American Journal of Multidisciplinary Research & Development (AJMRD)
Volume 05, Issue 06 (June - 2023), PP 11-27
ISSN: 2360-821X
www.ajmrd.com

Research Paper **Open Access**

Paediatric Cardiology and Rheumatology in Interpenetration From Foetal To Adulthood

Ivan Malčić, Marija Jelušić
Clinical Hospital Centre Zagreb and Medical Faculty Zagreb, Clinic for Pediatrics, Department of Pediatric Cardiology, Reference Centre for Pediatric Cardiology of the Republic of Croatia,
Correspondence address: Prof. Dr. Sci. Ivan Malčić, MD, PhD
Clinical Hospital Centre Zagreb, Rebro
Kišpatićeva 12, 10000 Zagreb, Croatia

I. INTRODUCTION

Although paediatric cardiology and rheumatology are formally separate subspecialties in most clinical centres, they are nevertheless imbued with their competencies in different ways and at different levels from foetal to adult age. Most of the entities described in the rheumatology chapters have common features; unknown causes, hereditary predisposition, need for a stimulus trigger, auto aggression and self-limitation, self-perpetuation, overlapping of different entities and numerous consequences on the cardiovascular system. Due to the large number of rheumatological and immunological entities, rheumatic fever and juvenile idiopathic arthritis are not described, and special chapters are dedicated to those diagnoses that leave the most severe and even fatal consequences on the cardiovascular system: systemic lupus erythematosus, ant phospholipid syndrome, systemic scleroderma, Kawasaki disease, polyarteritis nodosa and some forms of granulomatous vasculitis. We especially highlight the occurrence of complete congenital atrioventricular block (CCAVB) in pregnant women who develop characteristic ANA antibodies (anti-SSA/Ro and/or anti SSB/La) due to systemic connective tissue diseases (SLE, Sjögren sy., MCTD), but are also likely to have the same inflammation within the heart that leads to the development of restrictive cardiomyopathy associated with CCAVC. We must not forget pulmonary hypertension, which is intertwined with paediatric cardiology, not only on a clinical level, but also on a classification basis, in similar or the same signalling pathways at the level of small blood vessels of the lungs and/or heart, and concepts that penetrate at the level of the inflammatory process (chronic inflammation), self-perpetuation after triggering and mechanisms of disturbed balance (homeostasis of vasoconstriction and vasodilatation, prothrombotic and antithrombotic factors, maintenance of apoptosis functions, clarification of pericyte function, etc.). The treatment of both cardiac and rheumatic diseases includes similar or the same drugs due to the knowledge of the mechanisms of the occurrence of cardio-pulmonary and rheumatic diseases, both in children and in adults. We hope that this review will have a positive effect on the development of teamwork and increase their overall awareness of the consequences of rheumatic diseases on secondary changes in the cardiovascular system.

Cardiac changes in rheumatic entities other than neither rheumatic fever nor juvenile idiopathic arthritis

CARDIOVASCULAR DISEASES IN SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) was first described in 1872 (Kaposi). Verrucous vegetations on the heart were described in 1924 (Liebman, Sacks) and associated with SLE only in 1940 (Gross) (1,2). Over time, it was realized that SLE can be accompanied not only by non-bacterial verrucous endocarditis, but also by pericarditis (30-50%) and myocarditis (50-75%), but also by arrhythmias (conduction disorders), coronary diseases (coronary arteritis), premature coronary atherosclerosis and arterial hypertension. With the development of diagnostic methods and analysis of myocardial biopsies (Dallas's criteria) (3-5), a more thorough analysis of the forementioned changes is being approached, which in today's conditions is studied at the level of molecular genetics, analysis of homeostatic mechanisms, immunogenetics and electron-microscopic examination of cardiac structures after biopsy (4 ,5). Thanks to the possibilities of echocardiographic analysis, bacterial endocarditis (vegetation) can be distinguished very well from non-bacterial verrucous endocarditis where verrucous formations are located on the atrial surface of the mitral valves (3). Hypertension secondarily burdens the heart with lupus nephritis. According to some studies from 1992 (6), heart lesions in SLE were diagnosed by echocardiography in 57% of patients, most of them on the valves. If a patient with SLE also has antiphospholipid antibodies, mitral valve lesions with consecutive insufficiency are more common. An

increased prevalence of endocardial lesions with valvular regurgitation was found in patients with antiphospholipid antibodies. For this reason, it is concluded that with the existence of antiphospholipid antibodies, valvular diseases are becoming more common, and echocardiography is considered an indispensable method in the proper monitoring of these patients. According to evidence that autoantibodies damage heart structures such as valves, pericardium, conduction system and coronary arteries in patients with SLE, antiphospholipid syndrome (ASP), Sjogren's syndrome (SS) and other autoimmune diseases, cooperation with cardiologists is inevitable. Indeed, cardiovascular diseases are considered to the main cause of morbidity and mortality in SLE as well as APS, and many factors indicate an accelerated development of atherosclerosis (7).
In the following description, we will consider traditional and non-traditional risk factors in SLE patients with special reference to atherosclerosis, endothelial disfunction and the importance of antibodies.

Atherosclerosis and inflammation: In recent decades, it has been realized that the activation of monocytes, macrophages, T-cells, and cytokines play an important role in atherogenesis, and the role of CRP is also considered. In addition, autoantigens and autoantibodies have also important role in atherogenesis in general population (7, 10).

Endothelium and Atherosclerosis: Endothelial dysfunction is a key event in atherogenesis and appears before the histopathological evidence of atherosclerotic lesion, cause of regulation of local blood vessels function like vascular tone, cell adhesiveness, coagulation, inflammation, and permeability. Additionally, vascular inflammation may encourage systemic inflammation as an important mechanism in atherogenesis (11, 12). During the initial stages of atherosclerosis, monocytes and T cells adhere to the intact endothelium of the blood vessel wall. Several adhesion molecules can promote monocyte adhesion, including intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and selectin. (7, 10). These adhesion molecules are surface proteins, and they induce pro-inflammatory mediators, such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and C-reactive protein (CRP) (7, 10-12,13).

