cannot deny that even a gradient, which is considered as insignificant with time may lead to AH. One may assume that with time (i.e. age) the continuing even a small elevation of systolic gradient in the aorta may aggravate the effect of generalized disturbance of the aortic wall structure and increased stiffness and cause isolated systolic hypertension (4, 171). Reports of findings in cohorts of adults after CoA repair showed the associations of mild narrowing in the descending aorta with the development of hypertension as well (118, 169). It was also suggested to adopt a lower threshold for reintervention for residual aortic narrowing than posed in current guidelines in order to improve long-term outcomes in these patients (169).

There are some studies describing isolated systolic hypertension as the dominant phenotype after a successful CoA correction, consistent with the present study (17, 158, 161, 162). Isolated systolic hypertension is also the dominant phenotype of primary hypertension in children and adolescents (17, 222). However, the percentage of isolated systolic hypertension among CoA patients in our study was greater than among patients with primary hypertension. It is assumed that isolated systolic hypertension in adolescents with primary hypertension is caused by hyperkinetic circulation (223). Although we did not analyze hemodynamic parameters such as cardiac output and total peripheral resistance, one can speculate that the isolated systolic hypertension phenotype in children after CoA repair is caused by increased aortic stiffness (224).

The preductal CoA type typically requires surgery <1 years of age, hence the first age group was selected accordingly. The other two age groups were selected based on literature- Brown et al. has identified the age of 9 years as a cut-off point towards a significantly higher risk of development of AH (116). According to a few systematic reviews on hypertension after repair of CoA, the factors associated with AH include older age at the time of correction, age at follow-up, the method used to measure BP and the type of correction performed (8, 14). Brown et al. concluded that patients aged 9 years or older at the time of CoA repair had AH significantly more often at 5 to 15 years of follow-up. Choudhary et al. found that AH after CoA repair is associated with initial repair after 6 years of age (12, 116). On the other hand, Kenny et al. concluded that 1/3 of CoA patients become hypertensive despite early and

effective surgical or interventional repair and that AH is an inevitable consequence of CoA, even when anatomical repair was done in the first months of life (8). We did not find statistically significant differences in the prevalence of AH among the three groups of patients classified according to age at correction. However, numerically the prevalence of AH was the lowest in children treated in their 1st year (43.4 %) and the greatest in children treated after their 8th year of life (66.7 %). Children treated with surgery had the lowest prevalence of AH, while interventional CoA correction type and age were the main associates with AH in our study. Thus, our results correspond to other reports and indicate that, although age of correction may have an effect, even early correction is associated with high risk of AH.

However, the exact pathogenesis of late AH in CoA is still unclear (8, 165). Current evidence suggests that despite an early and successful CoA repair, structural and functional alterations of the pre-coarctation aorta are still present with preserved post-coarctation arteries (192, 193). Consistent histological findings at the time of surgery in CoA patients show a disrupted arrangement of elastin within the tunica media, significantly more collagen and less smooth muscle mass in the aorta above than below CoA; thus, a more rigid pre-coarctation aortic wall (194). The influence of the above-mentioned histological findings concerning the baroreceptors in the upper vascular bed may only explain the preoperative and early postoperative proximal hypertension (194). It is thought that aetiology of late systemic AH after CoA repair is multifactorial (8, 165). There are some known and some hypothetical factors which can play a role in the pathogenesis of late AH after CoA repair. Among the known factors there are those related with CoA itself such as aortic arch morphology (gothic arch) (155), CoA correction type, older surgical techniques (subclavian flap) (167, 168), older age at CoA presentation and timing of surgery, presence of re-coarctation (166), and method used to measure BP (8, 14). The known factors were eliminated from the study by selecting only patients with normal arches and the most recent operation technique - an end-to-end anastomosis - as well as disqualifying any patient with current re-coarctation from the study. Among factors which are hypothetical and still under investigation, in addition to the inherent arteriopathy involving the narrowed segment of the aorta, is the increased arterial stiffness of the pre-coarctation part of the aorta induced by chronic shear stress, and abnormal renal flow (157, 160, 169, 170). However, the real picture of pathophysiological mechanism of AH after CoA repair is not yet well understood.

Our results also indicate a high prevalence of underdiagnosed MH, which was not diagnosed prior to the enrolment to the study for half of MH patients.

Studies in adolescents and young adults after CoA repair revealed MH in 35-40% of patients (163, 225). Thus, MH becomes an even bigger issue in aging CoA population as higher MH numbers are found later in life. The main cause of misdiagnosis of MH is not routinely performed ABPM. Due to the missed diagnosis of MH, there is an undertreatment observed in this group of patients. Additionally, our results show undertreatment despite the timely MH diagnosis, as the low dose single antihypertensive therapy was carried on instead of higher drug doses or combination therapy. One might speculate that a patient after CoA repair with confirmed MH should benefit from more frequent regular follow-up ABPM measurements to evaluate the efficacy of treatment as well. Thus, more frequent AMBP performance in this population would help not only to diagnose MH, but also to lower a tendency to be undertreated as it is well known from adult studies, that untreated MH leads to higher cardiovascular risk events later in life (226). However, not only MH patients, but all AH patients in our study population despite the AH control level were observed with a tendency to single versus combination antihypertensive therapy. This shows a potential undertreatment of other AH HD phenotypes after CoA repair as well as possibly due to the lack of regular follow-ups and BP control performance at home. It is to be regretted that due to the cross-sectional design of our study we have not evaluated repetitive ABPM measurements and did not evaluate the duration of AH. However, this real time evaluation of AH shows real clinical picture of AH treatment. Additionally, our observations strongly emphasize the need of follow-up guidelines for this study population.

Our results indicated a high prevalence of LVH diagnosed for 36 of 110 (32.7%) patients irrespective of BP status. LVH is known to be a risk factor for adverse cardiac events. There is data suggesting that increased stiffness in the repaired aorta increases LV afterload leading to LV hypertrophy and diastolic filling abnormalities (185-187). Thus, LVH relationship to end-organ effects has been assessed using non-invasive techniques from echocardiography to cardiac MRI in CoA population (11, 154, 188). The literature shows that the prevalence of LVH in a successfully repaired CoA patients varies from 24% (225) to 38% (154) in adolescents and even higher 41-65% in adults (126, 227) (190) (191), with respectively higher prevalence in aging population, thus higher cardiovascular morbidity and mortality. The prevalence of LVH in this study population varies also partially due to the different LVH definitions and tools used to calculate LVH and relatively due to contrasting targeted populations (different age groups, CoA repair techniques, timing of CoA repair etc.) (11, 154, 188-190). Some studies have found the associations between LVH and higher systolic BP in CoA

population (190, 225). In our study the median LVMi of normotensive patients was lower in comparison to hypertensive patients with a tendency towards the significance. However, when we compared LMVi within controlled and uncontrolled AH patient groups, there were no significant difference found among them. Our results reveal high LVH prevalence in hypertensive paediatric CoA patients despite the AH control level.

We also evaluated LV geometry patterns in our study population and found that they are not uniform among children who undergone a successful CoA repair as well as with no difference among hypertensive and normotensive patients. In 49.1% of our population, LV geometry was normal with normal LVMi and RWT. In 18.1% of patients LVMi was normal, but RWT was elevated, indicating concentric remodelling. Both LVMi and RWT were elevated in 16.4% of patients (concentric LVH). While LVMi was elevated with a pattern of eccentric hypertrophy in 16.4% of patients. In patients with essential AH, pressure overload leads to concentric remodelling and eventually increase in systolic wall stress cause the shift to concentric LVH. While eccentric LVH is usually associated with volume overload and not pressure overload, and more often related with pathologies such as mitral regurgitation (228). We have found significantly highest BMI SDS in eccentric LVH group which is consistent with studies relating this LV geometry pattern with obesity (229). Additionally, the main associate with LVH in our study was increased BMI SDS irrespective of BP, systolic gradient in the descending aorta and other factors related to CoA, even though 80% of study population was within normal BMI ranges. This finding underlines the role of traditional cardiovascular risk factors such as overweight at least in patients with small gradients of systolic flow in the aorta and even in children with relatively normal BMI.

The LV geometry has been studied in couple of adult studies after a successful CoA repair (230, 231). In agreement with our findings, no uniform pattern of LV geometry was detected with no obvious explanation of pathogenetic mechanism. However, not only hypertensive, but also normotensive patients after a successful CoA repair have been related to high incidence of LVH with multiple patterns of LV geometry (230, 231). Whatever the pathogenetic mechanism, any type of LV remodelling is predictive of the higher incidence of cardiovascular events (228).

We also assessed the arterial structure and function in arteries exposed to high and low BP, i.e. high pressure in the right common carotid and right brachial artery, and low pressure in the superficial femoral artery.

The main finding of our study is that over 80% of children, following a successful CoA repair who had a low BP gradient between the right arm and

right leg, had significantly increased rcIMT with values corresponding to those observed in subjects 10-20 years older. Increased rcIMT was associated with LVH, re-coarctation in the past, interventional correction of CoA and a lower difference of BP between the leg and right arm. Additionally, we found significantly lower values of fIMT, as well as the increased local stiffness of the right carotid artery in all studied subjects. Moreover, we documented significant impairment of FMD in the right brachial artery.

We evaluated cIMT as a non-invasive reproducible marker of arteriosclerosis, which was reported as being a useful tool for cardiovascular risk assessment and prediction of end organ damage in adult CoA patients (4, 196, 197) with a recent estimation of cIMT exceeding 0.8 mm having a 15-fold higher cardiovascular risk (126). The main associates with elevated rcIMT were office BP difference among the right leg and arm and LVH, which indicate greater and longer exposure to elevated BP. As cIMT increases with age, higher than expected values of cIMT indicate a more advanced biological age. The average rcIMT SDS in our study population of +3.1 ±1.5 might resemble cIMT in healthy adults 10–20 years older. Highest cIMT was detected among our patients with concentric LVH pattern. Additionally, a statistically significant weak positive correlation between rcIMT and RWT demonstrated an independent association of increased rcIMT and concentric LV geometry. These findings relate to studies performed in general middle-aged subjects, where cIMT is found to be greater in patients with concentric LVH (232).

We have shown no association of increased rcIMT SDS with increased office right arm systolic BP SDS as well as cSBP. However, a negative correlation between right DC SDS and cSBP indicated that there was a significant relation between increased local stiffness and increased cSBP. Other studies have found premature arteriosclerosis and an increased risk of cardiovascular events in young adulthood in both hypertensive and normotensive patients following CoA (2, 185, 195). Dempsey et al. reported associations of increased peripheral BP with increased cIMT following CoA repair (198). However, this study included only 26 CoA patients, of whom only 12 were hypertensive, and did not classify those already treated with antihypertensives as hypertensive. In addition, in the Dempsey at al. study, cIMT was expressed as absolute but not standardised values.

An attempt to explain the increased cIMT in hypertensive patients following CoA repair by activation of gene expression leading to proliferation and hypertrophy of the smooth muscle cells and increased glycosaminoglycan production within the arterial wall was made in the past (199). In addition, some studies have shown that the increased arterial stiffness in hypertensive

patients was caused by altered proportions of collagen subtypes and the ratio of synthesis and degradation of collagen type-1 (204). Mechanistically, increased rcIMT in CoA patients may be explained by exposure to greater pulse pressure, which is typical for CoA patients, even for those who had normal BP. Greater pulse pressure was found to be an associate with cIMT in adolescents with primary hypertension (200). However, in CoA, pulse pressure is of a much greater magnitude. We found a negative association of right DC SDS with office and ABPM pulse pressure, which shows a relation between increased local stiffness and increased pulse pressure in children following a successful CoA repair. On the contrary, lower fIMT appears to be a consequence of lower exposure to pulsatile flow with lower pulse pressure amplitude.

Another important finding was that patients with treated re-coarctation in the past had significantly greater cIMT SDS compared with those without re-coarctation. This finding was significant even though the re-coarctation was treated completely and no present signs of re-coarctation with diastolic runoff were registered. It is known that re-coarctation remains one of the most prevalent complications of CoA due to inadequate aortic wall growth at the site of repair, and its prevalence is highly related to the age at correction, low birth weight and correction type, with a prevalence ranging 5-15% (87, 233) following early surgical repair and up to 50% after interventional treatment (234). One may assume that re-coarctation means that the pre-stenotic arteries of these patients were exposed to greater haemodynamic damage by elevated BP and pulse pressure than in patients who did not develop re-coarctation. Given the heterogenicity of our study population in correction types and timing, we consider the 38% prevalence of re-coarctation history in our study is moderate. The higher cIMT in this population shows that even treated re-coarctation with a low BP gradient may be considered a prognostically significant risk factor and may contribute to concomitant vascular damage.

According to our findings, CoA treatment strategy also presumably plays a role in arterial stiffness. Our results show that patients in whom CoA was stented had greater rcIMT than those who were treated by surgery. This finding corresponds with the results of Sarkola et al. (196). However, the interpretation of this result is difficult. One can only speculate that subjects who were stented had a stiffer aorta than those who qualified for balloon angioplasty or surgery. Additionally interventional CoA treatment with stent placement in our study was performed for older patients compared with surgery (median age at interventional treatment (6.9 (4.4-9.6)) versus surgery (0.2 (0.1-1.9)). The age distribution among different CoA correction modes in our study complies with the tactics used in other centres, where surgery is

preferred over interventional treatment for infantile CoA patients <4 months old (25, 79-81), and interventional treatment chosen to correct postductal CoA for children who weigh >20kg (25, 77, 83, 95-100). For children older than 4 months and weighing <20kg, a decision regarding CoA treatment mode is made on case-by-case basis (79, 83, 84).

Apart from the structural changes of the carotid wall, we found a prevalent reduction of carotid distensibility in our study population, corresponding to results in studies in adults (195, 196, 203). Another finding is the significantly decreased endothelial function in the majority of study patients compared to the adult reference data. However, abnormal vascular reactivity measures are not consistently found in patients following CoA repair (156, 192, 210), and there is no reference FMD data in children, thus we are not aware of how different FMD values might be present in the population of healthy children. We noticed that even a slightly higher peak and mean systolic gradient in the descending aorta is related to a decreased endothelial function in patients without diastolic runoff and without present re-coarctation, suggesting that even a small increase in systolic gradient may impact the devolvement of impaired endothelial function. Both impaired endothelial function, increased stiffness, and rcIMT in children following CoA repair might indicate advanced arteriosclerosis and are features of the EVA phenomenon.

The associations between cSBP and hypertensive cardiovascular mortality as well as target organ damage have already been shown in hypertensive adult population (235). We have found statistically significantly lower cSBP for patients with brachial normotension in comparison with hypertensive patients, p=0.0002. However, there was no difference in the cSBP among controlled and uncontrolled AH groups. A low number of patients does not allow to interpret usefulness of assessment of cSBP in clinical practice.

We have also evaluated antihypertensive agents used in real life of AH treatment for successfully corrected paediatric CoA patients. The primary medication in our study was BB with metoprolol as the first line agent used for more than a half of treated patients, and nebivolol was the second most used BB. The medication used in our study partially complies with a several clinical antihypertensive studies which were conducted within the CoA patient population. Moltzer et al. showed superiority of BB (metoprolol) over ARB on mean BP lowering, yet the large artery stiffness did not change with either treatment (179). The second line BB nebivolol used in our study was not evaluated in clinical trials for paediatric use and is not recommended for paediatric population according to the 2016 European hypertension guidelines

(17). However, due to the lack of clinical trials in paediatric population, physicians tend to select medication proven to work in adult population. ACEi was the second most popular antihypertensive group in our study group. Di Salvo et al., compared BB atenolol and ACEi enalapril regarding the tolerability and efficacy on late systemic AH and LVH in children and young adults after successful CoA repair and concluded that even though both medications were similarly effective in reducing systolic 24-h BP, only enalapril demonstrated a significant reduction of LVH (180). The other study performed by Brili et al. complemented the previous study by adding up that ACEi ramipril has also a potential to reverse the impaired endothelial function and decrease the expression of proinflammatory cytokine IL-6, sCD40L, and adhesion molecules even in normotensive young adults after a successful CoA repair (181). Therefore, both of these studies showed that ACEi has a potential to lower the cardiovascular mortality and morbidity in CoA patient population even irrespective of BP status.

Due to the lack of randomized control trials in CoA patients, the most recent 2020 ESC adult CHD guidelines recommend following the general rules of antihypertensive treatment in patients after CoA repair (77, 183). American Academy of Paediatrics guidelines do not recommend specific pharmacological treatment options for children after CoA repair (172), whereas, 2016 Paediatric European Society of Hypertension guidelines are more specific and recommend BB, CCB, and drugs affecting the renin-angiotensin-aldosterone system for patients after CoA repair (17). However, these recommendations are based only on a few very small sample size clinical studies (179, 184).

Additionally, several review articles have provided an overview of the actual worldwide clinical practice of antihypertensive use in this population. Vasodilators, thiazide diuretics, CCB are suggested in addition to the drugs evaluated by clinical trials mentioned above (160, 178). Although based on this limited data, the most appropriate agents for the late systemic hypertension after a successful isolated CoA repair should be ACEi followed by BB, and lastly by ARB (181, 182), which partially complies with our study group medication preferences.

Beyond the question of drug selection and drug combination, there remains the problem of proper dosing. We have observed that all antihypertensives were used within the lower recommended dose range. Even though the metoprolol dose was higher in the uncontrolled hypertension group, the median dose did not exceed 1 mg/kg for the majority of patients. While the recommended maximal dose of metoprolol is 2 mg/ kg (17). ACEi were also used within the lower dose range. On one hand, smaller doses of

antihypertensives might be one of the causes of higher prevalence of uncontrolled hypertension in our study population. On the other hand, it is hard for a paediatric cardiologist to titrate the dose to the highest tolerable and optimal for the targeted BP due to the potential side effects of these medication. Especially when there are not clear side effects in paediatric population due to the lack of randomized control clinical trials.

Another aspect important for the efficacy of antihypertensive therapy is the failure to adhere to the prescribed regimens which is hard to be tested and was not evaluated in our study. Nonadherence to chronic medication regimens, especially to antihypertensive agents is a well-described common problem in adult population which affects 43% to 65.5% of patients (236) and has also been reported among adolescents with primary AH (237).

The most important task for a physician is to guarantee that CoA has been corrected successfully, without a presence of re-coarctation or a significant narrowing at any part of the aorta. If the residual narrowing of the aorta exists, a timely intervention and relevant re-coarctation correction are necessary. And only if no significant residual narrowing exists, the non-pharmacological treatment and pharmacotherapy for the late AH may be continued. The general rules of non-pharmacological treatment of AH are recommended to all hypertensive patients, including those following a successful CoA repair (17, 160, 172, 178), although it was not assessed in this study. Even though there is a wide spectrum of antihypertensive medication recommended for treatment of AH in general paediatric population, the lack of clinical trials establishes a limited access to the most modern antihypertensive drugs not only for specific targeted hypertensive paediatric CoA population but for all hypertensive children in general (17, 172). Thus, the tough choice of antihypertensive drug still lies on the shoulders of a treating physician.

LIMITATIONS

This work has several limitations. First, its cross-sectional design limits analysis of cause-and-effect relationships, which includes a lack of analysis of hemodynamic parameters, and the subtle effects of different surgical approaches in CoA repair, which might be related with AH development. Second, due to a lack of normative values for brachial artery FMD in healthy children, the evaluation of endothelial function was based on normal values represented in an adult population, which may not be accurate in a paediatric population.

STRENGTHS AND POTENTIAL PERSPECTIVES

The main strength of the work is a multicentre design which led to the large cohort of children with a low BP gradient, and a full set of haemodynamic, cardiac, and vascular studies were conducted in a uniform methodological approach. Furthermore, unlike other studies, we analysed both absolute and standardised values, allowing the interpretation of results obtained from the subjects of different age and gender.

There are several potential perspectives of our study. First, a prospective observation of CoA patients would provide more data on the evolution of arterial changes. Second, our data indicate the need for more effective antihypertensive treatment and analysis of the effects of such treatment, both in terms of antihypertensive efficacy and arterial protection. Third, findings of a significantly accelerated biological age of the arterial tree exposed to elevated BP may stimulate a new arterial structure and functional analysis techniques in daily clinical practice. Fourth, a reliable analysis of the different modes of treatment including a type of surgery, length and type of stent, and anatomical conditions should be given to promote best clinical practices.