Inflammation and atherosclerosis in general population: Systemic inflammation, especially CRP, has been associated with cardiovascular disease (CVD) risk in the general population. CRP has an important role in atherogenesis of normal population, both in the early initiation of atherosclerotic lesions and in the conversion of stable to unstable plaques. The biological effect of CRP on atherosclerosis has proatherogenic properties by being capable of activating the complement system, inducing endothelial production of monocyte chemotactic protein1 and secretion of endothelin-1and interleukin 6 (IL-6). Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future CVD events. Therefore, CRP levels may be considered an independent risk factor for myocardial infarction and stroke in men with and without other traditional risk factors (7, 14). The strong predictive value of CRP can be explained by its long-term stability during dormancy of inflammatory disease, enhanced activity along with inflammatory disease, and independence in age and sex (7, 15).

Autoantigens and atherosclerosis: Numerous autoantigens and their corresponding autoantibodies have been involved in the pathogenesis of atherosclerosis (16). A cellular immune response specifically reported against heat shock protein, oxidized low-density lipoprotein, and β2-glycoprotein-1 has been reported, suggesting direct involvement of these molecules in atherosclerosis (17). It is believed that there are several such specific cell lines that react with specific antigens that can modulate atherosclerosis pro-atherogenic or anti-atherogenic.

Heat shock Proteins (HSP60/65) are a group of proteins that are involved in response to stress factors and may therefore become a target for autoimmunity (18). There are clinical, subclinical, and experimental data that anti-HSP60/ 65 has a proatherogenic role. Patients with high levels of anti-HSP65 were found to be at increased risk of subsequent cardiovascular events and cardiovascular mortality (26, 27). Furthermore, patients with sonographic evidence of carotid atherosclerotic lesions had significantly elevated levels of anti-HSP65 when compared to control group (19).
Antiphospholipid antibodies are a heterogeneous group of autoantibodies, including anticardiolipin antibody (ACL) and lupus anticoagulant (LAC), generally targeted to phospholipid-binding proteins (18). They can be found in human atherosclerotic lesions derived from carotid endarterectomies, are abundantly expressed within subendothelial regions and the intimal-medial border of human atherosclerotic plaques and localize with CD4-lymphocytes (19,20).

Systemic lupus erythematosus and atherosclerosis.

SLE is an autoimmune disease with various clinical forms manifestations that occur predominantly in young women (16). In the general population, atherosclerosis is more common in the elderly (21). The high incidence of atherosclerosis in young women with SLE was originally recorded in Bulkley's Roberts autopsy studies (22)1975. Urowitz et al. (23) described the bimodal distribution of causes of death in SLE: "early" peak caused by increased SLE activity or infections, and "late" peak caused by cardiovascular complications. Atherosclerosis in SLE patients is not only more frequent, but also has accelerated development compared to other SLE populations (16, 24). It is considered that the reason in

deposition of the immune complex in the vascular wall with consequent intimal damage and rapid rupture, but only in more severe forms of SLE (25,26). It is assumed that the deposition of the immune complex causes initial intimate damage, which is the reason for the accelerated development of atherosclerosis. (25). According to some authors, SLE has a negative impact on the development of cardiovascular and other complications only in subgroups of patients with SLE. It may be the case that CVD as well as many other manifestos (26). Additional research is needed to clarify the dilemmas.

Cardiovascular risk factors in SLE

The prevalence of clinically manifest ischemic heart disease ranges between 8% and 16% in various studies (27,28,29). Perfusion abnormalities are found in up to 38% of adult patients with SLE (29) and in 16% of children (30). Atherosclerosis has been shown to promote age and disease duration. (31), so the difference between traditional and non-traditional factors in the development of atherosclerosis and CVD is considered. For example, hypertension, because of renal impairment is known to be an important factor in the development of CVD in patients with SLE (32). Treatment with high doses of prednisolone is also an important non-traditional risk factor for CVD (33), but additional factors should be considered (34). Non-traditional risk factors in SLE include kidney disease and corticosteroid use. An association between renal disease and the prevalence of risk factors for CAD has been reported in several studies (35,36). Although the occurrence of coronary artery disease (CAD) is associated with the use of glucocorticoids, CAD is also found in patients with SLE who have never been treated with steroids (37). Other disease-related factors are inflammatory mediators that are released, because of chronic systemic inflammation associated with SLE, an endothelium-mediated immune complex cell damage and antiphospholipid antibodies (38). In patients with SLE, serum anti-HSP65 antibody concentrations are heterogeneous and inconclusive (39). The results available so far are too inconsistent to allow this any final conclusions about the role of inflammatory mediators in premature atherosclerosis. SLE is thought to be considered an independent cardiovascular risk factor. The contradictory nature of the available data to date does not allow conclusions to be drawn about the pathophysiology of accelerated atherosclerosis in patients with SLE or so additional prospective studies are needed (38).

In our prospective study, we examined organ damage in children with SLE for 29 years and found organ damage in 50% of children after 6 years of illness. The first organ systems to become damaged in affected patients was ocular (43%), followed by musculoskeletal (23%) and central nervous system (CNS) (14%), renal (7%), cardiovascular (7%) and finally by peripheral vascular system (2.3%) and diabetes (2.3%). Moreover, seizures were the most frequent feature of CNS damage, whereas cardiomyopathy was the most frequent feature of cardiovascular damage (40).

CARDIAC MANIFESTATIONS IN PRIMARY FORM OF ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an autoimmune disease due to the presence of antiphospholipid antibodies (APL) which causes arterial and venous thrombosis, and in pregnancy causes recurrent foetal loss and placental insufficiency (41). The antibodies found in these patients are lupus anticoagulant (LAC), anticardiolipin antibody (ACL), and antiβ2-glycoprotein I (β2 GPI) antibody. For clinical implications, not only their presence but also the trigger is required, and most often it is an infectious agent (42). APS occurs as a primary disorder (PAPS) or as a secondary to another autoimmune disease (SAPS), most commonly systemic lupus erythematosus (SLE). Complications due to clotting are more common in SAPS than in the isolated form (43). Although due to the nature of the underlying disorder (coagulation) different organs may be affected, here we look primarily at the cardiac manifestations of PAPS. The most common cardiac manifestations are valvopathies due to valve thickening, including thrombotic endocarditis (Liebman-Sacks endocarditis) and coronary artery disease (CAD). Other clinical manifestations are myocardial dysfunction, pulmonary hypertension and intracardiac thrombosis. The primary treatment for PAPS is anticoagulant therapy. The basic clinical manifestations of PAPS on the heart will be presented here.

Heart valve disease in APS Heart valve disease (HVD) in PAPS is manifested by moderate insufficiency, primarily of the mitral and aortic valves, and in the absence of a history of RF and infective endocarditis (41). Valve lesions in APS are manifested by their thickening (> 3mm) and vegetation (Liebman-Sacks endocarditis). Irregular nodules also appear on the atrial side of the mitral and aortic sides of the aortic valve (42,43). Some studies have shown that one-third of patients with APS have HVD when assessing TTE (44, 45), and up to 60% when assessing TEE (46, 47). The association and difference of valvular changes in SLE-SAPS and PAPS should also be investigated. Pathohistological changes in HVD are nonspecific and include fibrosis, calcification, vascular proliferation, verrucous thrombosis, and intra-valvular capillary thrombosis (47). Microscopically located on deformed valves with APS deposition of immunoglobulins including ACL (IgG) and complement components, along the outside of the cusp. It is possible that APL may cause a subendocardial inflammatory process through interaction with antigens on the valve surface creating irregular nodules (48). Thrombosis occurs, and inflammation subsequently leads to fibrosis and calcification and finally to valve deformation (49). Some studies show that 24% of patients with RF have positive anti-

pathohistological changes in CVD are nonspecific and include fibrosis, calcification, vascular proliferation, verrucous thrombosis, and intra-valvular capillary thrombosis (47). Microscopically located on deformed valves with APS deposition of immunoglobulins including ACL (IgG) and complement components, along the outside of the cusp. It is possible that APL may cause a subendocardial inflammatory process through interaction with antigens on the valve surface creating irregular nodules (48). Thrombosis occurs, and inflammation subsequently leads to fibrosis and calcification and finally to valve deformation (49). Some studies show that 24% of patients with RF have positive anti-β2GPI, and that patients with PAPS have antistreptococcal activity, recognizing M-protein in 16.6% of cases. This means that there were significant overlaps in humoral immunity. It was also found that 80% of patients in the acute phase of RF have positive ACL antibodies (49,50). Therefore, further studies are expected in the assessment between lesions on the valves in RF and APS.

Table1. Summary of cardiac involvement in APS (Pons-Estell Gi et al. J Autoimmun 2017)

Cardiac abnormality	Prevalence PAPS	Prevalence SAPS
Coronary artery disease **-Asymptomatic atherosclerosis** **-Myocardial infarction**	 15% 1,2%	 30-35% 3,8%
Valvular disease **Non-bacterial thrombotic vegetations** **Valvular fibrosis and thickening** **Valvular regurgitation**	33%	40-50%
Myocardial dysfunction **Diffuse cardiomyopathy** **Diastolic dysfunction**	No reliable data	No reliable data
Intracardiac thrombosis	No reliable data	No reliable data
Pulmonary hypertension	1-5,7%	0.5-14%

Coronary artery disease in APS. *Atherosclerosis*. The causes of atherosclerosis in APS compared to other atherosclerosis-related diseases (SLE, DM) are still the subject of scientific studies. Atherosclerosis leading to high cardiovascular morbidity and mortality mainly affects the younger population. (51, 52). Studies to assess the presence of accelerated atherosclerosis in PAPS of patients are inconclusive (52).

Venous thrombotic events with LAC are predominant in PAPS patients, while peripheral, coronary, and carotid thrombosis are more common in patients with significantly elevated IgG or IgM ACL titers (53). Similar results were found on the lack of association between ACL and antiβ2GPI antibodies and accelerated atherosclerosis in a group of rheumatological patients who underwent coronary heart disease with surgical considerations (46). Various studies have confirmed this the presence of autoantibodies directed against serum lipoproteins. If their level is high, a cross-reaction occurs (55,56).

Myocardial infarction: First description of myocardial infarction (57) prompted further research. It occurs more frequently in women (58), and acute myocardial infarct (AMI) with APS usually in the 4th decade of life (59) and most authors emphasize normal coronary angiography (58,60). It is more common in the APS-SLE group (3.8%) compared to AMI in PAPS (1.2%), but patients with PAPS die in 10% of cases, while patients with APS-SLE do not die from a heart attack. Some authors find normal coronary angiography in SLE-APS, but coronary obstruction in 25% of patients with PAPS, so this may be considered a cause (62).

Accelerated atherosclerosis of the coronary arteries, microvascular damage and coronary thromboembolism can lead to ischemia. Coronary embolism is a major cause of MI in young people (63).

Myocardial dysfunction: Distinguishing primary myocardial disease from other common causes of damage (diabetes mellitus, hypertension) is not always easy. Antibodies in the myocardium can cause ventricular dysfunction in APS. Coronary artery thrombosis and / or microvascular thrombosis it can also lead to ventricular dysfunction associated with APS causing myocardial ischemia (64, 65). Patients with SLE-APS have more frequent diastolic LV dysfunction, and PAPS systolic LV dysfunction (66, 67). Diffuse cardiomyopathy is less common in APS. In some cases, autopsy revealed widespread occlusive micro thrombosis of the small myocardial arterioles and the area around the affected myocardial microinfarction, leading to extensive myocardial necrosis (68). In one study, there was a significant correlation between high titter of ACL IgM and heart failure (69, 70).

Pulmonary hypertension. Venous thromboembolism is the most common manifestation of APS, with a very high risk of recurrence. If pulmonary embolism (PE) is associated with APS, chronic thromboembolic pulmonary hypertension (CTEPH) often occurs (71), which is the predominant non-valvular cardiac manifestation of APS. However, CTEPH itself is very rarely the cause of death (61). However, over time, right ventricular loading occurs with isolated tricuspid regurgitation and secondary pulmonary hypertension, which

may ultimately be the cause of right heart failure. Recurrent embolism, in situ thrombosis, immunologically mediated damage to the capillary endothelium of the small pulmonary vessels (arterioles) leads to progressive remodelling mediated by endothelin1. Such conversion to CTPEH by PAPS is slightly more than 3% of patients (72,73).