CONCLUSIONS

1. 56% of children after a successful coarctation of the aorta repair without evidence of re-coarctation have arterial hypertension with high prevalence of masked hypertension and isolated systolic hypertension.

2. Left ventricular hypertrophy is found in one-third of patients after successful coarctation of the aorta repair, irrespective of blood pressure control.

3. Children, following a successful coarctation of the aorta repair, present with significantly advanced arteriosclerosis of the arterial bed with an increased right carotid artery intima-media thickness, potentially decreased endothelial function, and elevated arterial stiffness associated with increased central systolic blood pressure.

4. Half of children after a successful coarctation of the aorta repair who receive antihypertensive therapy present with uncontrolled hypertension. The frequencies of single and combination therapies are comparable with predominance of β-adrenergic receptor blockers, followed by angiotensin-converting enzyme inhibitors within lower doses ranges.

PRACTICAL RECOMMENDATIONS AND FUTURE DIRECTIONS

Cautiousness while evaluating a residual narrowing of CoA is detrimental to intervene timely. While treating patients without residual re-coarctation, a 56% prevalence of AH indicates that higher cautiousness and closer monitoring of BP is needed in this specific targeted paediatric population. According to our results, a relatively high prevalence of underdiagnosed and undertreated MH in this specific paediatric population underlines the importance of ABPM in the routine management of patients after CoA repair. More frequent repetitive at least once a year ABPM performance would seem beneficial. Considering high rates of patients with diagnosed LVH, the specific therapy with ACEi should be more often selected not only to decrease BP, but also to reduce LVMi according to a few clinical trials (180, 181). We would also recommend embracing routine monitoring of EVA markers for paediatric CoA patients following the start of antihypertensive therapy and to correct the antihypertensive medication not only by the effective BP reduction but also according to the individual regression of EVA markers.

More targeted pathogenetic analysis of late hypertension mechanism after CoA repair followed by specifically targeted clinical trials would indicate the correct antihypertensive treatment direction for this population. Moreover, considering high rates of cardiovascular comorbidities, more randomized control trials should be conducted and summarized to unified guidelines to make a daily job of paediatric cardiologist easier and more science-guided.

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SUPPLEMENTS

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PUBLICATIONS LIST

Publications related to the thesis topic

1. Sendzikaite S, Sudikiene R, Tarutis V, Lubaua I, Silis P, Rybak A, Jankauskiene A, Litwin M. Prevalence of arterial hypertension, hemodynamic phenotypes, and left ventricular hypertrophy in children after coarctation repair: a multicenter cross-sectional study. Pediatr Nephrol. 2020 Nov;35(11):2147-2155. doi: 10.1007/s00467-020-04645-w. Epub 2020 Jun 11. PMID: 32529324.
2. Sendzikaite S, Sudikiene R, Lubaua I, Silis P, Rybak A, Brzezinska-Rajszys G, Obrycki Ł, Jankauskiene A, Litwin M. Multi-centre cross-sectional study on vascular remodelling in children following successful coarctation correction. J Hum Hypertens. 2021 Aug 3. doi: 10.1038/s41371-021-00585-6. Epub ahead of print. PMID: 34344993.

Other publications

1. Autoimmune polyendocrine syndrome with recurrent serositis. Paulius Kalibatas. Skaiste Sendzikaite. Rita Sudikiene. Laboratorinė medicina. 2017, vol. 19, No. 1, p. 66- 68.
2. Sendzikaite S, Heying R, Milanesi O, Hanseus K, Michel-Behnke I. COVID-19 FAQs in paediatric and congenital cardiology: AEPC position paper. Cardiol Young. 2021 Mar;31(3):344-351. doi: 10.1017/S1047951120005028. Epub 2021 Jan 7. PMID: 33407975; PMCID: PMC7900664.
3. Heying R, Albert DC, Voges I, Sendzikaite S, Sarquella-Brugada G, Pluchinotta F, Brzezinska-Rajszys G, Stein JI, Milanesi O; Contributors and reviewers of the AEPC council; Contributors of the AEPC working groups (current chairs and representative members); Association for European Paediatric and Congenital Cardiology recommendations for basic training in paediatric and congenital cardiology 2020. Cardiol Young. 2020 Nov;30(11):1572-1587. doi: 10.1017/S1047951120003455. Epub 2020 Oct 28. PMID: 33109300.
4. Tretter JT, Windram J, Faulkner T, Hudgens M, Sendzikaite S, Blom NA, Hanseus K, Loomba RS, McMahon CJ, Zheleva B, Kumar RK, Jacobs JP, Oechslin EN, Webb GD, Redington AN. Heart University: a new online educational forum in paediatric and adult congenital cardiac care. The future of virtual learning in a post-pandemic world? Cardiol Young.

2020 Apr;30(4):560-567. doi: 10.1017/S1047951120000852. Epub 2020 Apr 13. PMID: 32228736; PMCID: PMC7156582.

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PRESENTATIONS LIST

1. Oral presentation at 2nd International Congress of Hypertension in Children and Adolescents in Warsaw, Poland (May 2019) "Prevalence and hemodynamic phenotype of arterial hypertension, and left ventricular hypertrophy in children after coarctation repair ".
2. Oral presentation at 53rd Annual Meeting of the Association for European Paediatric and Congenital Cardiology in Seville, Spain (May 2019) "Prevalence of different forms of arterial hypertension and left ventricular hypertrophy in children after coarctation repair ".
3. Poster presentation atInternational Riga Stradins University Medical Conference (April 2019) "Influencing factors on 24-hour blood pressure measurements in childhood coarctation of the aorta".
4. Oral presentation at 6th International Conference on Prehypertension, Hypertension, Metabolic Disorders and Cardiovascular Diseases in Vilnius, Lithuania (March 2019) "Prevalence and hemodynamic phenotype of arterial hypertension, and left ventricular hypertrophy in children after coarctation repair ".
5. Oral presentation at 7th Vilnius-Gdansk Meeting on Hypertension, Kidney Disease and Cardiovascular Protection in Gdansk, Poland (September 2018) "Outcome of the aorta coarctation in infants".
6. Oral presentation at 4th International Conference Evolutionary Medicine: Health and Diseases in Changing Environment in Vilnius, Lithuania (June 2018) "Arterial hypertension and markers of early vascular aging in children with coarctation of the aorta".

7. Oral presentation at 52nd Annual Meeting of the Association for European Paediatric and Congenital Cardiology in Athens, Greece (May 2018) “Initial data of international study of early vascular aging in children with coarctation of aorta”.
8. Oral presentation at 1st International Congress of Hypertension in Children and Adolescents in Valencia, Spain (February 2018) “Insights into early vascular aging in children with coarctation of aorta “.
9. Oral presentation at the international conference “Childhood Hypertension - a Cross Talk Between Paediatric Cardiology and Nephrology” in Vilnius, Lithuania (May 2017) “Early vascular aging in congenital heart diseases”.

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SUMMARY (SANTRAUKA)

TURINYS

SANTRUMPŲ SĄRAŠAS

ABPM, 24 valandų arterinio kraujo spaudimo matavimo tyrimas
AH, arterinė hipertenzija
AKFI, angiotenziną konvertuojančio fermento inhibitoriai
AKS, kraujospūdis
AoK, aortos koarktacija
ARB, angiotenzino II receptorių blokatoriai
AŠA, Amerikos širdies asociacija
BB, beta adrenoblokatoriai
BCH, balto chalato hipertenzija
β, standumo indeksas
CWS, cirkumferentinė sienelės įtampa
DC, vietinis arterijų elastingumo koeficientas
DR, dešinioji ranka
Einc, inkrementinis elastingumo modulis
EVA, ankstyvas kraujagyslių senėjimas
FMD, neinvazinis endotelio funkcijos tyrimas deš. žasto arterijoje
HD, hemodinaminis
IF, išstūmimo frakcija
IKI, interkvartilinis intervalas
ĮŠY, įgimta širdies yda
KKB, kalcio kanalų blokatoriai
KMI, kūno masės indeksas
KPP, kūno paviršiaus plotas
KS, kairysis skilvelis
KSH, kairiojo skilvelio hipertrofija
KSMI, kairiojo skilvelio masės indeksas
LCSA, miego arterijos skerspjūvio plotas
MH, maskuota arterinė hipertenzija
mIMS, miego arterijos intimos-medijos storis
PI, pasikliautinieji intervalai
PS, pulsinis spaudimas
SN, standartinis nuokrypis
SNB, standartinio nuokrypio balas
SST, santykinis sienelės storis
šIMS, šlaunies arterijos intimos-medijos storis
ŠS, šansų santykis
VAS, vidutinis arterinis kraujo spaudimas
WCSA, miego arterijų skerspjūvio sienos plotas

1. ĮVADAS

Aortos koarktacija (AoK) – tai įgimta širdies yda (ĮŠY), priskiriama generalizuotoms arteriopatijoms. Šiai ydai būdingas įgimtas aortos sąsmaukos ar kitos jos dalies susiaurėjimas kartu su aortos sienelės struktūros pokyčiais. AoK jau ankstyvoje jaunystėje paskatina širdies ir kraujagyslių ligų vystymąsi (1-3) bei priešlaikinį jų nulemtą mirštamumą (4). Ši yda sudaro 5–8 proc. visų ĮŠY ir gali pasireikšti bet kuriame amžiuje (5, 6). Kritinė (preduktalinė) AoK pasireiškia jau naujagimystėje, o suaugusiųjų tipo (postduktalinė) gali būti pastebėta ir vyresniam vaikui ar net suaugusiajam, išgirdus širdies ūžesį ar nustačius arterinę hipertenziją (AH) (7). Vėlyva suaugusiųjų tipo AoK diagnostika sietina su nedideliu aortos susiaurėjimu arba su greitai po gimimo susiformavusia kolateraline kraujotaka (8). Gydymo būdo pasirinkimas priklauso nuo ydos nustatymo laiko, tipo, kompleksiškumo, pirminio ar pasikartojusio ydos varianto (7). Siekiant pagerinti ankstyvuosius ir vėlyvuosius AoK korekcijos rezultatus bei sumažinti AH pasireiškimą, ilgainiui susiformavo didelis širdies chirurgijos ir endovaskulinių gydymo būdų pasirinkimas. Tobulėjant gydymo technikoms, pailgėjo pacientų, sergančių AoK, išgyvenamumas. Nors AoK puikiai ir laiku ištaisoma, vis dėlto, remiantis jaunų suaugusiųjų populiacijoje atliktais tyrimais, AH išlieka pagrindine neišgydoma problema, kuri pasireiškia net 42–70 proc. pacientų (9–12). Trūksta duomenų apie AH, kraujospūdžio (AKS) hemodinaminius (HD) fenotipus ir kairiojo skilvelio hipertrofiją (KSH) vaikų amžiuje (14–17). Ypač mažai duomenų apie AKS fenotipus pagal 2016 metų Europos vaikų kardiologų draugijos rekomendacijas ir Amerikos širdies asociacijos (AŠA) 24 valandų arterinio kraujo spaudimo matavimo tyrimo (ABPM) klasifikaciją (13, 18).

Ankstyva arteriosklerozė ir padidėjusi širdies ir kraujagyslių ligų vystymosi rizika po sėkmingos AoK korekcijos pasireiškia ne tik sergantiems AH, bet ir tiems, kuriems nustatyta normotenzija (2). AoK korekcija nepanaikina iki aortos susiaurėjimo srities esančios įgimtos kraujotakos sistemos patologijos (19). Todėl šioje grupėje tiriami įvairūs žymenys širdies ir kraujagyslių rizikos stebėsenai. Atlikti tyrimai rodo, kad, lyginant sveiką kontrolinę grupę su suaugusiaisiais po AoK korekcijos, pastariesiems nustatoma pablogėjusi endotelio funkcija, padidėjęs miego arterijos intimos-medijos storis (mIMS) (20), padidėjęs standumas miego arterijose, pagausėjusi priešuždegiminių citokinų gamyba (4, 21). Vis dar išlieka nepakankamai ištirtas ankstyvas kraujagyslių senėjimas (EVA) vaikų amžiuje po sėkmingos AoK korekcijos.

Šiuo disertacijos darbu siekiama apibūdinti vaikų po sėkmingos AoK korekcijos AKS fenotipus, KSH bei pokyčius arterijos sienelės morfologijoje ir funkcijoje. Remiantis standartizuota analize, tikimasi pateikti duomenų apie AH reikšmingumą, gydymą, gydymo efektyvumą ir įtaką arterijų sienelių remodeliacijai.

2. DISERTACIJOS TIKSLAS IR UŽDAVINIAI

Įvertinti ankstyvą kraujagyslių senėjimą, vėlyvąją AH ir KSH vaikams po sėkmingos AoK korekcijos.

Disertacijos uždaviniai:

1. Nustatyti vėlyvosios AH paplitimą ir hemodinaminius fenotipus.
2. Nustatyti KSH ir jos ypatumus vaikams, sergantiems AH ir pasiekusiems normotenziją.
3. Įvertinti ankstyvo kraujagyslių senėjimo žymenis – arterijų sienelės struktūrą, endotelio funkciją ir centrinį AKS.
4. Įvertinti vėlyvosios AH antihipertenzinį gydymą ir jo efektyvumą.

Ginamieji teiginiai:

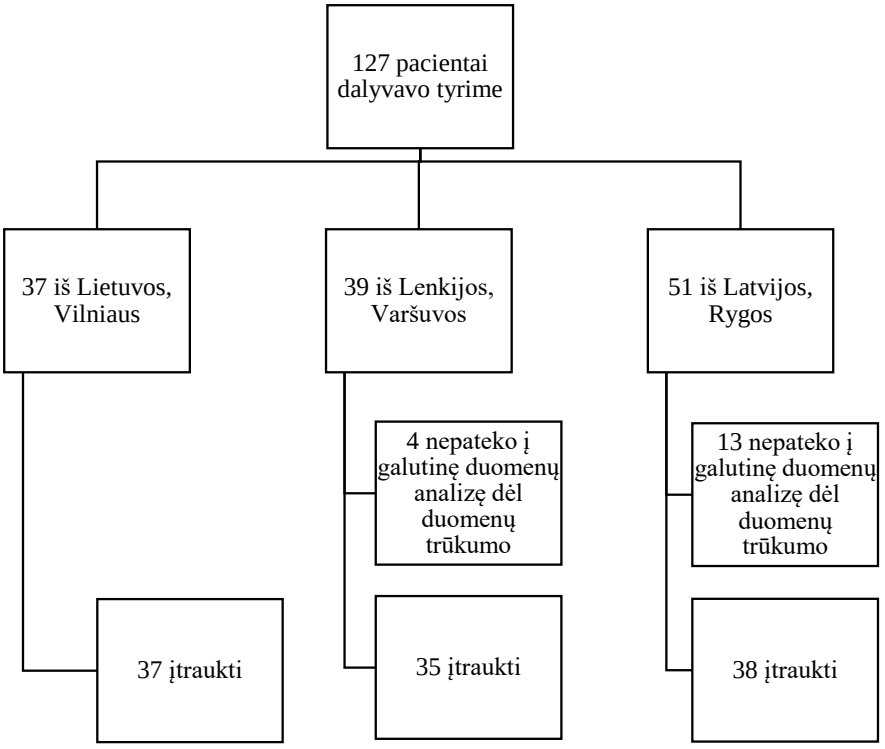
1. Padidėjęs vaikų po sėkmingos AoK korekcijos vėlyvosios AH paplitimas.
2. Padidėjęs vaikų po sėkmingos AoK korekcijos KSH paplitimas, kuris nesusijęs su AKS kontrolės lygiu.
3. Vaikams po sėkmingos AoK korekcijos pasireiškia ankstyvo kraujagyslių senėjimo požymiai: pokyčiai arterijų sienelės struktūroje, endotelio funkcijos sutrikimas ir padidėjęs centrinis arterijos standumas.
4. Po sėkmingos AoK korekcijos yra nepakankamai gydoma vėlyvoji AH.

3. METODAI

Disertacijos darbo analizė buvo atlikta naudojant duomenis iš doktorantės inicijuoto „EVA in Children after AoK repair“ (EVA in AoK) tyrimo.

EVA in AoK yra daugiacentris skerspjūvio tipo tyrimas, kuriuo nagrinėjamas AH, EVA ir KSH paplitimas bei jų galimi rizikos veiksniai vaikams po sėkmingos AoK korekcijos. Į tyrimą įtraukta 110 vaikų po

sėkmingos AoK korekcijos iš Lietuvos, Latvijos ir Lenkijos nuo 2017 m. sausio iki 2020 m. gegužės (1 pav.).



1 pav. Tyrimo imtis

Pacientus į tyrimą įtraukė centrų tyrėjai, vadovaudamiesi toliau nurodytais įtraukimo kriterijais.

Įtraukimo kriterijai:

- Vaikai – nuo 6 iki 18 m.
- Izoliuota AoK forma.
- Dešiniosios rankos ir kojos AKS skirtumas < 20 mmHg po endovaskulinės ar chirurginės AoK korekcijos.
- Iš gretutinių ĮŠY leistinos tik HD nereikšmingos šuntinės ĮŠY (mažas skilvelių ar prieširdžių pertvaros defektas) ir dviburis aortos vožtuvas su nežymiu nesandarumu ar nežymia stenoze.

Neįtraukimo kriterijai:

- Echokardiografijos tyrime diastolinė uodega CW dopleriu nusileidžiančioje aortoje, rekoarktacija.
- Bet kuri kita lėtinė liga.
- Ūminė liga.
- Genetinis sindromas.

3.1. Tyrimo organizavimas

Tyrimas visose šalyse vykdytas pagal centralizuotai parengtą, tarptautinį standartizuotų tyrimo vykdymo procedūrų planą. Tyrimo dalyviams atliktas išsamus klinikinis ištyrimas, širdies ir kraujagyslių sistemos tyrimai (AKS matavimas, ABPM, širdies ultragarsinis tyrimas). Taip pat atlikti EVA žymenų – arterijų sienelės struktūros, endotelio funkcijos ir centrinio kraujospūdžio tyrimai. Šiuos tyrimus dalyviams atlikdavo tie patys tyrėjai, vadovaudamiesi griežtai apibrėžtomis standartizuotomis procedūromis.

3.2. Atitiktis bioetikos reikalavimams

Tyrimą patvirtino kiekvieno tyrime dalyvaujančio centro vietiniai etikos komitetai. Lietuvos etikos komiteto leidimo numeris 158200-17-894-412. Latvijos etikos komiteto leidimo numeris 1/18-03-12. Lenkijos etikos komiteto leidimo numeris 41 /KBE/2017. Tyrimo protokolas atitinka Helsinkio deklaracijos principus. Visi tiriamieji ir jų tėvai ar įstatyminiai globėjai sutiko dalyvauti tyrime ir pasirašė informuotų asmenų sutikimo formas.

3.3. Tiriamųjų atranka disertacijos darbui

Į disertacijos darbo analizę buvo įtraukti visi įtraukimo kriterijus atitinkantys pacientai iš EVA in AoK tyrimo.

3.4. Rinkti duomenys

Tyrimo metu buvo renkami toliau nurodyti duomenys, kurie buvo panaudoti disertacijos darbo analizei:

- Gimimo data.

- Lytis.
- Antropometriniai duomenys (ūgis ir svoris).
- AoK tipas (kritinė naujagimystės tipo AoK ar suaugusiųjų tipo AoK).
- Rekoarktacijos korekcija anamnezėje.
- Paciento amžius AoK korekcijos metu.
- Laikas metais po AoK korekcijos.
- AoK korekcijos tipas (endovaskulinis ar chirurginis).
- Laikas metais nuo pirmosios AoK korekcijos datos.
- Laikas metais nuo paskutinės AoK korekcijos datos.
- Aortos vožtuvo anatomija (triburis ar dviburis).
- Antihipertenzinis AH gydymas iki įtraukimo į tyrimą.
- Sistolinio ir diastolinio AKS matavimas gydytojo kabinete ir ABPM.
- Širdies ultragarsinis tyrimas.
- Arterijų sienelės struktūra, endotelio funkcija ir neinvazyvus centrinis AKS.

3.5. Duomenų rinkimo procedūros

Antropometrija

Tiriamųjų ūgį ir svorį matavo vietiniai tyrėjai. Matavimams naudotos kalibruotos svarstyklės ir metrai.