Intracardiac thrombus: Intra-cardiac thrombus is a rare but potentially life threatening. The overall prevalence of intra-cardiac thrombi was 1.8% (74). Some reports describe thrombi appearing in all four cardiac chambers (75). Thrombotic micro-vasculopathy appears to add to myocardial ischemia with clot formation (76). Also, severe myocardial dysfunction may be the reason for the formation of LV thrombus in APS. High levels of ACL (IgG) were found in intracardiac thrombi (77).

Summary: We have described the cardiac manifestations of APS. APS is a multi-organ autoimmune disease with various cardiac manifestations. Valve involvement was the first reported cardiac manifestation of APS, including valvular thickening, valve nodules (also referred to as non-bacterial vegetations or Liebman-Sacks endocarditis) and valvular regurgitation/stenosis. APS is presumed to be associated with accelerated atherosclerosis of peripheral and coronary arteries: APL induces activation of endothelial cells, and thus may play a direct role in the process of atherogenesis. Other cardiac manifestations, in the form of myocardial dysfunction, pulmonary hypertension and intracardiac thrombi are less common. To date, a classification system that can distinguish the cardiac manifestations in PAPS from SAPS has not yet been established. We recommend that all APS patients with evidence of HVD to be screened for SLE. We recommend performing TTE in every APS patient as an initial evaluation. Due to the high prevalence of cardiac involvement in APS, clinicians should have a high index of suspicion, in the attempt to minimize cardiovascular complication rates.

NEONATAL LUPUS SYNDROME, COMPLETE ATRIOVENTRICULAR BLOCK AND RESTRICTIVE CARDIOMYOPATHY.

Definition. Neonatal lupus erythematosus (NLE) is a foetal disease caused by specific maternal autoantibodies directed against a group of small cytoplasmic and nuclear ribonucleoproteins and their associated ribonucleic acid proteins, which in the literature are called Ro-RNP or just Ro particles. Passive transfer of autoantibodies from mother to foetus is not sufficient for the development of symptoms because genetic and environmental factors are involved. Permanent changes remain only on the foetal heart as complete congenital atrioventricular block (Complete congenital AV-block CCAVB) - with cardiomyopathy (or without it). Mothers do not have to have clinical symptoms of systemic disease to carry the responsible antibodies (78).

Auto antigens, possible environmental and genetic factors. In 1985, Rechlin et al. found two autoantigens in the serum of patients with SLE and named them after the two patients in whom they were found (Robert-Ro and Lanne-La). It turned out that as early as 1975, Alspaugh and Tan found identical autoantigens in patients with Sjogren's syndrome (SS), and named them SS-A and SS-B. That is why even today these antigens are designated as anti-SSA/Ro and anti SSB/La. The 52 kDa Ro / SS-A antigen can bind via protein-protein interaction using the leucine zipper region located between amino acids 276 and 318 of the Ro60 antigen. While the function of the 60 and 52 kDa Ro is not yet known, the La protein is known to serve as a transcription termination factor for RNA polymerase III (79,80).

Antibodies to the mentioned antigens begin their transplacental transition into the foetal circulation in the 16.-th week of pregnancy and are three times more abundant in the foetal heart than in other tissues. They have at least three effects in the foetal heart: 1) inflammation (myocarditis); 2) arrhythmogenic effect; 3) apoptosis disorder. Pan carditis (endo-myo-pericarditis) leads to consequent fibrosis of the conduction system, which is clinically manifested as CCAVB. Along with numerous other studies, it is necessary to highlight the study by E. Miranda et al. who examined the movement of these antigens in apoptotic myocardial cells grown in culture. It is known that apoptosis, as a natural "cell death", plays an important role during embryogenesis in the morphological and functional maturation of organs. It seems that the described antibodies bind to apoptotic cells, which is a stimulus (trigger) for an inflammatory response that damages the surrounding tissues. However, despite numerous studies, many ambiguities remain, and the genetic background is only of theoretical significance, although there is confirmation of systemic connective tissue diseases dependent on the HLA system and the stimulating factor (81-83). When we talk about the inflammatory process induced by an unknown factor, progressive inflammation, disruption of apoptosis and other balance mechanisms, we use the terms used in the basics of paediatric cardiology, rheumatology, and pulmonology (pulmonary hypertension).

Pathogenesis of complete atrioventricular block. There is only a working hypothesis. Molecular elucidation of the link between anti-SSA / Ro or anti-SSB / La antibodies and heart damage is a challenging task when said antigens are found intracellularly. Apoptosis seems to be a critical part of this process. Maternal anti-SSA / Ro and anti-SSB / La antibodies in foetal circulation can unexpectedly redirect normal cleaning apoptotic cardiomyocytes with healthy cardiomyocytes towards cleaning wat macrophages (via FcR), which release inflammatory and/ or fibrosing cytokines. Elements of these guidelines include macrophages (representatives of inflammatory components) and fibroblast (representatives of scarring) (84).

Epidemiology. In children with a structurally healthy heart, the occurrence of CCAVB is almost always associated with the presence of anti-Ro/SSA and anti-La/SSB antibodies in the mother's serum. It occurs with an incidence of 1:14,000-1:20,000 live births and is thought to be caused by the transplacental transfer of the described maternal antibodies in 90% of cases. From PSG, CCAVB is found in left atrial isomerism, l-TGA and rarely in CCAVC, due to abnormal morphogenesis of conducting cardiac musculature. Congenital AV block usually develops between 16 and 24 weeks of pregnancy, which coincides with an increase in the transplacental transfer of maternal antibodies into the foetal circulation. Judging by the findings of foetal echocardiography, more than 30% of children with CCAVB die during pregnancy, so it is possible that some of these children belong to the NLE syndrome.

Pathology. In the following pathohistological findings, there is a fibrous transformation of the tissue of the atrioventricular node with calcification, and the distal part of the conduction system is normal. In some patients, this process is extended to other parts of the endo-myocardium with a morphological and hemodynamic picture of fibroelastosis. All available knowledge includes the following factors: 1. maternal autoantibodies are a central factor in pathological events in the foetal myocardium, 2. an alternative antigen that reacts with maternal autoantibodies can primarily be localized in the centre of the heart cell, but can be transferred by spontaneous spread of inflammation to the whole heart, 3. the antigen-antibody reaction is probably not sufficient for the development of a *sui generis* inflammatory process, but the influence of environmental and genetic factors is assumed, 4. described effect of anti-Ro is manifested by the disruption of calcium transport in cardiomyocytes, and the cross-reaction of autoantibodies with protein receptors of calcium channels leads to consequent fibrosis (85). Here, too, the basic events are mentioned in identical pleonasms with events in other cardio rheumatological diseases.

Clinical approach to complete atrioventricular block in NLE syndrome. Thanks to foetal echocardiography, the appearance of early foetal bradyarrhythmia raises the suspicion of the possible development of CCAVB as early as the 15th gestational week. Complete AV-block develops gradually from the lengthening of the PQ interval to the final occurrence of CCAVB in the 20th week of pregnancy. Arrhythmia should be monitored by foetal echocardiography (M-view and Doppler view), and a call or/and negative history requires a simultaneous laboratory finding of anti-SSA/Ro and anti-SSB/La antibodies. Every pregnant woman with a suspected (or already proven) systemic connective tissue disease (SS, SLE, MCTD) must report for a foetal cardiology examination before the completion of 15 weeks of pregnancy in order to start appropriate therapy in time (see table 2). The finding of corrected transposition of large blood vessels and left atrial isomerism should certainly be ruled out. According to the available studies, it seems that CABD develops in only 10% of children with the described predisposition, but the lesions are permanent if the development of CCAVB is not stopped with the use of dexamethasone (85, 86).

Treatment of congenital heart block. In case of any suspicion (especially proven), early treatment of CAVB with glucocorticoids (dexamethasone and betamethasone) should be started. If foetal bradycardia below 55/min develops badly, hydrops and pericardial effusion appear, so administration of β-adrenergic stimulants is recommended. Experience shows that the use of dexamethasone for 4 weeks (from 16-20 weeks of gestation) does not have any consequences on the development of the foetus, but there is an extensive debate about the treatment of children during pregnancy while there is no CCAVB, as well as after pregnancy in the case of already existing complex atrioventricular block (87, 88), 89). In addition to the links between cardiology and rheumatology described here, special importance should be given to other aspects related to embryonic age, i.e. the foetal period, and this primarily refers to the relationship between methotrexate and folic acid in the periconceptional period (two months before and two months after conception) and on the relationship between ductus arteriosus and anti-prostaglandin drugs in late pregnancy. There are other important aspects of rheumatology in pregnancy, not only regarding the influence of rheumatic diseases and drugs on the embryo and foetus, but also the influence of these factors on the pregnant woman. We hope that in the future we will think about these problems together.

Table 2. Recommended therapeutic approach to a complete foetal heart AV-block (Ref 89.).

Clinical Condition	Treatment
Degree of AV block	
• Grade 3 (> 3 weeks from diagnosis)	• ECHO 1x per week, treatment is not necessary.
• Grade 3 (<3 weeks from diagnosis)	• Dexamethasone 4 mg / day orally for 6 weeks. If there is no improvement, gradually discontinue, and if there is improvement, continue until delivery.
• Alternation of 2nd and 3rd degree blocks	
• 2nd degree block or mechanical extension of PR intervals	• Dexamethasone 4 mg / day for 6 weeks. If the block goes to level 3, gradually discontinue, and if a 2nd degree block remains, continue until deliver.
• AV-block with initial signs of myocarditis, heart failure and / or	• Dexamethasone 4 mg / day until delivery, then

foetal hydrops • Severe foetal hydrops	discontinue gradually. If the block progresses to grade 3, phased out if block lasts longer than 6 weeks. • Dexamethasone 4 mg / day until improvement, then discontinue gradually. • Dexamethasone 4 mg / day with maternal plasmapheresis to remove maternal antibodies. Consider the use of digoxin and diuretics. Childbirth when assessed that the foetal lungs are mature enough.

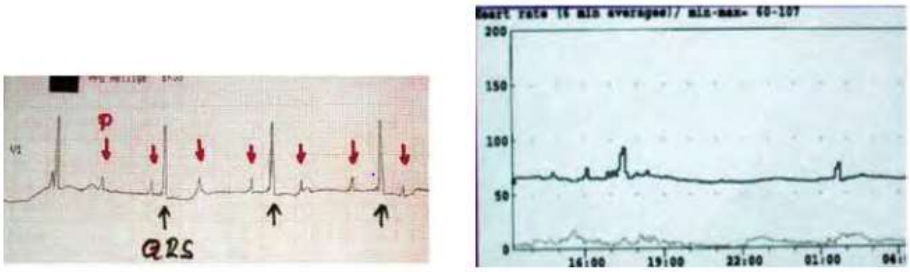

Fig 1. Permanently complete atrioventricular block in a child born with neonatal lupus syndrome who did not receive adequate prophylaxis between the 15th and 20th week of pregnancy (85).

PRIMARY CARDIOVASCULAR DISEASE IN SYSTEMIC SCLERODERMA

Systemic scleroderma (SSc) directly affects the muscular system (myositis), the heart (restrictive cardiomyopathy), coronary artery disease, conduction disorders (arrhythmias), serous membranes involvement (pericarditis), and indirectly the development of pulmonary hypertension (due to left heart disease - PAH/LHD) and arterial hypertension due to nephropathy. Previously, 20-25% of patients with SSc had symptoms arising from the cardiovascular system (90,91), but this number has increased significantly with the introduction of new diagnostic methods (thallium myocardial scintigraphy, single-photon emission computed tomography (SPECT) and MRI) (90, 91, 92). Myocardial biopsy analysis is also used in the diagnosis of cardiac changes (93). An echocardiographic examination can undoubtedly assess the functional state of the myocardium in patients with SSc, and thus determine adequate drugs therapy (ACEi, beta-blockers, aldosterone antagonists, calcium channel antagonists). According to the sensitivity of mentioned methods, today it is considered that as many as 46% of patients have limited systolic function during exercise, and 15% at rest (93). The evaluation and interpretation of the right ventricular function and the assessment of pulmonary vascular resistance (IpcPAH or CcpPAH) are of particular importance, so it is reasonable the treat the patients with SSc in close collaboration with rheumatologists and cardiologists.