AKS matavimas gydytojo kabinete ir ABPM

Sistolinio ir diastolinio AKS matavimus gydytojo kabinete atliko tyrėjai ant dešiniosios tiriamojo rankos (DR), naudodami validuotus ir tinkamai kalibruotus automatinius oscilometrinius AKS prietaisus. Analizei buvo naudojamas trijų su vienos minutės pertraukomis atliktų AKS matavimų rezultatų vidurkis. ABPM atliktas ant dešiniosios rankos *SpaceLabs Monitor 90207* prietaisu. Matavimai atlikti kas 20 minučių dienos metu ir kas 30 minučių nakties metu. Sėkmingai atliktas ir naudotas duomenų analizei ABPM, jei matavimų trukmė $\geq$ 20 h ir $\geq$ 80 proc. buvo sėkmingų matavimų.

Širdies ultragarsinis tyrimas

Transtorakalinis širdies ultragarsinis tyrimas buvo atliekamas vadovaujantis Amerikos echokardiografijos draugijos rekomendacijomis (22). Buvusios AoK srities ir aortos lanko vaizdinimui buvo naudojama dvimatė širdies echoskopija ir spalvų srauto doplerio tyrimai iš suprasterninio ir pošonkaulinio vaizdo. Sistoliniam gradientui nusileidžiančioje aortoje pamatuoti buvo naudojama standartinė suprasterninė padėtis ir nuolatinės bangos dopleris (23). Skilvelių funkcijai ir KSH įvertinti buvo naudojama kairioji šoninė gulėjimo padėtis.

Arterijų sienelės struktūros, endotelio funkcijos ir centrinio AKS matavimai

Arteriopatija vertinta matuojant dešiniosios miego (m) arterijos ir šlaunies (š) arterijos intimos-medijos storį (IMS) ultragarso aparatu su 12 MHz dažnio linijiniu davikliu, pritaikytu dvimačiam režimui (*Avante Health Solutions LOGIQ P5*). Matavimai atlikti dešiniojoje mIMS dėl su AoK susijusių HD ypatumų. Taikytas rankinis matavimo būdas, 10 taškų vidurkis naudotas duomenų analizei.

Endotelio funkcija tirta neinvaziniu endotelio funkcijos tyrimu dešiniojoje žasto arterijoje, naudojant didelės rezoliucijos ultragarsą. Vertintas žasto arterijos skersmens pokytis postišeminės reakcinės hiperemijos metu pagal tarptautines rekomendacijas (24).

Centrinis AKS buvo matuojamas neinvazyviai, naudojant „Vicorder“ oscilometrinį prietaisą („Skidmore Medical“, Vokietija). Tiriamieji buvo tiriami tylioje aplinkoje, gulimojoje padėtyje, 5 minutes pabuvus ramybėje pagal tarptautines rekomendacijas (25, 26).

3.6. Duomenų apibrėžimai ir transformacijos

AoK buvo suklasifikuota į kritinę naujagimystės tipo AoK ir suaugusiųjų tipo AoK.

Kūno masės indeksas (KMI) apskaičiuotas lygtimi: *KMI* = Svoris (kg) / Ūgis $(m)^2$. Apskaičiuojant standartinio nuokrypio balą (SNB) KMI buvo standartizuotas pagal amžių ir lytį, vadovaujantis CDC augimo kreivių duomenimis (27).

AH buvo apibrėžta pagal 2016 metų Europos vaikų kardiologų draugijos rekomendacijas (13). Vyresniems nei 16 metų amžiaus vaikams taikytos suaugusiųjų normos (13).

AH HD fenotipai nustatyti remiantis AKS matavimu gydytojo kabinete ir ABPM, remiantis Amerikos širdies asociacijos rekomendacijomis (18).

Balto chalato hipertenzija (BCH) diagnozuota, kai AKS gydytojo kabinete ≥ 95-to procentilio, o ABPM rezultatai normalūs.

Ambulatorinė prehipertenzija – kai AKS gydytojo kabinete ir vidutinis ABPM normos ribose, tačiau ABPM tyrimu padidėjęs AKS registruotas 25–50 proc. paros laiko.

Ambulatorinė hipertenzija – kai AKS gydytojo kabinete ir vidutinis ABPM ≥ 95-to procentilio ir ABPM tyrimu padidėjęs AKS registruotas 25–50 proc. paros laiko.

Sunki ambulatorinė hipertenzija – kai AKS gydytojo kabinete ir vidutinis ABPM ≥ 95-to procentilio ir ABPM tyrimu padidėjęs AKS registruotas > 50 proc. paros laiko.

Maskuota arterinė hipertenzija (25) – kai AKS gydytojo kabinete normos ribose, o vidutinis ABPM ≥ 95-to procentilio.

Visi vaikai, iki įtraukimo į tyrimą gydyti antihipertenziniais vaistais, registruoti kaip sergantys AH, neatsižvelgiant į AKS rezultatus.

Kontroliuojama AH – antihipertenziniais vaistais gydomi pacientai, kurių AKS gydytojo kabinete ir ABPM tyrimo rezultatai normalūs.

Kairiojo skilvelio masės indeksas (KSMI) buvo apskaičiuotas pagal de Simone formulę (28). KSH nustatyta, kai KSMI reikšmės buvo virš 95-to procentilio pagal remiantis amžiumi ir lytimi publikuotas sveikų vaikų normalias reikšmes (29). KSH paaugliams ≥ 16 metų amžiaus apibrėžtas kaip suaugusiesiems, indeksuojant pagal kūno pav. ploto kvadratinį metrą (13).

Santykinis sienelės storis (SST) buvo apskaičiuotas ir normalizuotas pagal amžių naudojant de Simone ir kt. pasiūlytą lygtį. Normalizuoto rodiklio reikšmės, viršijančios 95-tą procentilį (0,38), buvo laikomos KS koncentrinės remodeliacijos požymiu (30).

Remiantis KSMI ir SST rezultatais, buvo nustatyta KS geometrija. Normali KS geometrija, kai KSMI ≤ 95-to procentilio, SST ≤ 0,38. Koncentrinė remodeliacija, kai KSMI ≤ 95-to procentilio, SST > 0,38. Koncentrinė KSH, kai KSMI > 95-to procentilio, SST > 0,38. Ekscentrinė KSH, kai KSMI > 95-to procentilio, SST ≤ 0,38.

Arterijų sienelės struktūros ir endotelio funkcijos rodiklių transformacijos: miego arterijų skerspjūvio sienos plotas (WCSA), vietinis arterijų elastingumo koeficientas (angl. *distensibility coefficient*) (DC),

β standumo indeksas (angl. *β stiffness index*), miego arterijos skerspjūvio plotas (LCSA), inkrementinis elastingumo modulis (Einc) ir cirkumferentinė sienelės įtampa (CWS) buvo apskaičiuoti išvestinėmis formulėmis (31). Atliktas neinvazinis endotelio funkcijos tyrimas deš. žasto arterijoje (FMD), naudojant didelės rezoliucijos ultragarsą. Matuojamas procentinis žasto arterijos skersmens pokytis postišeminės reakcinės hiperemijos metu. Pokytis < 10 proc. laikomas nenormaliu (24). Skaičiavimams naudotos suaugusiųjų FMD normalios reikšmės, nes nebuvo anksčiau publikuotų sveikų vaikų normalių reikšmių.

Visi parametrai, priklausantys nuo amžiaus, lyties ar ūgio (KMI, AKS, mIMS, šIMS, DC, Einc ir β standumo indeksas), buvo standartizuoti apskaičiuojant SNB pagal publikuotas sveikų vaikų normalias reikšmes (21, 31).

3.7. Statistinė analizė

Visų tolydžiųjų kintamųjų atitiktis normaliajam skirstiniui buvo patikrinta naudojant Shapiro–Wilko testą. Tolydieji kintamieji buvo aprašomi naudojant vidurkį ir standartinį nuokrypį (SN) arba medianą ir interkvartilinį intervalą (32), priklausomai nuo duomenų skirstinio normalumo. Kategoriniai duomenys buvo aprašyti naudojant dažnius. Normaliai pasiskirsčiusių tolydžiųjų kintamųjų dispersijų lygybė buvo tikrinama F testu. Dviejų nepriklausomų grupių normaliai pasiskirstę ir lygiomis dispersijomis tolydieji kintamieji buvo lyginami taikant parametrinį dviejų grupių Studento T kriterijų, o normaliai pasiskirstę, bet skirtingomis dispersijomis – Welcho t kriterijų. Daugiau nei dviejų nepriklausomų grupių normaliai pasiskirstę tolydieji kintamieji buvo lyginami tarpusavyje taikant parametrinį ANOVA testą. Dviejų nepriklausomų grupių nenormaliai pasiskirstę tolydieji kintamieji buvo lyginami taikant Manno–Whitney–Wilcoxono rangų sumų kriterijų. Daugiau nei dviejų nepriklausomų grupių nenormaliai pasiskirstę tolydieji kintamieji buvo lyginami tarpusavyje taikant Kruskalo–Walliso ranginį kriterijų.

Dažnių pasiskirstymas tarp dviejų ir daugiau grupių buvo lyginamas taikant χ^2 kriterijų. Koreliacija tarp dviejų tolydžiųjų kintamųjų buvo vertinta apskaičiuojant Pearsono (normalusis skirstinys) arba Spearmano (nenormalusis skirstinys) koeficientus. IMS buvo apskaičiuota taikant LMS metodą pagal publikuotas normalių reikšmių L, M ir S reikšmes (21).

Siekiant nustatyti įvairių kintamųjų ryšį su tolydžiosiomis ir kategorinėmis vertinamosiomis baigtimis, buvo atitinkamai sudaryti vieno kintamojo logistinės regresijos modeliai. Siekiant nustatyti kintamuosius,

kurie yra nepriklausomai susiję su kategorinėmis vertinamosiomis baigtimis, buvo atitinkamai sudaryti daugybinių kintamųjų logistinės regresijos modeliai su žingsnine kintamųjų atranka.

p reikšmė < 0,05 buvo naudojama statistiškai reikšmingiems rezultatams apibrėžti. Tendencija reikšmingumo link apibrėžta, kai $p \geq 0,05$, bet < 0,1. Statistinė analizė buvo atlikta naudojant *R* programą. Papildoma duomenų analizė atlikta *Microsoft Excel* programa.

4. REZULTATAI

4.1. Tiriamųjų charakteristikos

Šimtas dešimt pacientų po sėkmingos AoK korekcijos įtraukti šio disertacijos darbo analizei. Berniukai sudarė 62,7 proc. tiriamųjų, o pacientų amžiaus mediana buvo 12,3 (8,9–15,7) metų. Tiriamųjų charakteristikos pateiktos 1 lentelėje. AoK gydyta chirurginiu būdu 66,4 proc. pacientų, o endovaskulinis gydymo būdas taikytas 33,6 proc. Operuoti jaunesni pacientai (amžiaus mediana 0,2 metų (0,1–1,9)), lyginant su gydytais endovaskuliniu būdu (amžiaus mediana 6,9 metų (4,4–9,6), $p < 0,05$). Suaugusiųjų AoK tipas buvo dominuojantis, diagnozuotas 63,6 proc. pacientų. Operacija buvo pirmo pasirinkimo gydymo būdas kritinės naujagimystės tipo AoK korekcijai (90 proc. pacientų). O 47,1 proc. suaugusiųjų tipo AoK pacientų gydyti endovaskuliniu būdu. Prieš įtraukiant į tyrimą 42 pacientams anamnezėje buvo gydyta rekoarktacija. Net 97,7 proc. pacientų rekoarktacijos atvejai koreguoti endovaskuliniu būdu – 21 pacientui atlikta balioninė angioplastika, 20 pacientų rekoarktacijos sritis stentuota. Pacientų amžiaus mediana po paskutinės rekoarktacijos korekcijos buvo 6,7 (2,3–10,4) metų.

1 lentelė. Tiriamųjų charakteristikos

Tiriamųjų charakteristikos	**Reikšmės (vidurkis ir SN arba mediana ir IKI)**
Pacientų skaičius (vyriškoji lytis / moteriškoji lytis)	110 (69/41)
Amžius, metais	12,3 (8,9–15,7)
KMI	18,1 (16,5–22,3)
KMI SNB	0,1 ± 1,1
Amžius metais pirmos AoK korekcijos metu	1,3 (0,1–6,5)
Laikas metais po pirmos AoK korekcijos	8,9 ± 4,5

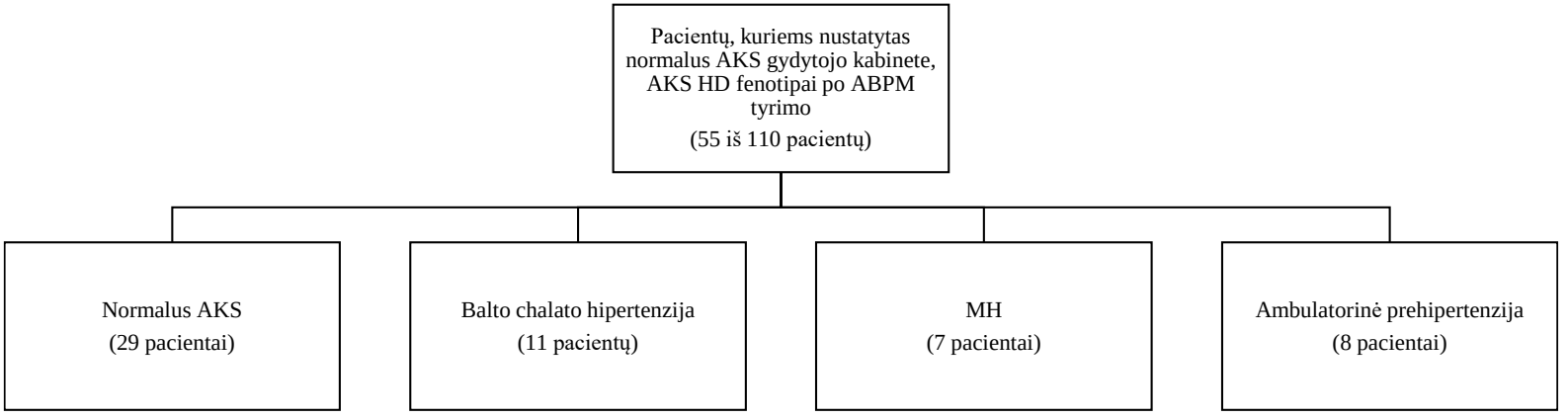
Tiriamųjų charakteristikos	Reikšmės (vidurkis ir SN arba mediana ir IKI)
Laikas metais po paskutinės AoK korekcijos	6,7 (2,3–10,4)
Paciento amžius metais, kai atlikta chirurginė AoK korekcija	0,2 (0,1–1,9)
Paciento amžius metais, kai atlikta endovaskulinė AoK korekcija	6,9 (4,4–9,6)
Maksimalus sistolinis gradientas nusileidžiančioje aortoje, mmHg	27 (20–34)
Vidutinis sistolinis gradientas nusileidžiančioje aortoje, mmHg	11 (9–15)
DR sistolinis AKS gydytojo kabinete, mmHg	119 ± 14
DR diastolinis AKS gydytojo kabinete, mmHg	65 ± 10
DR sistolinio AKS gydytojo kabinete SNB	1,1 ± 1,1
DR diastolinio AKS gydytojo kabinete SNB	0,2 ± 0,9
Vidutinis sistolinis ABPM, mmHg	119 ± 12
Vidutinis diastolinis ABPM, mmHg	62 ± 7
Sistolinio ABPM SNB	0,77 ± 1,3
AKS skirtumas tarp kojų ir DR, mmHg	2,0 (–7 – 12)
Centrinis sistolinis AKS, mmHg	110 ± 11
ABPM VAS, mmHg	82 (77–87)
ABPM VAS SNB	0,2 (–0,7 – 1,0)
PS gydytojo kabinete, mmHg	54,3 ± 14,1
ABPM PS, mmHg	56,5 ± 12,3

Santrumpos: *ABPM, 24 valandų arterinio kraujo spaudimo matavimo tyrimas; KMI, kūno masės indeksas; AKS, kraujospūdis; AoK, aortos koarktacija; IKI, interkvartilinis intervalas; VAS, vidutinis arterinis kraujo spaudimas; SNB, standartinio nuokrypio balas; DR, dešinioji ranka; PS, pulsinis spaudimas.*

4.2. Kraujospūdžio vertinimas

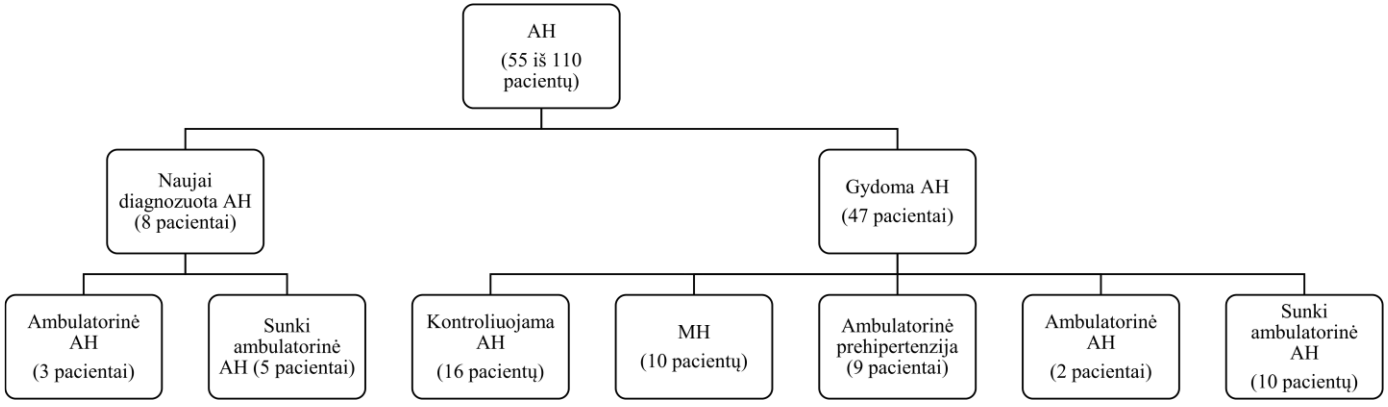
AH paplitimas pagal AKS matavimus gydytojo kabinete – 50 proc. (55 iš 110 pacientų). AKS fenotipai po ABPM pateikti 2 ir 3 paveiksluose. Dominuojantis AH HD fenotipas – izoliuota sistolinė hipertenzija. Nekontroliuojama AH arba MH nustatyta 30 iš 55 (54,5 proc.) pacientų. Antihipertenziniais vaistais iki įtraukimo į studiją buvo gydomi 47 iš 110

(42,7proc.) pacientų, kurie buvo priskiriami sergantiesiems AH. Iš šių 47 pacientų tik šešiolikai nustatytos normalios ABPM reikšmės, devyniems diagnozuota ambulatorinė prehipertenzija, dviem – ambulatorinė hipertenzija, dešimčiai – sunki ambulatorinė hipertenzija ir dešimčiai – MH. Naujai diagnozuota AH aštuoniems iš 110 pacientų. Atlikę ABPM tyrimą medikamentiškai dėl AH negydytiems bei turintiems normalų AKS gydytojo kabinete tiriamiesiems, nustatėme MH dar 7 pacientams. Tad įvertinus AKS matavimus gydytojo kabinete ir 24 val. AKS tyrimo rezultatus, AH paplitimas – 56 proc. AH dažniau pasireiškė pacientams, kuriems nustatytas mažesnis AKS skirtumas tarp kojų ir DR (AKS skirtumo tarp kojų ir DR mediana AH grupėje 1 (–10 – 11), normalaus AKS grupėje 4 (–2 – 13) mmHg, $p < 0,05$).



Santrumpos: *ABPM, 24 valandų arterinio kraujo spaudimo matavimo tyrimas; AKS, kraujospūdis; AoK, aortos koarktacija; MH, maskuota arterinė hipertenzija; HD, hemodinaminis.*

2 pav. Pacientų, kuriems nustatytas normalus AKS gydytojo kabinete, fenotipai po ABPM tyrimo



Santrumpos: *ABPM, 24 valandų arterinio kraujo spaudimo matavimo tyrimas; AH, arterinė hipertenzija; AKS, kraujospūdis; MH, maskuota arterinė hipertenzija; HD, hemodinaminis.*

3 pav. AH sergančių pacientų AKS HD fenotipai po ABPM tyrimo

Iš 55 pacientų, kuriems nustatytas normalus AKS gydytojo kabinete, 12,7proc. (7 iš 55 pacientų) nustatyta MH, 14,5 proc. (8 iš 55 pacientų) – ambulatorinė prehipertenzija ir 52,7 proc. (29 iš 55 pacientų) – normotenzija pagal ABPM rezultatus (2 pav.). Balto chalato hipertenzija buvo diagnozuota 20,0 proc. (11 iš 55) pacientų, kuriems nustatytas padidėjęs AKS gydytojo kabinete, tačiau normalūs ABPM rezultatai. Iš 47 gydytų antihipertenziniais vaistais pacientų normotenziją pasiekė 16 (34,0 proc.). Iš pacientų, kuriems nustatyta nekontroliuojama AH (n = 20) ir MH (n = 17), dominuojantis AKS HD fenotipas buvo izoliuota sistolinė hipertenzija (32 pacientai iš 37; 86,5 proc.). Tik 5 (13,5 proc.) tiriamiesiems nustatyta sistolodiastolinė AH, dviem iš jų patvirtinta sunki ambulatorinė hipertenzija, trims – MH.