Reports of cardiac involvement in systemic scleroderma according to large, randomized studies; The degree and intensity of changes in the heart according to the modified Metzger criteria can be found in Table 3. A modified Metzger severity scale (94) classifies the severity of organ involvement and is predictive mortality (95). The study reported 12.6% of 103 patients (66% had mild cardiac involvement, 7.8% moderate, 1.9% severe and none had end-stage cardiac disease (96).

Table3. Metzeger severity scale for cardiac involvement with systemic scleroderma

Grade	Characteristics
O involvement	Normal ECG, LVEF>50%
1 (Mild)	Conduction defects on ECG, LVEF 45-49%
2. (Moderate)	Arrhythmias on ECG, LVEF 40-44%
3. (Severe)	Arrhythmias requiring treatment on ECG, LVEF 30-40%
4. (End-stage)	Congestive heart failure, LVEF< 30%

Steen and Metzeger reported that 15% of 913 patients with SSc in a prospective study developed severe heart disease, which they defined as cardiomyopathy with a decrease in LV ejection fraction (LVEF) and symptoms of CHF, symptomatic pericarditis (pericardial pain), cardiac decompensation from effusion or arrhythmia attributable to SSc requiring treatment (97) They also commented that those who developed severe cardiac involvement were more likely to do so in the first 3 years of disease onset.

The nature of cardiac disease reported varied. Palpitations were commonly recorded (98), along with pericarditis and pericardial effusions (100). Many studies reported abnormalities in conduction, from bundle branch block [99) to arrhythmias requiring intervention, others only reported any abnormality in ECG. Further

manifestations included cardiomegaly (99, 100), diastolic dysfunction and abnormal LVEF (101). No case study differentiated SSc-cardiomyopathy from idiopathic heart disease IHD) when reporting cardiac morbidity. Eloranta et al. (102) included myocardial infarction in their definition of cardiac involvement, reporting cardiac involvement in 39% of their 70 patients-cohort.

Association of other features with myocardial disease. Although the literature is limited, it appears men may have a greater risk of SSc-cardiomyopathy (103). Cardiac involvement may be more prevalent in black patients with SSc (104). Other studies suggest no difference in prevalence across Caucasian, Asian, and Hispanic groups (105, 106).

According the different outcomes of large studies, different diagnostic approaches and secondary diseases, SSc includes dangerous heart diseases, primarily cardiomyopathy (possibly a restrictive type due to diastolic dysfunction), and more multicenter, randomized studies are expected in the future.

KAWASAKI DISEASE

Kawasaki disease (KD) is a self-limiting acute vasculitis which was first described by Japanese pediatrician Tomisaku Kawasaki in 1967. KD is systemic vasculitis that primarily affects small and medium-sized arteries in almost all organs. To this day, the cause of the disease is unknown. The hypothesis of a superantigen leading to upregulation of the immune response has been supported by some studies and refuted by others (107). The same hypothesis appears in the discussion of nodular polyarteritis. It mainly affects children and young people, and is more common in the Asian population, mostly in winter and spring (107). Cardiovascular consequences are the leading cause morbidity and are responsible for almost all deaths because of coronary vasculitis associated with a hypercoagulable condition, leading to myocardial infarction and sudden death. Despite severe complications, the mortality rate in the acute phase of the disease is low (1%) (108, 109). The first changes in the vascular endothelium spread sub endothelially with mononuclear infiltration of predominantly CD8 + T lymphocytes integrity of the blood vessel and its aneurysmal transformation. In the acute phase, myocarditis, pericarditis, and endocarditis (valvulitis) can be diagnosed within a few weeks, fibrous conversion of collagen and elastic fibers begins, and the coronary artery becomes stenotic or occluded with additional consequent thrombosis and previous formation of aneurysmal dilatations. (107-110). Independent of numerous diagnostic and clinical criteria (Fever persisting at least 5 days, changes in extremities - erythema and edema of hands and feet and subacute membranous desquamation of fingertips and periungual peeling, polymorphous exanthema, bilateral, painless bulbar conjunctival injection without exudate, changes in lips and oral cavity, diffuse injection of oral and pharyngeal mucosae, cervical lymphadenopathy usually unilateral) here we will look only at cardiovascular changes.

Cardiovascular complications and imaging:

Cardiovascular complications are the leading cause of morbidity in KD (Table 4). Primary development of coronary artery aneurysms (CAA) appears in the subacute phase in untreated children and occurs in 15-20% of cases. Right coronary artery aneurysms (RCA) are prone to progressive dilatation, and those in the left coronary artery (LCA) are more prone to focal stenosis [107-110, 112,113).

Table 4: Cardiovascular manifestation of CD.

Manifestations (in order of frequency):
Coronary artery aneurysms
Myocarditis
Pericarditis with pericardial effusion
Systemic arterial aneurysms
Valvular disease
Mild aortic root dilatation
Myocardial infarct

Myocarditis is the most common non-coronary complication and is present in 50-70% of patients in the acute phase (108). Pericarditis with pericardial effusion also often occurs in about 25% of patients in the acute phase (114). Mitral regurgitation occurs in papillary muscle dysfunction and rupture of the chordae tendineae (110), and myocardial infarction and valvulitis are found in only 1% of patients (114, 115). Aortic root dilatation can be found in the acute phase as well as associated aortic insufficiency (114,115). Systemic arterial aneurysms occur in approximately 2% of patients with KD, usually those who also have CAA [2]. The most affected arteries are axillary, common iliac, internal iliac and subclavian. The peripheral aneurysms also tend to regress, like to CAA 112, 116).

Echocardiography is the technique of choice in the assessment of clinical abnormalities because it is non-invasive, widely available and has a high sensitivity for the detection of proximal abnormalities in the

coronary arteries (108, 107). This primarily refers to measuring the dimensions of the proximal visible enlargement of the coronary arteries. If this is not possible for technical reasons, and there are other indications for suspected progressive coronary angiopathy, computed tomography (CT) and magnetic resonance imaging (MRI) are included in the diagnostic process. Although selective coronary angiography remains the "gold standard", however, should be avoided due to potential complications, especially in smaller children (118).

Conclusion. KD can be considered a systemic disease as self-limiting vasculitis of unknown ethology, so in a broader sense it can also be considered a rheumatic disease. Most rheumatic diseases are of unknown ethology, develop after an unknown trigger in a possibly immunodeficient organism, and have the character of auto aggression and self-limiting. In KD, cardiovascular consequences are a major factor in morbidity and mortality and should be treated in a team effort (infectologist, immunologist, rheumatologist, paediatric cardiologist and, if necessary, cardiac surgeon). Attached are original images from my own experience (119).

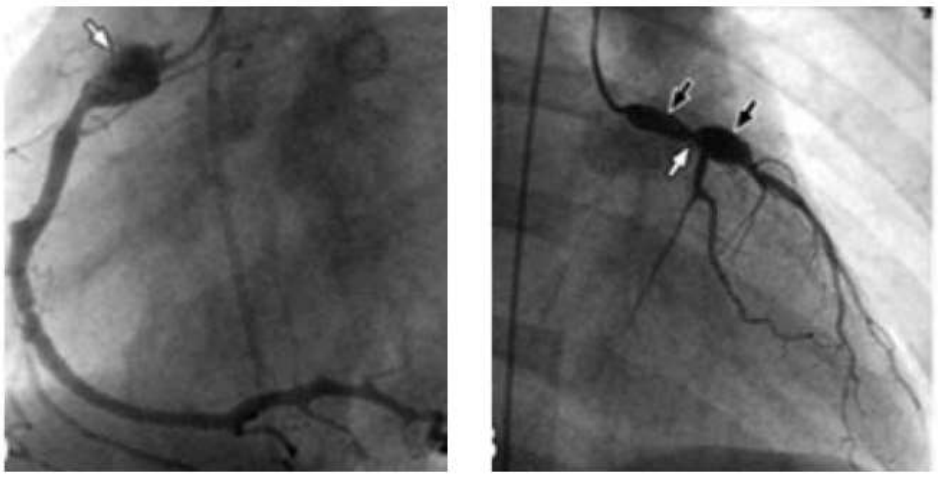

Fig 2. Coronary angiography in an eight-year-old child with Kawasaki disease. The right coronary artery has a giant aneurysm with a diameter greater than 8 mm, The left coronary artery in the same patient has a double aneurysmal enlargement which is not larger than 8 mm**.** Obstructive stenosis develops between the two aneurysmal dilatations.

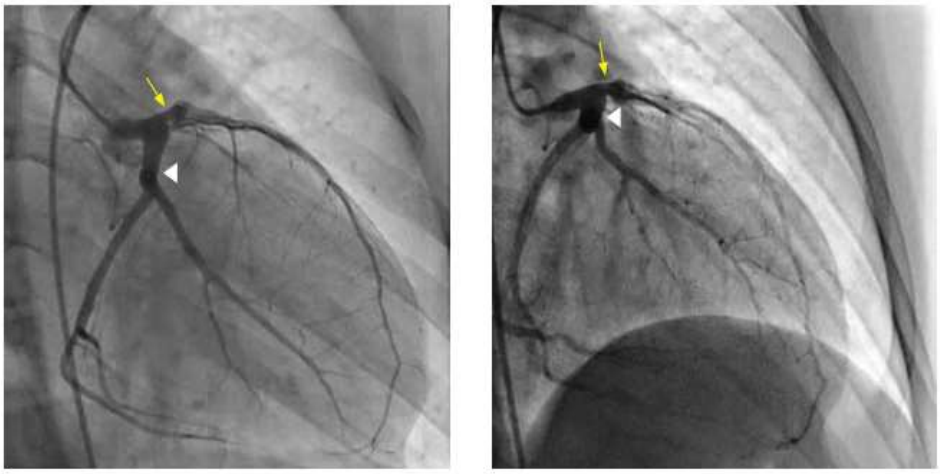

Fig 3. Coronaropathy three years after overcoming KD. In the left main, the trunk LCA (LM) - shows severe LAD stenosis proximal (arrow) and multiple stenosis on the long segment behind it. It is also displayed pathological dilatation of the CX (head arrow). Second projection; proximal stenosis of the LAD (arrow), proximal dilatation of the CX (head arrowhead), multiple stenosis of the LAD on the long segment, distant minor aneurysmatic capillary changes distally.

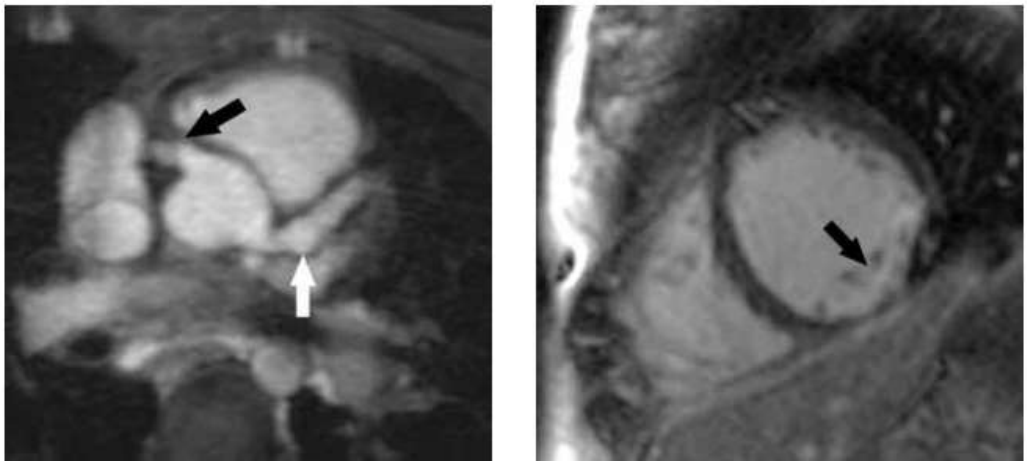

Fig 4: MR coronary angiography in patients with KD. Aneurysmal enlargement of the right (black arrow) and left coronary artery (white arrow). Dilated cardiomyopathy and myocardial infarction (arrow) in Kawasaki disease.