4.3. Maksimalaus gradiento nusileidžiančioje aortoje analizė

Tiriamiesiems, kuriems diagnozuota AH, nustatytas statistiškai reikšmingai didesnis maksimalus gradientas nusileidžiančioje aortoje (32,0 (20,2–36,0) mmHg), palyginti su normalų AKS turinčiais pacientais (25,0 (19,0–30,0) mmHg, $p = 0,02$). Tačiau nei vienam tiriamajam nusileidžiančioje aortoje CW dopleriu nenustatyta diastolinė uodega bei abiejų grupių tiriamųjų AKS skirtumas tarp DR ir kojų buvo < 20 mmHg. Pacientai, kuriems anamnezėje buvo gydyta rekoarktacija, taip pat turėjo reikšmingai didesnį maksimalų gradientą nusileidžiančioje aortoje (30 (22,3–36) mmHg), palyginti su pacientais, kuriems rekoarktacija nebuvo diagnozuota (26 (19,0–32) mmHg; $p = 0,03$). Nors vertinant vidutinį sistolinį gradientą pacientų, kuriems anamnezėje buvo gydyta rekoarktacija, grupėje nustatyta tik tendencija reikšmingumo link (12,5 ± 4,2, palyginti su 11,2 ± 3,5, $p = 0,1$).

4.4. Amžiaus AoK korekcijos metu įtaka AH išsivystymui

Chirurginė AoK korekcija atlikta jaunesniame amžiuje lyginant su endovaskuline korekcija ($p < 0,0001$). Chirurginis gydymas taip pat buvo populiaresnis pacientų, kuriems būdingas normalus AKS, grupėje (44 iš 55 (80,0 proc.)), lyginant su sergančiais AH (29 iš 55 (52,7 proc.)), $p = 0,002$; $X^2 = 9,2$; 2 lentelė. Normalus AKS nustatytas net 56,6 proc. pacientų, kuriems AoK korekcija atlikta iki vienų metų amžiaus. Tačiau išskirsčius tiriamuosius į tris amžiaus AoK korekcijos metu grupes (< 12 mėnesių, nuo 12 mėnesių iki 9 m. ir ≥ 9 metų), amžius korekcijos metu nebuvo siejamas su AH išsivystymu, $p = 0,3$, 3 lentelė. Vidutinis gradientas nusileidžiančioje aortoje reikšmingai nesiskyrė tarp trijų grupių, $p = 0,3$). Siekiant įvertinti amžiaus

AoK korekcijos metu įtaką AH išsivystymui atlikta dvinarė vieno kintamojo logistinė regresija su amžiumi AoK korekcijos metu kaip tolydžiuoju kintamuoju. Nustatyta tendencija reikšmingumo link tarp amžiaus AoK korekcijos metu ir AH išsivystymo (p = 0,07).

Siekiant nustatyti nepriklausomus kintamuosius, kurie reikšmingai susiję su AH išsivystymu, atlikta dvinarė daugelio kintamųjų logistinė regresija su žingsnine atranka. Pradiniame duomenų rinkinyje buvo šie kintamieji: amžius, amžius AoK korekcijos metu, lytis, KMI SNB, AoK korekcijos tipas, maksimalus ir vidutinis gradientas nusileidžiančioje aortoje, rekoarktacija anamnezėje. Endovaskulinis AoK gydymo būdas buvo nepriklausomai susijęs su AH išsivystymu (β = 1,1, p = 0,009) bei nustatyta amžiaus įtakos tendencija reikšmingumo link (β = 0,1, p = 0,08), šio modelio McFaddeno pseudo-R^2 – 0,1.

2 lentelė. Normotenzinių ir hipertenzinių tiriamųjų charakteristikos

Kintamieji	Normotenziniai 55 pacientai	Hipertenziniai 55 pacientai	*p*
Amžius, metais	**11,3 (8,5–14,1)**	**13,1 (10,0–16,2)**	**0,04**
Amžius metais AoK korekcijos metu	0,6 (0,03–4,3)	2,8 (0,08–6,9)	0,05
KMI	**17,9 (15,8–20,6)**	**18,8 (17,2–20,6)**	**0,04**
KMI SNB	–0,01 ± 1,1	0,2 ± 1,2	0,31
AoK korekcijos tipas (endovaskulinis, chirurginis)	**11/44**	**26/29**	**0,002**
DR sistolinis AKS gydytojo kabinete, mmHg	**112,2 ± 11,8**	**127,0 ± 12,8**	**< 0,0001**
DR sistolinio AKS gydytojo kabinete SNB	**0,5 ± 0,9**	**1,7 ± 1,0**	**< 0,0001**
DR diastolinio AKS gydytojo kabinete SNB	0,2 ± 0,9	0,2 ± 0,8	0,44

Kintamieji	Normotenziniai 55 pacientai	Hipertenziniai 55 pacientai	*p*
Vidutinis sistolinis ABPM, mmHg	**113,5 ± 10,4**	**125,1 ± 11**	**< 0,0001**
Vidutinis diastolinis ABPM, mmHg	62,7 ± 7,2	62,9 ± 7,9	0,92
Centrinis sistolinis AKS, mmHg	**106,0 ± 10,3**	**114,3 ± 11,6**	**0,0002**
Maksimalus sistolinis gradientas nusileidžiančioje aortoje, mmHg	**25,0 (19,0–30,0)**	**32 (20,2–36,0)**	**0,02**
Vidutinis sistolinis gradientas nusileidžiančioje aortoje, mmHg	11,0 (9,0–13,0)	12,5 (9,25–15,8)	0,09
Laikas metais po pirmos AoK korekcijos	8,9 ± 4,2	8,9 ± 4,8	1,00
Laikas metais po paskutinės AoK korekcijos	7,6 (2,9–10,0)	6,0 (1,8–11,2)	0,50
Rekoarktacija anamnezėje / nebuvo rekoarktacijos anamnezėje	17/38	25/30	0,10
KSH	15 iš 55 (27,3 %)	21 iš 55 (38,2 %)	0,20
KSMI g/m ūgiui 2,7	33,9 (30,7–40,6)	38,1 (33,3–42,7)	0,07

Santrumpos: *ABPM, 24 valandų arterinio kraujo spaudimo matavimo tyrimas; KMI, kūno masės indeksas; AKS, kraujospūdis; AoK, aortos koarktacija; IKI, interkvartilinis intervalas; SNB, standartinio nuokrypio balas; DR, dešinioji ranka; KSH, kairiojo skilvelio hipertrofija; KSMI, kairiojo skilvelio masės indeksas*.

3 lentelė. AH skirtingose AoK korekcijos amžiaus grupėse

AKS vertinimas	I grupė (< 12 mėnesių amžiaus AoK korekcijos metu). N = 53	II grupė (tarp 12 mėnesių ir 9 metų amžiaus AoK korekcijos metu). N = 42	III grupė (≥ 9 metų amžiaus AoK korekcijos metu). N = 15	*p*
AH	23 (43,4 %)	22 (52,4 %)	10 (66,7 %)	0,30
Normotenzija	30 (56,6 %)	20 (47,6 %)	5 (33,3 %)	

Santrumpos: *AH, arterinė hipertenzija; AKS, kraujospūdis; AoK, aortos koarktacija.*

4.5. Kairiojo skilvelio hipertrofijos paplitimas

KSH buvo diagnozuota 36 iš 110 (32,7 proc.) pacientų. KSH paplitimas reikšmingai nesiskyrė tarp sergančiųjų AH (21 iš 55 (38,2 proc.)) ir tų pacientų, kuriems nustatyta normotenzija (15 iš 55 (27,3 proc.)), p = 0,22. Pacientų, turinčių normalų AKS, KSMI mediana buvo 33,9 g/m ūgio 2,7 (30,7–40,6) palyginti su AH sergančiųjų mediana 38,1 g/m ūgio 2,7 (33,3–42,7), p = 0,07. Vidutinis SST (normalizuotas amžiui) buvo 0,4 ± 0,07. SST nesiskyrė tarp sergančiųjų AH (0,4 ± 0,08) ir pacientų, kuriems nustatyta normotenzija (0,4 ± 0,06), p = 0,70. Vertinant KS geometriją, 54 (49,1 proc.) tiriamiesiems nustatyta normali geometrija, 20 (18,1 proc.) – koncentrinė remodeliacija, 18 (16,4 proc.) – koncentrinė KSH, o 18 (16,4 proc.) – ekscentrinė KSH. Pagal KS geometriją pasiskirsčiusių tiriamųjų charakteristikos pateiktos 4 lentelėje. KS geometrijos pasiskirstymas AH sergančiųjų ir pacientų, kuriems nustatyta normotenzija, grupėse nesiskyrė (5 lentelė). Nustatyta silpna reikšminga koreliacija tarp PS gydytojo kabinete ir KSMI (r = 0,2, p = 0,02) bei tarp ABPM PS ir KSMI (r = 0,3, p = 0,007).

Siekiant įvertinti KSH išsivystymą lemiančius veiksnius atlikta dvinarė vieno kintamojo logistinė regresija su amžiumi, amžiumi AoK korekcijos metu, kūno paviršiaus plotu (KPP), KMI SNB, lytimi, sistoliniu AKS gydytojo kabinete, sistoliniu ABPM, AoK korekcijos metodu, dviburio aortos vožtuvo morfologija, buvusia rekoarktacija anamnezėje, maksimaliu ir vidutiniu gradientu nusileidžiančioje aortoje, minimalia aortos stenoze ir nesandarumu. Nustatyta tik KMI SNB reikšminga asociacija su KSH išsivystymu, ŠS 1,7, 95 % PI (1,1–2,5), p = 0,01. KMI SNB (ŠS 0,6, 95 % PI (0,4–0,9), p = 0,02) ir rekoarktacija (ŠS 3,0, 95 % PI (1,3–6,8), p = 0,01) buvo vienintelės kovariatės, sietinos su didesniu šansu išsivystyti koncentrinei KS geometrijai. KMI SNB buvo didžiausias ekscentrinės KSH grupėje, p = 0,0006 (6 lentelė).

4 lentelė. Pagal KS geometriją pasiskirsčiusių tiriamųjų charakteristikos.

Kintamasis	Normali KS geometrija	Koncentrinė remodeliacija	Koncentrinė KSH	Ekscentrinė KSH	Kruskalo–Walliso X^2	*p*
Amžius, metais	11,6 (8,6–15,3)	12,2 (8,3–14,8)	13,0 (9,6–16,1)	13,5 (10,1–15,9)	1,7	0,64
Amžius metais AoK korekcijos metu	2,5 (0,08–6,4)	0,1 (0,03–5,6)	0,6 (0,1–5,7)	1,2 (0,2–6,9)	2,7	0,45
KMI	**18,1 (16,6–21,1)**	**16,4 (15,4–18,6)**	**19,1 (17,6–22,5)**	**22,6 (18,2–24,8)**	**13,0**	**0,005**
KMI SNB	**0,1 ± 1,0**	**–0,7 ± 1,0**	**0,2 ± 1,1**	**0,8 ± 1,2**		**0,0006**
AoK korekcijos tipas (endova skulinis, chirurginis)						
Maksimalus sistolinis gradientas nusileidžiančioje aortoje, mmHg	27,5 (24,0–35,3)	25,0 (16,5–33,3)	26,1 (20,3–33,5)	26,0 (19,3–31,0)	3,5	0,32
Vidutinis sistolinis gradientas nusileidžiančioje aortoje, mmHg	13,0 (10,0–16,0)	11,0 (8,0–15,0)	11,8 (9,6–14,9)	11,5 (9,0–13,3)	3,3	0,35
Laikas metais po pirmos AoK korekcijos	8,4 ± 4,1	9,2 ± 5,1	9,6 ± 4,7	9,2 ± 4,8		0,73
Laikas metais po paskutinės AoK korekcijos	6,8 (4,0–10,7)	6,6 (1,3–9,1)	2,7 (1,9–8,2)	7,3 (1,8–11,3)	4,5	0,22

Kintamasis	Normali KS geometrija	Koncentrinė remodeliacija	Koncentrinė KSH	Ekscentrinė KSH	Kruskalo–Walliso X^2	*p*
Centrinis sisto-linis AKS, mmHg	108,7 ± 12,5	109,2 ± 11,2	112,2 ± 11,0	112,7 ±10,5		0,57
Dešinioji mIMS	**0,5 (0,5–0,52)**	**0,5 (0,5–0,6)**	**0,6 (0,5–0,6)**	**0,5 (0,5–0,6)**	**19,4**	**0,0002**
Dešinioji mIMS SNB	**2,6 ± 1,4**	**3,3 ± 1,2**	**4,4 ± 1,4**	**3,1 ± 1,4**		**0,0001**
Dešinioji šIMS	0,3 (0,2–0,3)	0,2 (0,2–0,3)	0,3 (0,2–0,3)	0,3 (0,2–0,3)	4,1	0,26
Dešinioji šIMS SNB	–1.8 (–3,0 – –1,1)	–2,8 (–1,7 – –1,9)	–1,5 (–2,7 – –0,7)	–1,33 (–2,0 – –0,7)	4,2	0,25
FMD	6,0 (3,4–8,0)	3,5 (2,3–5,0)	5,3 (2,5–7,9)	3,7 (2,9–6,0)	3,7	0,30
KS IF %	67,9 (64,0–73,0)	70,0 (66,9–73,4)	68,5 (64,4–72,3)	64,8 (61,0–70,3)	4,9	0,18

Santrumpos: *KMI, kūno masės indeksas; AKS, kraujospūdis; AoK, aortos koarktacija; SNB, standartinio nuokrypio balas; DR, dešinioji ranka; IF, išstūmimo frakcija; mIMS, miego arterijos intimos-medijos storis; šIMS, šlaunies arterijos intimos-medijos storis; FMD, neinvazinis endotelio funkcijos tyrimas deš. žasto arterijoje; KS, kairysis skilvelis; KSH, kairiojo skilvelio hipertrofija.*

5 lentelė. KS geometrijos pasiskirstymas AH sergančiųjų ir tų pacientų, kuriems nustatyta normotenzija, grupėse.

KS geometrija	AH	Normotenzija	X^2	*p*
Normali	N = 26	N = 28	0,15	0,70
Koncentrinė remodeliacija	N = 8	N = 12	0,98	0,32
Koncentrinė KSH	N = 9	N = 9	0	1,00
Ekscentrinė KSH	N = 12	N = 7	1,59	0,21

Santrumpos: *KS, kairysis skilvelis; KSH, kairiojo skilvelio hipertrofija.*

6 lentelė. KS geometrijos pasiskirstymas ir KMI SNB reikšmės tarp tiriamųjų, kuriems nustatyta skirtinga KS geometrija.

SST	KSMI	
	≤ 95 %	> 95 %
≤ 0,38	Normali geometrija N = 54 (49,1 %) KMI SNB = 0,1 ± 1,0	Ekscentrinė KSH N = 18 (16,4 %) KMI SNB = 0,8 ± 1,2
> 0,38	Koncentrinė remodeliacija N = 20 (18,1 %) KMI SNB = –0,66 ± 1,0	Koncentrinė KSH N = 18 (16,4 %) KMI SNB = 0,2 ± 1,1

Santrumpos: *KS, kairysis skilvelis; KSH, kairiojo skilvelio hipertrofija; KMI, kūno masės indeksas; KSMI, kairiojo skilvelio masės indeksas; SNB, standartinio nuokrypio balas; SST, santykinis sienelės storis.*

4.6. Miego arterijos intimos-medijos storis, lokalus miego arterijos standumas ir FMD matavimai

Vidutinis mIMS SNB buvo 3,1 ± 1,5. mIMS virš 1,65 SNB nustatyta 91 iš 110 (82,7 proc.) pacientų. mIMS virš 3 SDS aptikta 46,4 proc. (51 iš 110) pacientų. mIMS mediana po sėkmingos AoK korekcijos buvo 0,51 (0,47–0,57) – ženkliai didesnė nei tos pačios lyties ir amžiaus sveikų vaikų 50-to procentilio mediana 0,38 (0,37–0,39), $p < 0,05$ ir 95-to procentilio mediana 0,45 (0,44–0,46), $p < 0,05$. mIMS tiriamųjų grupėje atitinka 20–30 metų jaunų suaugusiųjų reikšmes (33).

Anamnezėje gydytų dėl rekoarktacijos tiriamųjų vidutinis mIMS SNB buvo 3,6 ± 1,4, palyginti su pacientais, kuriems rekoarktacijos nebuvo 2,8 ± 1,4, $p < 0,05$ (4 pav.). Šis radinys patvirtintas ir logistine regresija, ŠS 4,0, 95 % PI (1,1–14,7), $p = 0,04$. Taip pat stebėta sustorėjusios mIMS SNB tendencija reikšmingumo link endovaskulinio gydymo grupėje, ŠS 3,2, 95 %

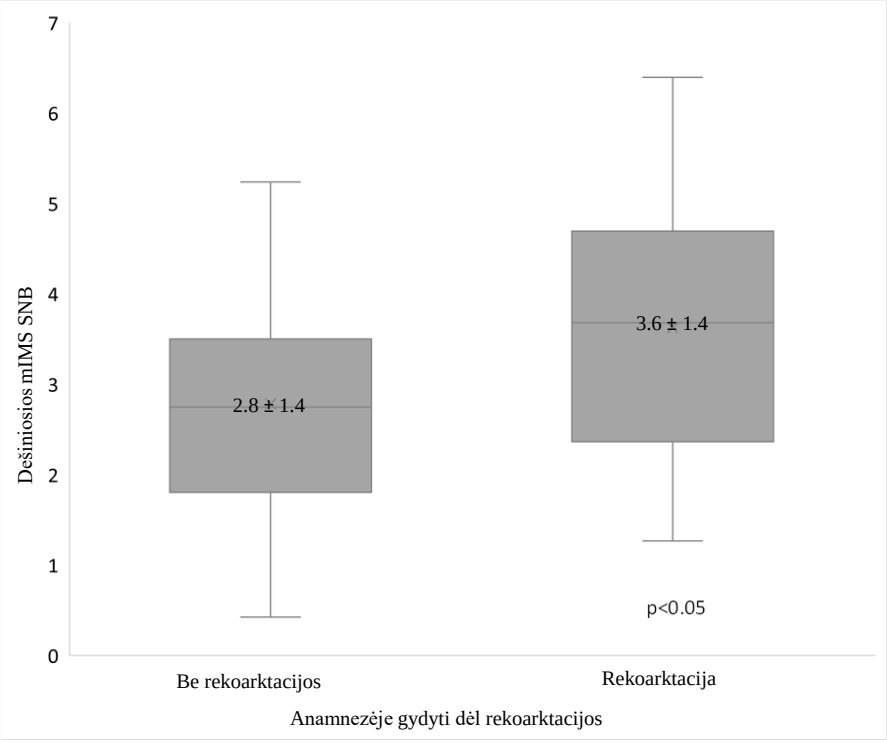
PI (0,9–11,7), $p = 0,08$. Pagal AoK gydymo būdą tiriamuosius išskirsčius į tris grupes (balioninės angioplastikos, stentavimo ir chirurgijos), reikšmingai storesnė mIMS SNB stebėta stentavimo grupėje (3,8 ± 1,2), palyginti su chirurginės korekcijos grupe (3,0 ± 1,5) ir balioninės angioplastikos grupe (2,7 ± 1,5), $p < 0,05$ (5 pav.). Nustatyta vidutinio stiprumo reikšminga mIMS SNB koreliacija su AKS skirtumu tarp kojų ir DR, r = –0,4, $p < 0,05$ (6 pav.). mIMS SNB buvo reikšmingai didesnis tiriamiesiems, kuriems nustatyta KSH (3,7 ± 1,6), palyginti su normalios KSMI grupe (2,8 ± 1,4, $p < 0,05$). Nustatyta silpna reikšminga mIMS SNB koreliacija su KSMI, r = 0,2, $p < 0,05$. Palyginus mIMS SNB skirtingos KS geometrijos grupėse, ploniausia mIMS SNB nustatyta normalios KS geometrijos grupėje 2,6 ± 1,4, storiausia – koncentrinės KSH grupėje 4,4 ± 1,4, $p = 0,0001$ (7 lentelė). Nustatyta silpna reikšminga, teigiama mIMS koreliacija su SST (r = 0,31, $p = 0,001$).

Plonesnė ar lygi –1,65 SDS šIMS nustatyta 59 pacientams (53,6 proc.). Rastos reikšmingos koreliacijos tarp šIMS ir PS gydytojo kabinete (r = 0,27, $p < 0,05$) bei tarp šIMS ir ABPM PS (r = 0,25, $p < 0,05$).

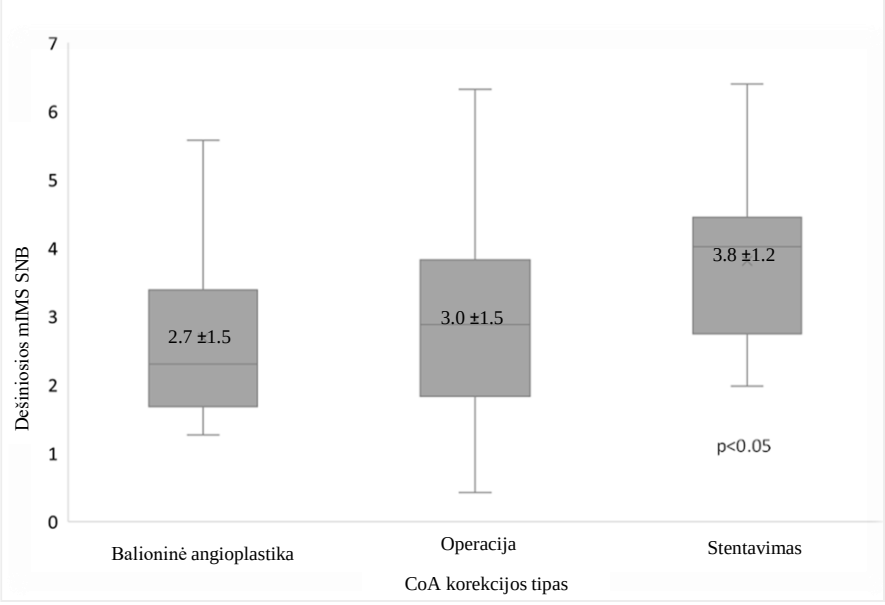
Visų pacientų dešiniosios miego arterijos DC SNB buvo mažiau nei –1,65. Dešiniosios miego arterijos Einc buvo lygus ar didesnis nei 1,65 SNB 93,6 proc. (103 iš 110) pacientų, o dešinioji β buvo normos ribose. Nustatytos reikšmingos neigiamos koreliacijos tarp dešiniosios DC SNB ir centrinio sistolinio AKS (r = –0,5, p < 0,05), amžiaus AoK korekcijos metu (r = –0,3, p < 0,05), PS gydytojo kabinete (r = –0,4, p < 0,05) ir ABPM PS (r = –0,3, p < 0,05) (7, 8, 9 ir 10 pav.).

Dešiniosios žasto arterijos FMD buvo mažiau nei 10,0 proc. 91 iš 110 tiriamųjų (82,7 proc.). Rekoarktacija anamnezėje (ŠS 0,2, 95 % PI (0,03–0,8), $p < 0,05$), AKS skirtumas tarp kojų ir DR (ŠS 0,9, 95 % PI (0,9–1,0), $p < 0,05$) ir vidutinis sistolinis gradientas nusileidžiančioje aortoje (ŠS 1,2, 95 % PI (1,0–1,5), $p < 0,05$) buvo susiję su sumažėjusia FMD. Vidutinio sistolinio gradiento nusileidžiančioje aortoje mediana buvo reikšmingai didesnė mažesnio nei 10 proc. FMD grupėje (12,0 (9,5–15,0) mmHg), palyginti su normalaus FMD rezultato grupe (7,0 (5,0–14,0) mmHg), $p < 0,05$. Maksimalaus gradiento nusileidžiančioje aortoje mediana buvo didesnė mažesnio FMD grupėje (27,0 (21,0–34,0) mmHg), palyginti su normaliu FMD (16,0 (12,0–33,0) mmHg), $p < 0,05$ (11 pav.).

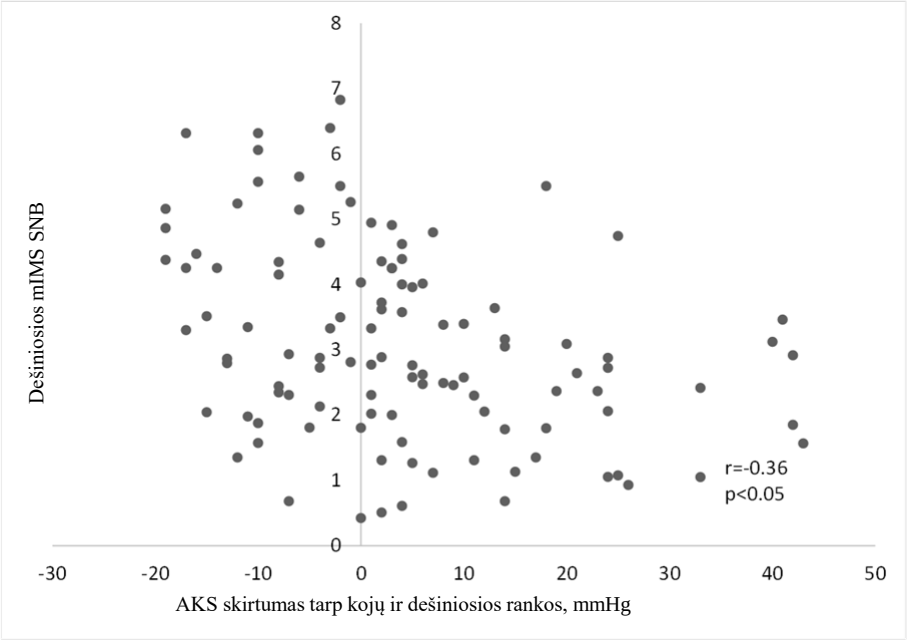
Siekiant nustatyti nepriklausomus kintamuosius, kurie reikšmingai susiję su mIMS SNB ≥ 3 SDS, buvo sudarytas dvinarės daugelio kintamųjų logistinės regresijos modelis su žingsnine kintamųjų atranka. AKS skirtumas tarp kojų ir DR (β = –0,04, $p < 0,05$) ir KSH (β = 1,5, $p < 0,05$) buvo nepriklausomai susiję su sustorėjusia mIMS, modelio McFaddeno pseudo-R^2 0,3.



4 pav. mIMS SNB pagal gydymą dėl rekoarktacijos anamnezėje



5 pav. mIMS pasiskirstymas pagal AoK korekcijos būdą

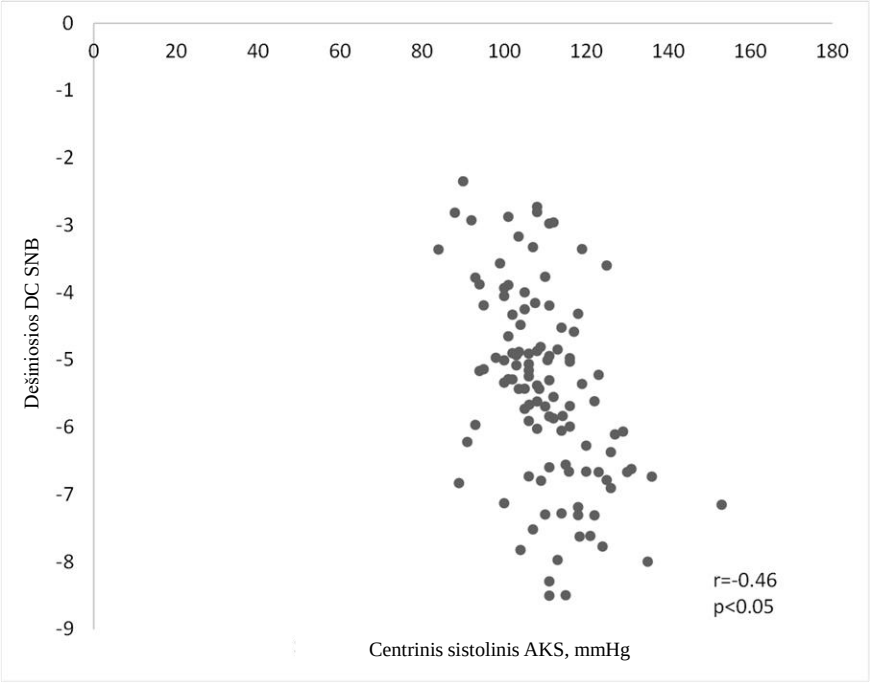


6 pav. mIMS SNB ir AKS skirtumo tarp kojų ir DR koreliacija

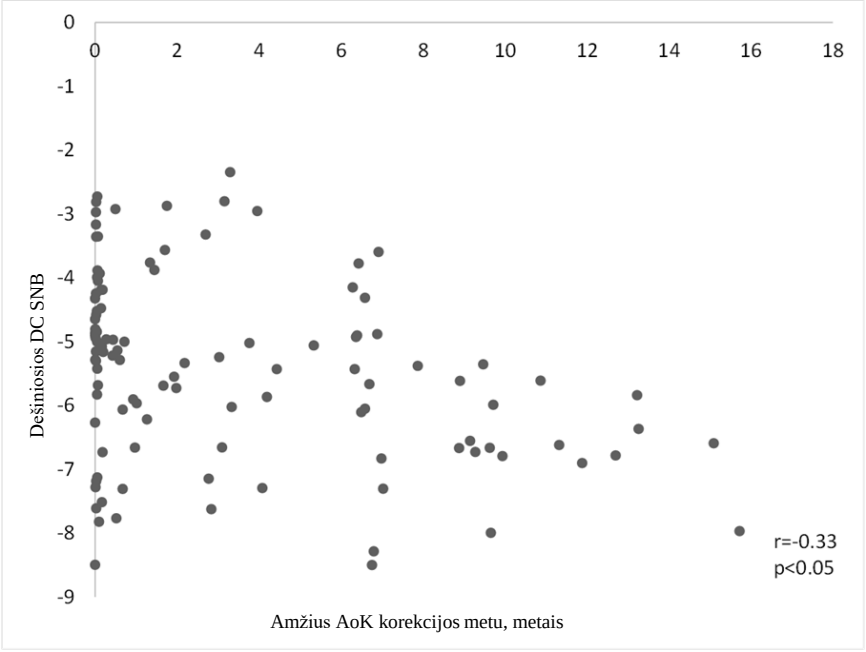
7 lentelė. KS geometrijos pasiskirstymas ir mIMS SNB reikšmės tarp tiriamųjų, kuriems nustatyta skirtinga KS geometrija

SST	KSMI	
	≤ 95 %	> 95 %
≤ 0,38	Normali geometrija N = 54 (49,1 %) mIMS SNB = 2,6 ± 1,4	Ekscentrinė KSH N = 18 (16,4 %) mIMS SNB = 3,1 ± 1,4
> 0,38	Koncentrinė remodeliacija N = 20 (18,1 %) mIMS SNB = 3,3 ± 1,2	Koncentrinė KSH N = 18 (16,4 %) mIMS SNB = 4,4 ± 1,4

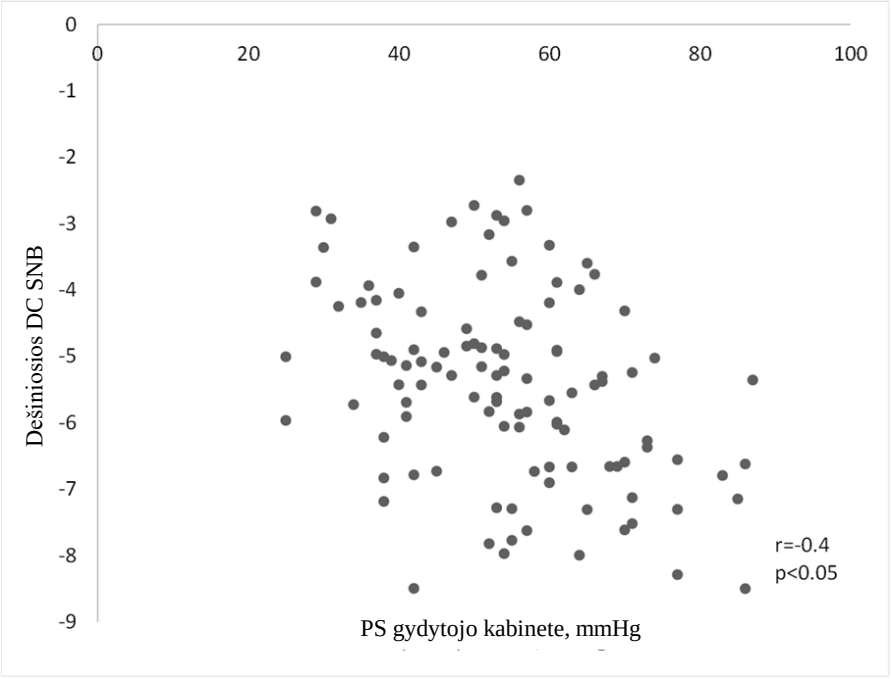
Santrumpos: *KS, kairysis skilvelis; KSH, kairiojo skilvelio hipertrofija; KSMI, kairiojo skilvelio masės indeksas; SNB, standartinio nuokrypio balas; SST, santykinis sienelės storis; mIMS, miego arterijos intimos-medijos storis.*



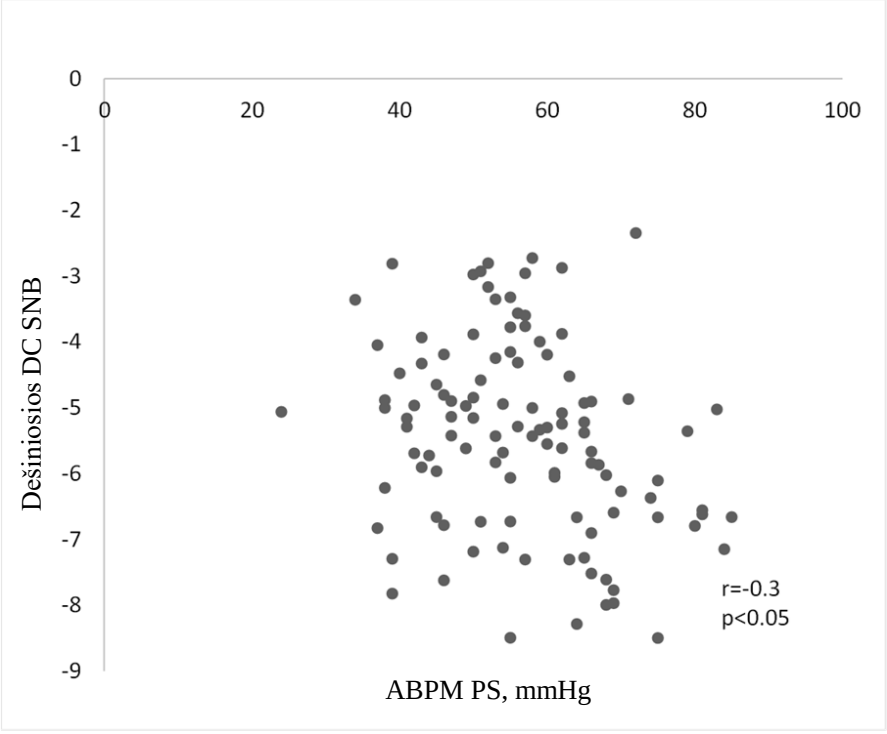
7 pav. DC SNB ir centrinio sistolinio AKS koreliacija



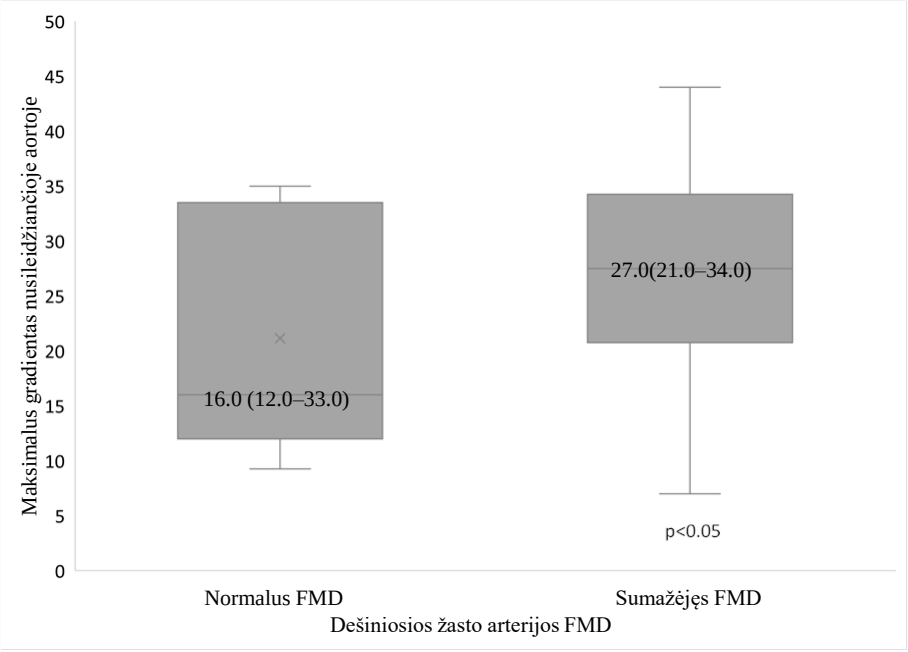
8 pav. Dešiniosios DC SNB ir amžiaus AoK korekcijos metu koreliacija



9 pav. Dešiniosios DC SNB ir PS gydytojo kabinete koreliacija



10 pav. Dešiniosios DC SNB ir ABPM PS koreliacija



11 pav. Maksimalaus gradiento nusileidžiančioje aortoje pasiskirstymas pagal FMD

4.7. Antihipertenzinis vėlyvosios AH gydymas

Antihipertenziniais vaistais gydyti tiriamieji (47 iš 110) buvo suskirstyti į dvi grupes – kontroliuojamos AH ir nekontroliuojamos AH grupes. Kontroliuojamos AH grupei (25 iš 47) priskirti pacientai, kurių AKS gydytojo kabinete ir ABPM tyrimų rezultatai normalūs ar kuriems nustatytas ambulatorinės prehipertenzijos HD fenotipas, o nekontroliuojamai AH grupei (22 iš 47) – pacientai, kuriems nustatyti ambulatorinės ir sunkios ambulatorinės AH fenotipai bei MH. Šių dviejų grupių pacientų charakteristikos pateiktos 8 lentelėje.

8 lentelė. Kontroliuojamos ir nekontroliuojamos AH grupių tiriamųjų charakteristikos

Kintamieji	Kontroliuojama AH (25 pacientai)	Nekontroliuojama AH (22 pacientai)	*p*
KLINIKINĖ CHARAKTERISTIKA			
Tiriamųjų skaičius	17/8	14/8	0,75

(vyriškoji lytis / moteriškoji lytis)			
Amžius, metais	13,2 (11,4–16,8)	12,3 (8,8–16,3)	0,52
KMI	18,6 (16,7–22,6)	20,5 (17,5–22,4)	0,46
KMI SNB	0,2 (–1,1 – 0,7)	0,6 (–0,3 – 1,3)	0,15
Amžius metais AoK korekcijos metu	0,7 (0,1–6,9)	4,0 (2,0–9,1)	0,10
Laikas metais po pirmos AoK korekcijos	7,2 (5,9–14,0)	6,5 (4,4–9,8)	0,92
Laikas metais po paskutinės AoK korekcijos	4,1 (1,4–12,8)	6,0 (2,0–7,8)	0,42
DR sistolinis AKS gydytojo kabinete, mmHg	124,0 (120,0–130,0)	126,5 (114,3–138,8)	0,32
DR diastolinis AKS gydytojo kabinete	68,0 (60,0–71,0)	60,0 (56,3–70,0)	0,93
DR sistolinio AKS gydytojo kabinete SNB	1,5 (1,0–2,0)	1,9 (1,1–2,5)	0,08
DR diastolinio AKS gydytojo kabinete SNB	0,3 (–0,2 – 0,5)	–0,1 (–0,6 – 0,4)	0,21
Vidutinis sistolinis ABPM, mmHg	**118,0 (112,0–124,0)**	**132,0 (124,3–136,5)**	**< 0,01**
Vidutinis diastolinis ABPM, mmHg	63,0 (56,0–66,0)	62,5 (58,0–64,8)	0,87
Vidutinio sistolinio ABPM SNB	**0,7 (0,3–1,0)**	**1,9 (1,6–2,3)**	**< 0,01**
AKS skirtumas tarp kojų ir DR, mmHg	3,0 (–1,0 – 13,0)	–5,5 (–13,8 – 9,3)	0,10
ABPM VAS, mmHg	82,0 (77,0–87,6)	82,0 (75,3–85,8)	0,77
ABPM MVAS SNB	0,1 (–1,2 – 0,7)	–0,1 (–0,7 – 0,7)	0,81

PS gydytojo kabinete, mmHg	61,0 (53,0–66,0)	63,5 (55,3–73,3)	0,23
Rekoarktacija anamnezėje / nebuvo rekoarktacijos anamnezėje	13/12	7/15	0,16
ŠIRDIES ECHOSKOPIJOS PARAMETRAI			
KSMI	38,8 ± 6,2	36,8 ± 7,0	0,31
KS IF	66,5 (62,3–72,3)	69,0 (67,0–72,0)	0,88
Maksimalus sistolinis gradientas nusileidžiančioje aortoje, mmHg	28,5 (15,8–34,0)	34,0 (26,3–37,8)	0,02
Vidutinis sistolinis gradientas nusileidžiančioje aortoje, mmHg	12,0 (6,0–16,0)	14,0 (11,0–15,8)	0,16
Aortos vožtuvo morfologija (dviburis / triburis)	18/7	12/10	0,21
Nežymi aortos vožtuvo stenozė / be stenozės	4/21	2/20	0,48
Nežymus aortos vožtuvo nesandarumas / be nesandarumo	16/9	10/12	0,20
KRAUJAGYSLIŲ REMODELIACIJOS PARAMETRAI			
Centrinis sistolinis AKS (mmHg)	111,0 (106,0–118,0)	116,0 (109,5–124,0)	0,12
Dešiniosios mIMS SNB	2,8 (1,9–3,6)	2,9 (2,3–4,3)	0,44
Dešiniosios šIMS SNB	–2.8 (–3,5 – –1,7)	–2,3 (–4,1 – –1,3)	0,34
FMD %	**6,0 (4,4–9,3)**	**4,5 (2,5–6,6)**	**0,03**
Dešiniosios DC SNB	–5,5 (–6,6 – –4,7)	–5,8 (–6,7 – –4,9)	1,00

Dešiniosios Einc SNB	3,4 (2,6–4,0)	4,1 (3,4–5,0)	0,98
Dešiniosios β SNB	–0,8 (–1,8 – 0,1)	–0,5 (–0,9 – 0,3)	0,91

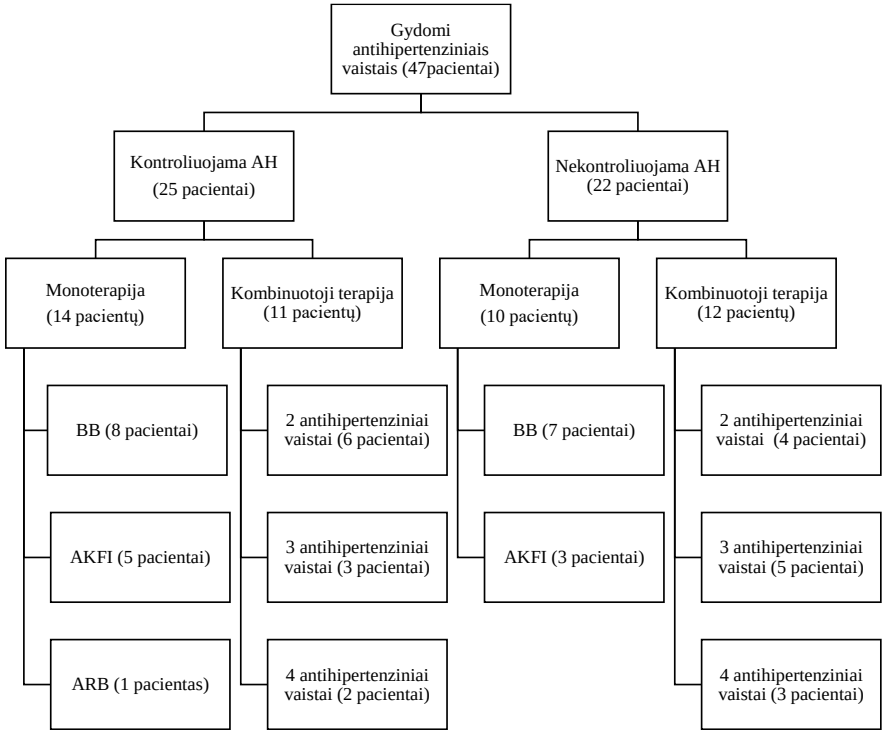
Santrumpos: *KMI, kūno masės indeksas; AKS, kraujospūdis; AoK, aortos koarktacija; SNB, standartinio nuokrypio balas; DR, dešinioji ranka; IF, išstūmimo frakcija; mIMS, miego arterijos intimos-medijos storis; šIMS, šlaunies arterijos intimos-medijos storis; FMD, neinvazinis endotelio funkcijos tyrimas deš. žasto arterijoje; KS, kairysis skilvelis; ABPM, 24 valandų arterinio kraujo spaudimo matavimo tyrimas; VAS, vidutinis arterinis kraujo spaudimas; PS, pulsinis spaudimas; KSMI, kairiojo skilvelio masės indeksas; AH, arterinė hipertenzija; DC, vietinis arterijų elastingumo koeficientas; Einc, inkrementinis elastingumo modulis; β, standumo indeksas.*

Kontroliuojamos ir nekontroliuojamos AH grupių antihipertenzinis gydymas pateiktas 12 paveiksle. Kombinuotajai terapijai naudoti medikamentai pateikti 13 paveiksle.

Net 46,8 proc. tiriamųjų AH buvo nepakankamai gydoma. Pusė gydytų antihipertenziniais vaistais pacientų buvo gydomi monoterapija ir pusė kombinuotąja terapija. Gydymas monoterapija ar kombinuotąja terapija reikšmingai nesiskyrė kontroliuojamos ir nekontroliuojamos AH grupėse ($X^2 = 0,5$, $p = 0,5$). Antihipertenzinis gydymas monoterapija ir kombinuotąja terapija skirtingose AH HD fenotipų grupėse pavaizduotas 14 paveiksle.

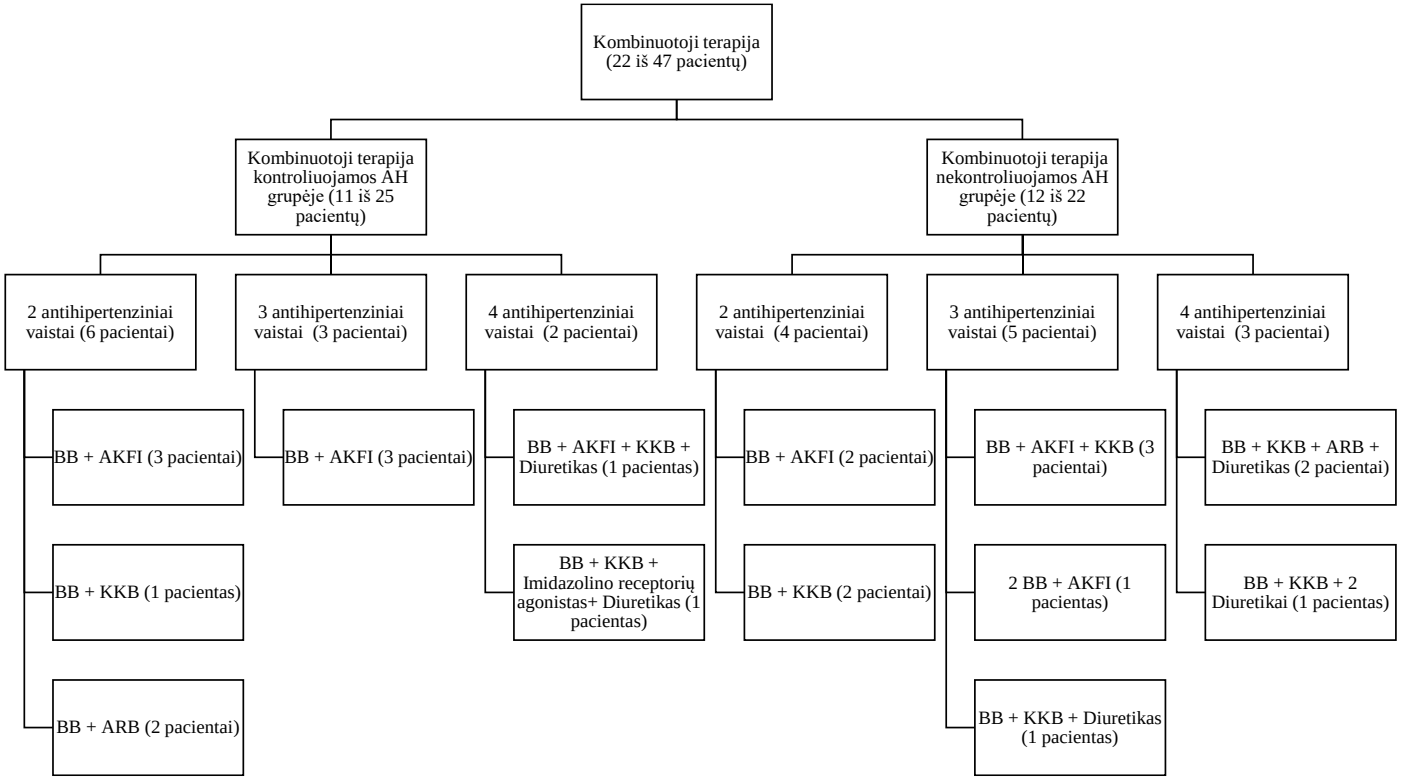
Beta adrenoblokatoriai (BB) buvo dažniausiai naudojama vaistų grupė ir monoterapijai, ir kombinuotajai terapijai. Net 80,1 proc. (38 iš 47 pacientų), gavusių antihipertenzinį gydymą, gydyti BB. Pirmo pasirinkimo BB – metoprololis, naudotas daugiau nei pusei gydytųjų BB (25 iš 47 pacientų). Didesnė metoprololio dozė skirta nekontroliuojamos AH grupėje (0,8 mg/kg (0,6–1,0)), palyginti su kontroliuojamos AH grupe (0,5 mg/kg (0,3–0,8), $p = 0,03$. Antro pasirinkimo BB buvo nebivololis (12 iš 47 pacientų), naudotas tik kombinuotajai terapijai ir daugiausia nekontroliuojamos AH grupėje (8 iš 12 pacientų). Nebivololio dozės mediana buvo didesnė nekontroliuojamos AH grupėje su tendencija reikšmingumo link (0,08 (0,06–0,1) *versus* 0,05 (0,04–0,06), $p = 0,08$). Antra pagal populiarumą vaistų grupė buvo angiotenziną konvertuojančio fermento inhibitoriai (AKFI), kuriais gydyti 44,7 proc. (21 iš 47) pacientų. Ramiprilis buvo populiariausias AKFI (14 iš 21), skirtas monoterapijai ir kombinuotajai terapijai. Ramiprilio dozės mediana buvo 2,63 mg/m^2 (1,99–3,02). Enalaprilis buvo antras pagal populiarumą naudotas AKFI (7 iš 21 paciento), jo dozės mediana – 0,17 mg/kg (0,12–0,19) (9 lentelė). Kalcio kanalo blokatorius (KKB) amlodipinas buvo dažniau

naudojamas nekontroliuojamos AH grupėje kombinacijoje su kitais vaistais (p = 0,04), tačiau amlodipino dozė nesiskyrė tarp AH grupių (9 lentelė). Kitų vaistų pasiskirstymas tarp AH grupių taip pat reikšmingai nesiskyrė.



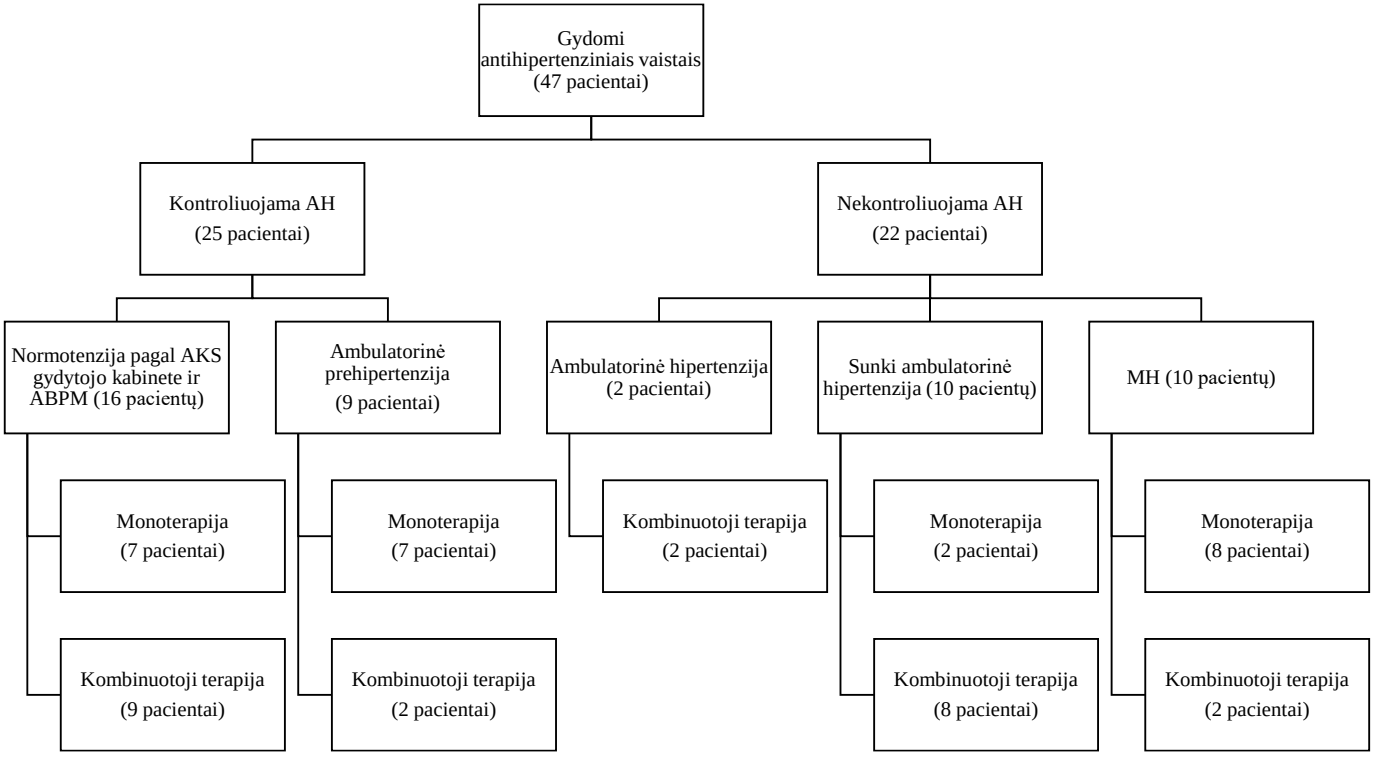
Santrumpos: *AKFI, angiotenziną konvertuojančio fermento inhibitoriai; AH, arterinė hipertenzija; ARB, angiotenzino II receptorių blokatoriai; BB, beta adrenoblokatoriai.*

12 pav. Vėlyvosios AH antihipertenzinis gydymas



Santrumpos: *AKFI, angiotenziną konvertuojančio fermento inhibitoriai; AH, arterinė hipertenzija; ARB, angiotenzino II receptorių blokatoriai; BB, beta adrenoblokatoriai; KKB, kalcio kanalų blokatoriai.*

13 pav. Vėlyvosios AH kombinuotajai terapijai naudoti antihipertenziniai vaistai



Santrumpos: *ABPM, 24 valandų arterinio kraujo spaudimo matavimo tyrimas; AH, arterinė hipertenzija; AKS, kraujospūdis; MH, maskuota arterinė hipertenzija; HD, hemodinaminis.*

14 pav. Antihipertenzinis gydymas monoterapija ir kombinuotąja terapija skirtingose AH HD fenotipų grupėse

9 lentelė. Vėlyvosios AH gydymui naudoti vaistai

Kintamieji	Kontroliuojama AH (25 pacientai)	Nekontroliuojama AH (22 pacientai)	*p*
ANTIHIPERTENZINIS GYDYMAS			
BB	19 (76,0 %)	19 (86,4 %)	0,47
AKFI	12 (48,0 %)	9 (40,9 %)	0,63
KKB	**3 (12,0 %)**	**9 (40,9 %)**	**0,04**
ARB	3 (12,0 %)	0 (0 %)	0,24
Diuretikas	2 (8 %)	4 (18,2 %)	0,40
Antihipertenzinių vistų dozės			
Metoprololis mg/kg	**0,5 (0,3–0,8)**	**0,8 (0,6–1,0)**	**0,03**
Nebivololis mg/kg	0,05 (0,04–0,1)	0,08 (0,06–0,1)	0,08
Ramiprilis mg/m^2	2,4 (2,0–3,0)	2,7 (2,0–3,0)	0,90
Enalaprilis mg/kg	0,17 (0,16–0,21)	0,13 (0,11–0,15)	0,57
Amlodipinas mg/kg	0,14 (0,12–0,15)	0,10 (0,09–0,13)	0,28

Santrumpos: *AKFI, angiotenziną konvertuojančio fermento inhibitoriai; AH, arterinė hipertenzija; ARB, angiotenzino II receptorių blokatoriai; BB, beta adrenoblokatoriai; KKB, kalcio kanalų blokatoriai.*

5. DISKUSIJA

Ženkliai išaugusią pacientų po AoK korekcijos populiaciją nulėmė širdies chirurgijos ir endovaskulinio gydymo techninė pažanga (10, 34, 35). Iššūkiu išlieka dažnos komplikacijos po AoK korekcijos: sisteminė AH, aortos aneurizmos formavimasis, galvos kraujagyslių komplikacijos ir ankstyva vainikinių arterijų liga (10). Aprašomas širdies ir kraujagyslių pažaidos dažnis, kartu ir miokardo infarkto dažnis (36) AoK populiacijoje ~11 proc. per 10 metų (37), o rizika išsivystyti galvos smegenų aneurizmai bei insultui siekia 10 proc. (38). Minėtos priežastys susijusios su didžiąja dalimi mirčių santykinai jauname amžiuje (4, 35). Tyrimai rodo, kad AoK korekcija neišsprendžia įgimtos aortos sienelės patologijos proksimaliau AoK srities bei sąlygoja blogesnę prognozę net ir po sėkmingos AoK korekcijos (19, 39). AH yra pati reikšmingiausia AoK komplikacija (14–17). Publikacijose pateikiami skirtingi duomenys apie AH pasireiškimą po AoK korekcijos galimai dėl vartojamų skirtingų AH ir sėkmingos AoK korekcijos apibrėžimų (13, 40–43). Trūksta duomenų apie AH pasireiškimą po sėkmingos AoK korekcijos vaikų amžiuje, naudojant 2016 metų Europos vaikų kardiologų draugijos rekomendacijas bei skirstant AH į HD fenotipus pagal AKS gydytojo kabinete ir ABPM tyrimo rezultatus. Vėlyvos AH diagnozė išlieka iššūkiu daugeliui suaugusiųjų ir vaikų kardiologų, pasireiškia net iki 70 proc. po HD efektyvios AoK korekcijos (9–12, 14–17, 32, 40, 44–47. Mūsų nustatytas 56 proc. AH pasireiškimas po HD sėkmingos AoK korekcijos patenka į žemesnį anksčiau publikuotų paauglių ir jaunų suaugusiųjų tyrimų intervalo rėžį (42–70 proc.) (9–12). Mūsų tyrimas skyrėsi nuo didesnį AH pasireiškimą nurodžiusių tyrimų tuo, kad įtraukėme tik tiriamuosius po HD sėkmingos AoK korekcijos bei nei vienas iš tiriamųjų neturėjo rekoarktacijos įtraukties metu. Mūsų rezultatai rodo didelį AH pasireiškimą vaikų amžiuje net ir po HD sėkmingos AoK korekcijos. Mes taip pat nustatėme 12,7 proc. MH pacientams, turintiems normalų AKS gydytojo kabinete, kurie iki tol nebuvo gydyti antihipertenziniais vaistais, bei 18,2 proc. jau gydytiems iki įtraukties. Mūsų tyrime dominuojantis AH HD fenotipas buvo izoliuota sistolinė AH, kuri pasireiškė net 86,5 proc. hipertenzinių pacientų. Taip pat nustatėme, kad pacientai, sergantys AH, turėjo didesnį maksimalų gradientą nusileidžiančioje aortoje (32,0 (20,2–36,0) mmHg, palyginti su normotenziniais pacientais (25,0 (19,0–30,0)), $p = 0,02$, tačiau gradientas buvo mažesnis nei 40 mmHg. Maksimalus sistolinis gradientas nusileidžiančioje aortoje taip pat buvo didesnis anamnezėje dėl rekoarktacijos gydytiems tiriamiesiems. Tačiau atlikus dvinarę daugelio kintamųjų logistinę regresiją, nestebėta gradiento

nusileidžiančioje aortoje įtakos AH susiformavimui. Remdamiesi šiais rezultatais, negalime paneigti, kad net ir nereikšmingai padidėjęs gradientas nusileidžiančioje aortoje su laiku gali sąlygoti AH išsivystymą. Galima daryti prielaidą, kad laikui bėgant (t. y. su amžiumi) net ir nedidelis sistolinio gradiento padidėjimas nusileidžiančioje aortoje gali sustiprinti generalizuotą aortos sienelės struktūros sutrikimą, sąlygoti padidėjusį standumą bei sukelti izoliuotą sistolinę AH (4, 48). Suaugusiųjų kohortose po AoK korekcijos atlikti tyrimai parodė ryšį tarp nežymaus nusileidžiančiosios aortos susiaurėjimo ir AH išsivystymo (35, 49). Taip pat buvo pasiūlyta nustatyti žemesnį liekamojo aortos susiaurėjimo pakartotinės intervencijos slenkstį nei nustatytas dabartinėse gairėse, siekiant pagerinti ilgalaikius šių pacientų rezultatus (49).

Yra keletas tyrimų, kuriuose izoliuota sistolinė hipertenzija apibūdinama kaip dominuojantis AH HD fenotipas po sėkmingos AoK korekcijos, atitinkantis šį tyrimą (13, 40–42). Izoliuota sistolinė hipertenzija taip pat yra dominuojantis vaikų ir paauglių pirminės AH fenotipas (13, 50). Tačiau izoliuotos sistolinės AH procentas tarp AoK pacientų mūsų tyrime buvo didesnis nei tarp pacientų, sergančių pirmine AH. Daroma prielaida, kad paauglių, sergančių pirmine AH, izoliuotą sistolinę AH sukelia hiperkinetinė kraujotaka (51). Nors neanalizavome HD parametrų, tokių kaip širdies išstumiamas tūris ir bendras periferinis pasipriešinimas, galima spėti, kad izoliuotą sistolinės AH fenotipą vaikams po AoK korekcijos sukelia padidėjęs aortos standumas (52).

Amžiaus įtakos AH išsivystymui analizei pacientai buvo suskirstyti į tris grupes. Kritinė naujagimystės AoK dažniausiai operuojama iki 1 metų amžiaus, todėl ši grupė buvo pasirinkta kaip pirmoji. Kitos dvi grupės pasirinktos pagal ankstesnių AoK tyrimų amžiaus klasifikaciją. Brown ir kt. nustatė, kad 9 metai yra atskaitos taškas link žymiai didesnės AH išsivystymo rizikos (34). Remiantis keletu sisteminių apžvalgų apie AH po AoK korekcijos, nustatyti su AH susiję veiksniai yra vyresnis amžius korekcijos metu, amžius stebėjimo metu, AKS matavimo metodas ir AoK korekcijos būdas (8, 15). Brown ir kt. padarė išvadą, kad tie pacientai, kuriems atlikta AoK korekcija esant ≥ 9 metų amžiaus, dažniau sirgo AH 5–15 metų stebėjimo metu po ydos korekcijos. Choudhary ir kt. nustatė, kad AH po AoK korekcijos sietina su ydos korekcija vyresniame nei 6 metų amžiuje (12, 34). Kita vertus, Kenny ir kt. padarė išvadą, kad 1/3 AoK pacientų suserga AH nepaisant ankstyvo ir veiksmingo chirurginio ar endovaskulinio gydymo ir kad AH yra neišvengiama AoK pasekmė, net jei yda koreguota pirmaisiais gyvenimo mėnesiais (8). Statistiškai reikšmingų skirtumų tarp AH paplitimo trijose pacientų grupėse, suskirstytose pagal amžių AoK korekcijos metu,

neradome. Tačiau pirmaisiais gyvenimo metais koreguotos AoK grupėje AH paplitimas buvo mažiausias (43,4 proc.), o didžiausias – po 8-ųjų gyvenimo metų (66,7 proc.). Po chirurginės AoK korekcijos AH paplitimas buvo mažesnis lyginant su endovaskuliniu gydymo būdu. Endovaskulinis gydymo būdas ir amžius buvo pagrindiniai veiksniai, turintys įtakos AH išsivystymui mūsų tiriamųjų grupėje. Mūsų tyrimo rezultatai neprieštarauja kitų tyrimų išvadoms ir rodo, kad net ankstyva AoK korekcija yra susijusi su didele AH rizika.

Tiksli vėlyvosios AH patogenezė po AoK korekcijos nėra aiški (8, 53). Aortos sienelės pažeidimas proksimaliau AoK išlieka net ir po geros ydos korekcijos (54, 55). Histologiškai nustatytas sutrikęs elastino išsidėstymas viduriniame aortos sienelės sluoksnyje, padidėjęs kolageno kiekis ir sumažėjusi lygiųjų raumenų masė kylančiosios aortos regione lyginant su aortos segmentu distaliau AoK korekcijos (56). Šių histologinių pokyčių įtaka baroreceptoriams paaiškinama priešoperacinė ir ankstyva pooperacinė AH (56). Manoma, kad vėlyvosios AH po AoK korekcijos etiologija yra daugiafaktorė (8, 53). Yra keletas žinomų ir hipotetinių veiksnių, galinčių turėti įtakos vėlyvosios AH išsivystymui po AoK korekcijos. Žinomi yra susiję su pačia širdies yda – tai ir gotikinis aortos lanko tipas (57), senesnis AoK korekcijos metodas (58, 59) ir vėlyvesnis korekcijos laikas bei rekoarktacija (60). Žinomi veiksniai buvo pašalinti iš tyrimo, atrinkus pacientus, turinčius normalią aortos lanko anatomiją, be rekoarktacijos įtraukties metu ir po naujausios galas su galu anastomozės operacijos.

Tarp hipotetinių AH išsivystymą sąlygojančių mechanizmų literatūroje aprašomi šie: arteriopatija, padidėjęs arterijų standumas, pakitusi kraujotaka ir pakitusi inkstų homeostazė (45, 47, 49, 61). Tačiau tikrasis lėtinės AH po AoK korekcijos patofiziologinis mechanizmas dar nėra gerai suprantamas.

Mūsų rezultatai taip pat rodo didelį MH paplitimą. MH nebuvo diagnozuota pusei tiriamųjų iki įtraukimo į tyrimą. Dar didesnis 35–40 proc. MH paplitimas buvo paskelbtas tyrime, atliktame paauglių ir jaunų suaugusiųjų po AoK korekcijos populiacijoje (43, 62). MH tampa dar didesne senstančios AoK populiacijos problema, nes MH pasireiškimas nustatomas vėliau. MH nenustatoma laiku dėl nepakankamai dažnai atliekamo ABPM tyrimo šioje pacientų grupėje. Dėl praleistos MH diagnozės šie pacientai gydomi dėl AH nepakankamai arba negydomi. Mūsų rezultatai rodo, kad net ir laiku diagnozavus MH, šie pacientai dažniau gydomi mažų dozių antihipertenzinių vaistų monoterapija, o kombinuotoji terapija taikoma retai. Galima spėti, kad pacientui po AoK korekcijos su patvirtinta MH turėtų būti naudingi dažnesni reguliarūs ABPM tyrimai, siekiant įvertinti gydymo veiksmingumą. Negydoma ar nepakankamai gydoma MH siejama su didesne

širdies ir kraujagyslių ligų rizika (63). Mūsų tyrime monoterapija buvo dažniau taikoma nei kombinuotoji terapija ne tik MH, bet ir kitiems AH HD fenotipams gydyti. Tai rodo galimai nepakankamą AH gydymą po AoK korekcijos galimai dėl nepakankamos reguliarios AKS kontrolės. Deja, dėl mūsų skerspjūvio tipo tyrimo nebuvo galimybės įvertinti AH trukmės ir atlikti kartotinių ABPM tyrimų. Tačiau šis realaus laiko AH įvertinimas rodo tikrą klinikinį AH gydymo vaizdą. Remiantis mūsų ir kitais tyrimais, egzistuoja didelis AH stebėsenos ir gydymo gidų poreikis šioje populiacijoje.

Mūsų rezultatai taip pat rodo didelį KSH pasireiškimą nepaisant AKS kontrolės lygio. KSH diagnozavome 36 iš 110 (32,7 proc.) pacientų. Yra žinoma, kad KSH susijusi su didesne širdies ir kraujagyslių ligų rizika. Padidėjęs koreguotos aortos srities standumas didina KS sistolinį spaudimą, skatina KSH ir trikdo KS diastolinį pildymąsi (64–66). KSH įtaka organų taikinių pažeidimui AoK populiacijoje buvo nagrinėta neinvaziniais metodais, tokiais kaip širdies magnetinio rezonanso tomografija, širdies echoskopija (11, 67, 68). Aprašomas KSH pasireiškimas po sėkmingos AoK korekcijos svyruoja nuo 24 proc. (62) iki 38 proc. (67) paauglystėje ir ženkliai didesnis pasireiškimas ~41–65 proc. suaugusiųjų amžiuje (37, 69–71), sąlygojantis didesnę širdies ir kraujagyslių ligų riziką ir mirtingumą vyresniame amžiuje. Aprašomo KSH pasireiškimo skirtumai galimi ir dėl skirtingų vartojamų KSH apibrėžimų, skirtingų diagnostikos metodų bei dėl skirtingų tiriamųjų grupių (skirtingų amžiaus grupių, AoK korekcijos metodikų, AoK korekcijos laiko ir kt.) (11, 67, 68, 70, 72). Kai kurie tyrimai nurodo ryšį tarp KSH ir didesnio centrinio sistolinio AKS AoK populiacijoje (70, 62). Mūsų tyrime normotenzinių pacientų KSMI mediana buvo mažesnė su tendencija reikšmingumo link, palyginti su sergančiais AH tiriamaisiais. Lygindami kontroliuojamos ir nekontroliuojamos AH grupes, skirtumų tarp KSMI neradome. Mūsų rezultatai rodo didelį KSH pasireiškimą AH sergantiems vaikams po sėkmingos AoK korekcijos be reikšmingo skirtumo tarp skirtingų AH kontrolės lygių. Mes taip pat aptikome didelę KS geometrijos rūšių įvairovę be reikšmingo skirtumo tarp normotenzinių ir sergančiųjų AH tiriamųjų po sėkmingos AoK korekcijos. Normalią KS geometriją nustatėme 49,1 proc. tiriamųjų, koncentrinę remodeliaciją 18,1 proc., koncentrinę KSH 16,4 proc., ekscentrinę KSH 16,4 proc. tiriamųjų. Yra žinoma, kad pacientams, sergantiems pirmine AH, dėl perkrovos slėgiu vystosi koncentrinė remodeliacija, dėl kurios padidėja sistolinė sienelės įtampa ir vystosi koncentrinė KSH, o ekscentrinės KSH vystymasis siejamas su perkrova tūriu, o ne slėgiu, ir dažnai stebimas mitralinio vožtuvo nesandarumo atveju (73). Mes aptikome reikšmingai didesnį KMI SNB ekscentrinės KSH grupėje. Kituose tyrimuose šis KS geometrijos tipas siejamas su nutukimu

(74). Taip pat mūsų tyrime KSH buvo siejama su didesniu KMI SNB, nepriklausomai nuo AKS, nepriklausomai nuo AKS kontrolės lygio, nors net 80 proc. mūsų tiriamųjų buvo normalaus KMI rėžiuose. Šis radinys pabrėžia tradicinių širdies ir kraujagyslių ligų rizikos veiksnių svarbą pacientams po geros AoK korekcijos ir net turint reliatyviai normalų KMI. KS geometrija buvo tyrinėta keliuose suaugusiųjų po AoK korekcijos tyrimuose (75, 76). Kaip ir mūsų tyrime, taip ir šiuose nebuvo rastas dominuojantis KS geometrijos tipas bei nebuvo paaiškinti galimi skirtingų variantų patogenetiniai mechanizmai. Ne tik sergantys AH pacientai, bet ir tie, kuriems nustatyta normotenzija, po sėkmingos AoK korekcijos buvo siejami su padidėjusiu KSH pasireiškimu ir skirtingais KS geometrijos variantais (75, 76). Net ir neišaiškinus patogenetinio mechanizmo, bet kuris KS remodeliacijos tipas siejamas su didesne širdies ir kraujagyslių ligų rizika (73).

Šiame moksliniame darbe taip pat buvo tirta arterijos sienelės struktūra ir funkcija didelio ir mažo spaudimo zonose – dešiniojoje miego arterijoje, dešiniojoje žasto arterijoje ir paviršinėje šlaunies arterijoje. Pagrindinis mūsų tyrimo radinys – reikšmingai sustorėjusi mIMS net 80 proc. tiriamųjų po sėkmingos AoK korekcijos. mIMS reikšmės atitiko 10–20 metų vyresnių žmonių normalias reikšmes. Sustorėjusi mIMS buvo siejama su KSH, rekoarktacija anamnezėje, endovaskuliniu AoK korekcijos metodu ir mažesniu AKS skirtumu tarp kojos ir DR. Taip pat nustatėme reikšmingai mažesnes šIMS reikšmes ir padidėjusį vietinį dešiniosios miego arterijos standumą visiems pacientams. Taip pat dokumentavome reikšmingai pablogėjusį FMD dešiniojoje žasto arterijoje. mIMS vertinome kaip neinvazyvų arteriosklerozės žymenį, kuris padeda prognozuoti organų taikinių pažaidos riziką suaugusiųjų AoK pacientams (4, 77, 78). Neseniai publikuotame tyrime pateikta mIMS reikšmė 0,8 mm siejama su 15 kartų didesne širdies ir kraujagyslių ligų rizika (37). Pagrindinės kovariantės, sietinos su mIMS sustorėjimu, mūsų tyrime buvo AKS skirtumas tarp kojų ir DR bei KSH. O tai siejama su didesne ir ilgesne padidėjusio AKS ekspozicija. Kadangi mIMS storėja su amžiumi, didesnės, nei tikėtasi, mIMS reikšmės rodo vyresnį biologinį amžių. Vidutinis mIMS mūsų tiriamųjų populiacijoje +3,1 ± 1,5 atspindi 10–20 metų vyresnių suaugusiųjų mIMS. Storiausia mIMS buvo nustatyta koncentrinį KSH tipą turintiems tiriamiesiems. Taip pat nustatyta statistiškai reikšminga silpna, teigiama koreliacija tarp mIMS ir SST, kuri rodo nepriklausomą ryšį tarp sustorėjusios mIMS ir koncentrinės KS geometrijos. Šie radiniai siejami su bendroje vidutinio amžiaus žmonių populiacijoje atliktais tyrimais, kuriuose tiriamiesiems, turintiems koncentrinį KSH tipą, nustatoma sustorėjusi mIMS (79).

Neradome jokių sąsajų tarp sustorėjusios mIMS ir padidėjusio DR sistolinio AKS SNB gydytojo kabinete bei centrinio AKS. Tačiau gauta reikšminga neigiama koreliacija tarp dešiniosios DC SNB ir centrinio sistolinio AKS rodo reikšmingą ryšį tarp padidėjusio vietinio standumo ir padidėjusio centrinio AKS. Kituose jaunų suaugusiųjų po sėkmingos AoK korekcijos tyrimuose nustatyta ankstyva arteriosklerozė ir padidėjusi širdies ir kraujagyslių ligų rizika nepriklausomai nuo AKS dydžio (2, 64, 80). Dempsey ir kt. aptiko ryšį tarp padidėjusio periferinio AKS ir sustorėjusios mIMS po AoK korekcijos (81). Tačiau šis tyrimas įtraukė tik 26 AoK pacientus, iš kurių tik 12 diagnozuota AH, o šie neišskirstyti pagal AKS kontrolės lygius. Taip pat Dempsey ir kt. tyrime buvo naudojamos absoliučios, o ne standartizuotos mIMS reikšmės.

Anksčiau mIMS sustorėjimas pacientams, turintiems AH po AoK korekcijos, buvo aiškinamas genų ekspresijos aktyvinimo sąlygota lygiųjų raumenų ląstelių proliferacija ir hipertrofija bei padidėjusia glikozaminoglikanų sinteze arterijos sienelėje (82). Be to, kai kurie tyrimai parodė, kad padidėjusį arterijų standumą AH sergantiems pacientams sukėlė pakitusios kolageno potipių proporcijos ir 1 tipo kolageno sintezės ir skilimo santykis (83). Mechaniškai padidėjęs mIMS AoK pacientams gali būti paaiškinamas didesniu PS, kuris būdingas AoK pacientams, net ir tiems, kurių AKS buvo normalus. Nustatyta, kad paauglių, sergančių pirmine AH, padidėjęs PS yra susijęs su sustorėjusia mIMS (84). Tačiau AoK pacientų PS yra daug didesnis. Mes nustatėme neigiamą koreliaciją tarp dešiniosios DC SNB ir PS gydytojo kabinete bei ABPM PS, tai rodo ryšį tarp padidėjusio vietinio standumo ir padidėjusio PS vaikams po sėkmingos AoK korekcijos. Priešingai, atrodo, kad mažesnis šIMS yra mažesnio pulsuojančio srauto su mažesniu pulso slėgio amplitudės poveikiu pasekmė.

Kitas svarbus mūsų tyrimo radinys buvo tai, kad pacientai, kuriems anamnezėje gydyta rekoarktacija, turėjo storesnę mIMS SNB, palyginti su tais, kurie dėl rekoarktacijos gydyti nebuvo. Šis radinys buvo reikšmingas, nors visiems tiriamiesiems rekoarktacija buvo visiškai išgydyta ir įtraukimo į tyrimą metu nebuvo užregistruota rekoarktacijos pasikartojimo požymių, diastolinės uodegos širdies echoskopijos tyrime. Rekoarktacija išlieka viena dažniausių AoK komplikacijų dėl neadekvataus aortos sienelės AoK korekcijos srityje augimo. Rekoarktacija dažnesnė mažo gimimo svorio vaikams, priklauso nuo amžiaus korekcijos metu, AoK korekcijos tipo. Rekoarktacijos pasireiškimo dažnis svyruoja nuo 5–15 proc. po ankstyvos chirurginės AoK korekcijos (85, 86) iki 50 proc. po endovaskulinio gydymo (87). Galima daryti prielaidą, kad rekoarktacija reiškia, kad šių pacientų arterijos, esančios iki buvusio aortos susiaurėjimo, patyrė didesnį HD

pažeidimą dėl padidėjusio AKS ir PS nei pacientų, kuriems rekoarktacijos anamnezėje nebuvo. Atsižvelgdami į mūsų tiriamosios populiacijos nevienalytiškumą pagal korekcijos tipus ir laiką, manome, kad 38 proc. rekoarktacijos pasireiškimas pacientų anamnezėje yra vidutinis. Storesnė mIMS šioje populiacijoje rodo, kad net visiškai išgydyta rekoarktacija gali būti laikoma prognostiškai reikšmingu rizikos veiksniu ir gali prisidėti prie kraujagyslių pažeidimo.

Remiantis mūsų tyrimo radiniais, AoK gydymo strategija taip pat gali turėti įtakos arterijų standumui. Mūsų rezultatai rodo, kad stentu gydytų tiriamųjų mIMS buvo storesnė, palyginti su operuotais. Ši išvada atitinka Sarkolos ir kt. tyrimo išvadą (77), tačiau rezultato interpretacija sudėtinga. Galime tik spėlioti, kad tiriamųjų, kuriems buvo atliktas AoK stentavimas, aorta buvo standesnė nei tų, kuriems buvo atlikta balioninė angioplastika ar operacija. Be to, mūsų tyrime endovaskulinis AoK gydymas stentu buvo atliktas vyresnio amžiaus vaikams (6,9 (4,4–9,6)), palyginti su chirurginiu gydymu (0,2 (0,1–1,9)). Amžiaus pasiskirstymas tarp skirtingų AoK korekcijos rūšių mūsų tyrime atitinka kituose centruose taikomą praktiką, kur kūdikiams iki 4 mėnesių amžiaus pirmenybė teikiama chirurginiam gydymui, o ne endovaskuliniam (88–91), o suaugusiųjų tipo AoK koreguoti pacientams, sveriantiems > 20 kg, pasirenkamas endovaskulinis gydymas (88, 92–99). Vaikams, vyresniems nei 4 mėnesių ir sveriantiems < 20 kg, sprendimas dėl AoK gydymo priimamas individualiai, konsiliumo metu (89, 93, 100).

Be struktūrinių miego arterijos sienelės pokyčių, mūsų tiriamojoje populiacijoje pastebėjome vyraujantį vietinį miego arterijų elastingumo sumažėjimą, atitinkantį suaugusiųjų tyrimų rezultatus (77, 80, 101). Kitas atradimas yra žymiai sumažėjusi tiriamųjų FMD, palyginti su sveikų suaugusiųjų normaliomis reikšmėmis. Tačiau nenormalūs kraujagyslių reaktyvumo rodikliai ne visada nustatomi pacientams po AoK korekcijos (54, 102, 103), ir nėra sveikų vaikų normalių FMD reikšmių, tad nežinome, kaip FMD reikšmės skiriasi sveikų vaikų populiacijoje. Pastebėjome, kad net neženkliai padidėjęs maksimalus ir vidutinis gradientas nusileidžiančioje aortoje buvo susijęs su sumažėjusia FMD pacientams po sėkmingos AoK korekcijos. Tai rodo, kad net nežymus gradiento padidėjimas nusileidžiančioje aortoje gali sąlygoti blogesnę endotelio funkciją. Ir pablogėjusi endotelio funkcija, ir padidėjęs standumas bei sustorėjusi mIMS gali sąlygoti pažengusią arteriosklerozę ir nulemti ankstyvo kraujagyslių senėjimo fenomeno požymius vaikams po sėkmingos AoK korekcijos. Ryšys tarp padidėjusio centrinio sistolinio AKS ir mirtingumo nuo širdies ir kraujagyslių ligų bei organų taikinių pažeidimo jau buvo įrodytas AH sergančiųjų suaugusiųjų populiacijoje (104). Mes nustatėme statistiškai

reikšmingai žemesnį centrinį sistolinį AKS pacientams, turintiems normalų AKS, palyginti su sergančiais AH, $p = 0{,}0002$. Tačiau neradome reikšmingo centrinio sistolinio AKS skirtumo tarp kontroliuojamos ir nekontroliuojamos AH grupių. Centrinio sistolinio AKS nauda klinikinėje praktikoje negali būti vertinama šiuo tyrimu dėl nedidelio pacientų skaičiaus.

Taip pat įvertinome antihipertenzinius vaistus, naudojamus po sėkmingos AoK korekcijos pasireiškusiai lėtinei AH gydyti. Dažniausiai mūsų tiriamiems pacientams skirta vaistų grupė buvo BB. Mūsų tiriamųjų gydymui naudoti antihipertenziniai medikamentai iš dalies atitinka keletą klinikinių antihipertenzinio gydymo tyrimų suaugusiųjų AoK populiacijoje. Moltzer ir kt. parodė BB (metoprololio) pranašumą, palyginti su ARB, mažinant vidutinį AKS, tačiau didžiųjų arterijų standumas nepasikeitė nė vieno gydymo metu (105). AKFI buvo antra pagal populiarumą antihipertenzinių vaistų grupė mūsų tyrime, tačiau išanalizavus Di Salvo ir kt. atliktą klinikinį tyrimą, paaiškėja, kad AKFI turėjo būti naudojami dažniau dėl įrodyto pranašumo prieš BB ne dėl antihipertenzinio poveikio, o dėl sąlygojamo mažesnio sergamumo ir mirštamumo nuo širdies ir kraujagyslių ligų. Di Salvo ir kt. palygino BB atenololį ir AKFI enalaprilį vėlyvosios sisteminės AH gydymui ir įtakai KSH vaikų ir jaunų suaugusiųjų po sėkmingos AoK korekcijos grupėje. Šiame tyrime padaryta išvada, kad nors abu vaistai yra panašiai veiksmingi mažinant sistolinį ABPM, tik enalaprilis žymiai sumažino KSH (106). Kitas tyrimas, kurį atliko Brili ir kt., papildė ankstesnį tyrimą, t. y. kad AKFI ramiprilis taip pat gali pagerinti sutrikusią endotelio funkciją ir sumažinti priešuždegiminio citokino IL-6, sCD40L ir adhezijos molekulių ekspresiją jauniems suaugusiesiems po sėkmingos AoK korekcijos, net tiems, kuriems nustatyta normotenzija (107). Taigi abu tyrimai rodo, kad AKFI gali sumažinti AoK pacientų sergamumą ir mirštamumą nuo širdies ir kraujagyslių ligų, net esant gerai AoK korekcijai ir normaliam AKS. Atsižvelgiant į nepakankamai ištirtą vėlyvosios AH mechanizmą ir randomizuotų kontrolinių tyrimų trūkumą, naujausiose 2020 ESC suaugusiųjų įgimtų širdies ydų giduose rekomenduojama laikytis bendrų antihipertenzinio gydymo taisyklių, pateiktų 2018 ESC/ESH rekomendacijose (92, 108). Aiškių vėlyvosios AH gydymo rekomendacijų nėra ir naujausiose 2017 m. Amerikos pediatrijos akademijos gairėse (109). 2016 m. Europos vaikų kardiologų draugijos gairės yra konkretesnės ir rekomenduoja vaikams po AoK korekcijos BB, KKB ir vaistus, turinčius įtaką renino, angiotenzino ir aldosterono sistemai (13). Tačiau šios rekomendacijos pagrįstos tik keliais labai mažos imties klinikiniais tyrimais (105, 110).

Keliuose apžvalginiuose straipsniuose buvo pateikta tikroji pasaulinė antihipertenzinio gydymo praktika šioje populiacijoje. Be anksčiau minėtų

klinikinių tyrimų metu įvertintų vaistų, siūlomi vazodilatatoriai, tiazidiniai diuretikai, KKB (47, 111). Remiantis visų minėtų tyrimų duomenimis, tinkamiausi medikamentai vėlyvajai sisteminei AH po sėkmingos izoliuotos AoK korekcijos turėtų būti AKFI, BB ir ARB (107, 112), o tai iš dalies atitinka ir mūsų tiriamųjų vartotus vaistus.

Antihipertenzinio vaisto dozės parinkimas yra kitas svarbus AH gydymo veiksmingumo aspektas. Pastebėjome, kad visi antihipertenziniai vaistai buvo naudojami mažesnėmis rekomenduojamomis dozėmis. Nors metoprololio dozė buvo didesnė nekontroliuojamos AH grupėje, daugumai pacientų vidutinė vaisto dozė neviršijo 1 mg/kg. Vis dėlto rekomenduojama maksimali metoprololio dozė yra 2 mg/ kg (13). AKFI taip pat buvo naudojami mažesnėmis dozėmis. Viena vertus, mažesnės antihipertenzinių vaistų dozės gali būti viena iš didesnio nekontroliuojamos AH pasireiškimo priežasčių mūsų tiriamojoje populiacijoje. Kita vertus, vaikų kardiologui sunku titruoti dozę iki didžiausios toleruotinos ar optimalios tiksliniam AKS dėl galimo šių vaistų šalutinio poveikio. Ypač kai nėra aiškių duomenų apie šalutinio poveikio pasireiškimą vaikų populiacijoje dėl randomizuotų kontroliuojamų klinikinių tyrimų trūkumo.

Kitas svarbus aspektas kalbant apie antihipertenzinio gydymo veiksmingumą yra laikymasis nustatyto vaistų vartojimo režimo, kurį sunku patikrinti ir kuris nebuvo įvertintas mūsų tyrime. Vaistų vartojimo režimo nesilaikymas yra gerai žinoma ir ištyrinėta problema suaugusiųjų ir paauglių, sergančių pirmine AH, populiacijoje, manoma, kad tai paveikia nuo 43 proc. iki 65,5 proc. pacientų (113, 114).

Svarbiausia užduotis gydytojui yra užtikrinti gerą AoK korekciją, be rekoarktacijos ar reikšmingo susiaurėjimo bet kurioje aortos dalyje. Jei stebimas liekamasis aortos susiaurėjimas, būtina laiku ir tinkamai koreguoti. Ir tik jei nėra reikšmingo aortos susiaurėjimo, galima medikamentiškai gydyti vėlyvąją AH po AoK korekcijos. Bendros nemedikamentinio gydymo taisyklės rekomenduojamos visiems sergantiems AH pacientams, taip pat ir po sėkmingos AoK korekcijos (13, 47, 109, 111), nors šiame tyrime tai nebuvo vertinta. Nors AH gydyti bendrajai vaikų populiacijai rekomenduojamas platus antihipertenzinių vaistų spektras, klinikinių tyrimų trūkumas lemia ribotą prieigą prie moderniausių vaistų ne tik konkrečiai tikslinei vaikų AoK populiacijai, bet ir visiems AH sergantiems vaikams (13, 109). Taigi sunkus antihipertenzinio vaisto pasirinkimas išlieka iššūkiu.

6. IŠVADOS

1. Vėlyvoji arterinė hipertenzija diagnozuota 56 proc. vaikų po sėkmingos aortos koarktacijos korekcijos. Dominuoja izoliuotos sistolinės hipertenzijos ir maskuotos hipertenzijos fenotipai.
2. Kairiojo skilvelio hipertrofija nustatyta trečdaliui pacientų, nepriklausomai nuo kraujospūdžio kontrolės lygio.
3. Pažengusi arteriosklerozė – sustorėjusi miego arterijos intima-medija, padidėjęs arterijų standumas ir potencialiai sumažėjusi endotelio funkcija pasireiškia vaikams po sėkmingos aortos koarktacijos korekcijos. Padidėjęs lokalus arterijų standumas buvo susijęs su padidėjusiu centriniu sistoliniu kraujospūdžiu.
4. Pusė gavusių antihipertenzinį gydymą vaikų po sėkmingos aortos koarktacijos korekcijos buvo gydyti nepakankamai. Beta adrenoblokatoriai ir angiotenziną konvertuojančio fermento inhibitoriai buvo dažniausiai skiriamos antihipertenzinių vaistų grupės monoterapijai ir kombinuotajai terapijai, bet mažesniame vaistų dozių intervale, nei rekomenduojama.

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TRUMPOS ŽINIOS APIE DISERTANTĘ

Skaistė Sendžikaitė 2012 m. baigė vientisąsias medicinos studijas Vilniaus universiteto Medicinos fakultete (VU MF), 2018 m. užbaigė VU MF vaikų ligų ir vaikų kardiologijos rezidentūros programą. Nuo 2015 m. dirbo gydytoja asistente, nuo 2018 m. - gydytoja vaikų kardiologe, o nuo 2021 m. dirba vyresniąja gydytoja vaikų kardiologe Vilniaus universiteto ligoninės Santaros klinikose.

Disertantei 2016 m. suteikta Europos vaikų kardiologų draugijos jaunojo tyrėjo mokslo premija vykdyti daugiacentrį biomedicininį tyrimą "Ankstyvas kraujagyslių senėjimas vaikams, sergantiems aortos koarktacija", kurį disertantė inicijavo 2017-01 mėn. Tyrime dalyvavo Lietuvos, Latvijos ir Lenkijos centrai. Šio tyrimo pagrindu parašyta disertacija.

Nuo 2018-08 mėn. iki 2021-05 mėn. buvo Europos vaikų kardiologų draugijos tarybos narė, atsakinga už jaunuosius vaikų kardiologus. Nuo 2018-08 mėn. iki dabar yra Europos vaikų kardiologų draugijos Edukacijos komiteto narė. Nuo 2019-08 mėn. iki dabar – JAV virtualaus vaikų kardiologijos mokymosi centro redakcijos komandos narė. Disertantė taip pat yra *Cardiology in the Young* ir *Frontiers in Pediatrics* bei *Frontiers in Cardiovascular Medicine* žurnalų redakcijos komandos narė.

Stažavosi Cincinnati vaikų ligoninėje (Cincinatis, JAV), Vaikų memorialiniame sveikatos institute (Varšuva, Lenkija), Stradins universiteto vaikų klinikinėje ligoninėje (Ryga, Latvija).

Publikavo 7 publikacijas tarptautiniuose recenzuojamuose mokslo leidiniuose.

PUBLIKACIJŲ SĄRAŠAS

Su disertacijos tema susijusios publikacijos

1. Sendzikaite S, Sudikiene R, Tarutis V, Lubaua I, Silis P, Rybak A, Jankauskiene A, Litwin M. Prevalence of arterial hypertension, hemodynamic phenotypes, and left ventricular hypertrophy in children after coarctation repair: a multicenter cross-sectional study. Pediatr Nephrol. 2020 Nov;35(11):2147-2155. doi: 10.1007/s00467-020-04645-w. Epub 2020 Jun 11. PMID: 32529324.
2. Sendzikaite S, Sudikiene R, Lubaua I, Silis P, Rybak A, Brzezinska-Rajszys G, Obrycki Ł, Jankauskiene A, Litwin M. Multi-centre cross-sectional study on vascular remodelling in children following successful

coarctation correction. J Hum Hypertens. 2021 Aug 3. doi: 10.1038/s41371-021-00585-6. Epub ahead of print. PMID: 34344993.

Kitos publikacijos

1. Autoimmune polyendocrine syndrome with recurrent serositis. Paulius Kalibatas. Skaiste Sendzikaite. Rita Sudikiene. Laboratorinė medicina. 2017, t. 19, Nr. 1, p. 66–68.
2. Sendzikaite S, Heying R, Milanesi O, Hanseus K, Michel-Behnke I. COVID-19 FAQs in paediatric and congenital cardiology: AEPC position paper. Cardiol Young. 2021 Mar;31(3):344-351. doi: 10.1017/S1047951120005028. Epub 2021 Jan 7. PMID: 33407975; PMCID: PMC7900664.
3. Heying R, Albert DC, Voges I, Sendzikaite S, Sarquella-Brugada G, Pluchinotta F, Brzezinska-Rajszys G, Stein JI, Milanesi O; Contributors and reviewers of the AEPC council:; Contributors of the AEPC working groups (current chairs and representative members):. Association for European Paediatric and Congenital Cardiology recommendations for basic training in paediatric and congenital cardiology 2020. Cardiol Young. 2020 Nov;30(11):1572-1587. doi: 10.1017/S1047951120003455. Epub 2020 Oct 28. PMID: 33109300.
4. Tretter JT, Windram J, Faulkner T, Hudgens M, Sendzikaite S, Blom NA, Hanseus K, Loomba RS, McMahon CJ, Zheleva B, Kumar RK, Jacobs JP, Oechslin EN, Webb GD, Redington AN. Heart University: a new online educational forum in paediatric and adult congenital cardiac care. The future of virtual learning in a post-pandemic world? Cardiol Young. 2020 Apr;30(4):560-567. doi: 10.1017/S1047951120000852. Epub 2020 Apr 13. PMID: 32228736; PMCID: PMC7156582.
5. McMahon CJ, Heying R, Budts W, Cavigelli-Brunner A,Shkolnikova M, Michel-Behnke I, Kozlik-Feldmann R, Wåhlander H, DeWolf D, Difilippo S, Kornyei L, Giovanna Russo M, Kaneva-Nencheva A, Mesihovic-Dinarevic S, Vesel S, Oskarsson G,Papadopoulos G, Petropoulos AC, Saylan Cevik B, Jossif A, Doros G, Krusensjerna-Hafstrom T, Dangel J, Rahkonen O, Albert-Brotons DC, Alvares S, Brun H, Janousek J, Pitkänen-Argillander O, Voges I, Lubaua I, Sendzikaite S, Magee AG, Rhodes MJ, Blom NA, Bu'Lock F, Hanseus K, Milanesi O. Paediatric And Adult Congenital Cardiology Education And Training In Europe. Cardiol Young. 21-Dec-2021 priimtas spausdinti.

PRANEŠIMAI DISERTACIJOS TEMA

1. Žodinis pranešimas antrajame tarptautiniame vaikų ir paauglių hipertenzijos kongrese Varšuvoje, Lenkijoje „Prevalence and hemodynamic phenotype of arterial hypertension, and left ventricular hypertrophy in children after coarctation repair“ (2019 m. gegužė).
2. Žodinis pranešimas 53-iame kasmetiniame tarptautiniame vaikų Europos kardiologų ir įgimtų širdies ydų kongrese Sevilijoje, Ispanijoje „Prevalence of different forms of arterial hypertension and left ventricular hypertrophy in children after coarctation repair“ (2019 m. gegužė).
3. Stendinis pranešimas Rygos Stradinio universiteto organizuojamoje tarptautinėje medicinos ir sveikatos mokslų konferencijoje „Influencing factors on 24-hour blood pressure measurements in childhood coarctation of the aorta“ (2019 m. balandis).
4. Žodinis pranešimas šeštojoje Prehipertenzijos, hipertenzijos, metabolinių ir kardiovaskulinių ligų konferencijoje Vilniuje, Lietuvoje „Prevalence and hemodynamic phenotype of arterial hypertension, and left ventricular hypertrophy in children after coarctation repair“ (2019 m. kovas).
5. Žodinis pranešimas 7-oje Vilnius–Gdanskas Hipertenzijos konferencijoje Gdanske, Lenkija „Outcome of the aorta coarctation in infants“ (2018 m. rugsėjis).
6. Žodinis pranešimas 4-oje tarptautinėje konferencijoje „Evoliucinė medicina: sveikata ir ligos besikeičiančioje aplinkoje“ Vilniuje, Lietuvoje „Arterial hypertension and markers of early vascular aging in children with coarctation of the aorta“ (2018 m. birželis).
7. Žodinis pranešimas 52-ame kasmetiniame tarptautiniame vaikų Europos kardiologų ir įgimtų širdies ydų kongrese Atėnuose, Graikijoje „Initial data of international study of early vascular aging in children with coarctation of aorta“ (2018 m. gegužė).
8. Žodinis pranešimas pirmajame tarptautiniame vaikų ir paauglių hipertenzijos kongrese Valencijoje, Ispanijoje „Insights into early vascular aging in children with coarctation of aorta“ (2018 m. vasaris).
9. Žodinis pranešimas tarptautinėje konferencijoje –Childhood hypertension - a cross talk between paediatric cardiology and nephrology“ Vilniuje, Lietuvoje „Early vascular aging in congenital heart diseases“ (2017 m. gegužė).

PADĖKOS

Noriu padėkoti visiems, kas prisidėjo idėjomis, profesionalia, organizacine bei technine pagalba. Ypatingą padėką norėčiau išreikšti prof. dr. Augustinai Jankauskienei, prof. dr. Mieczysławui Litwinui, prof. dr. Ingūnai Lubaua ir dr. Ritai Sudikienei už profesionalią pagalbą, konstruktyvią kritiką, neskaičiuojamą laiką, skirtą vertingoms diskusijoms, bei palaikymą, supratingumą ir geranoriškumą kiekviename žingsnyje.

Taip pat norėčiau padėkoti VULSK Pediatrijos centro ir Širdies ir krūtinės chirurgijos centro personalui už techninę pagalbą ir recenzentams prof. dr. Sigitai Glaveckaitei, dr. Ramunei Vankevičienei ir dr. Karoliui Ažukaičiui – už vertingas pastabas bei rekomendacijas.

NOTES

NOTES

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