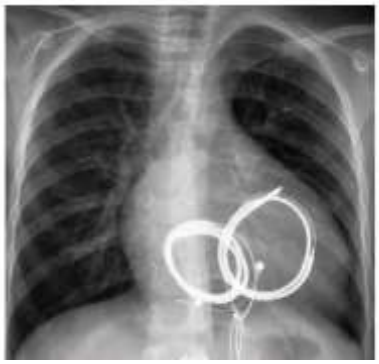

Fig 5. X - ray of ischemic cardiomyopathy after overcoming Kawasaki disease) with severe arrhythmias (due to of which the ICD is installed)

Conclusion. As cardiovascular sequelae are a major factor in morbidity and mortality cardiovascular imaging plays a vital role in the evaluation of all patients with KD. Although echocardiography remains the primary imaging technique in the evaluation of cardiovascular complications, especially in the acute phase, in selected patients cardiac CT and MR allow a non-invasive and reliable assessment of cardiovascular complications, as well as at follow-up, especially after childhood. Invasive coronary angiography should be reserved for patients with more complex coronary lesions or for therapeutic measures.

Among the diseases that are basically called vasculitis syndromes, antiphospholipid syndrome (leukocytoclastic vasculitis) and Kawasaki disease (systemic self-limiting vasculitis of unknown ethology) have significant changes in the cardiovascular system. Two other vasculitis entities with a large impact on the cardiovascular system should be included here: **nodular polyarteritis** (vasculitis of small blood vessels) and granulomatous ANCA-negative vasculitis of large blood vessels as well as **Takayashu's arteritis** (moya-moya disease or pulse-less syndrome). Other vasculitis diseases that have less impact on the cardiovascular system (especially in childhood) cannot be described in this review (120).

POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) as systemic necrotizing vasculitis was first described by Kussmaul and Maier in 1866. Although more than a century has passed since its first recognition. According to the literature data, it is most described as a "case report" in childhood. The heart disease is described at age 18-74 years (average age 41.2 years). Only 26% (9/34) of patients who registered serious heart disease had a positive history of childhood PAN. Coronary changes were so intense that as many as 35.3% (12/34) of patients experienced cardiac arrest and only one survived. 73.5% of patients (25/34) were admitted to hospital due to acute coronary syndromes, with chest pain and dyspnoea. The duration of cardiac manifestations from the beginning to the diagnosis of coronary heart disease ranged from a few minutes to 1 year. (121)

The first ANCA-positive PAN was described in the domestic literature in 1996 and published in the international press with proof of ANCA-positive antibodies (122) but a 26-year-old patient experienced a severe

heart attack due to extensive changes in coronary arteries (123) According to the EULAR / PRINTO / PRES guidelines, PAN (124) can be divided into four forms: 1) microscopic polyarteritis / polyangiitis manifested by necrotizing glomerulonephritis and pulmonary capillarity's and having positive antineutrophil cytoplasmic antibodies (PAN) directed to myeloperoxide (2), which is associated with HBsAg and affects the renal arteries, 3) cutaneous polyarteritis that is restricted to the skin and has negative ANCA antibodies and 4) systemic PAN that rarely has positive antineutrophil cytoplasmic antibodies (ANCA)), and is manifested by necrotizing arteritis of small and medium-sized arteries with organ involvement. Our patient certainly belongs to group 4. Therefore, all ANCA-positive patients should be under permanent control for possible type 4 PAN- in whom severe coronary heart disease is expected in adulthood.

Vasculitis involving the coronary arteries can lead to occlusion of a blood vessel and consequent acute myocardial infarction. Myocardial infarction is rare in general in the younger population and even rarer as a clinical presentation of nodular polyarteritis. However, patients in whom a clinical picture of PAN with positive ANCA-P antibodies (type 4) has been identified are potential adult candidates for severe coronary heart disease.

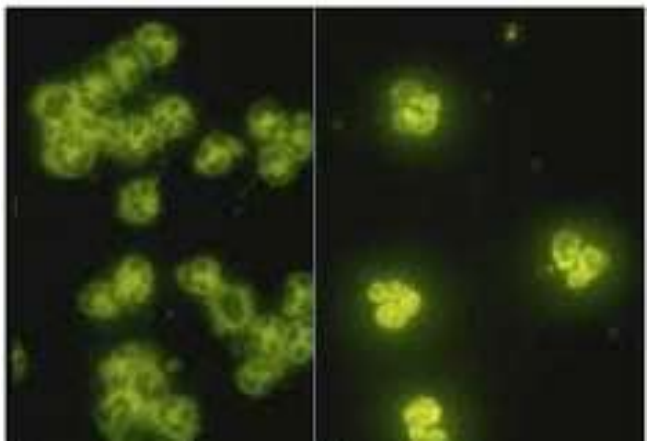

Fig 6. Antineutrophil cytoplasmic antibodies (ANCA-P) (122)

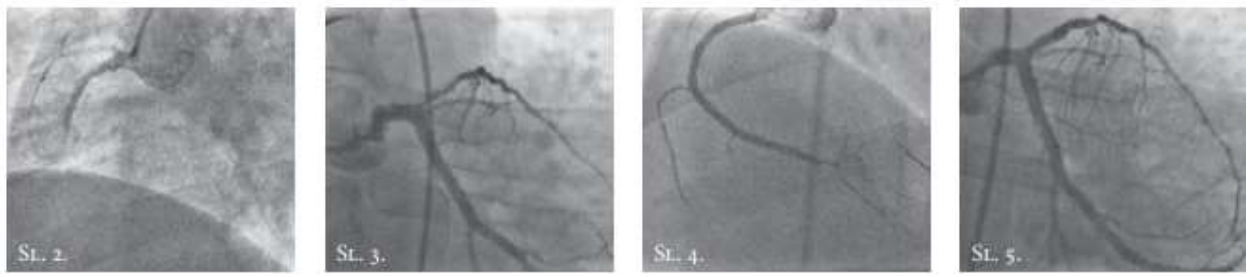

Fig 7. 95-99% ostial stenosis of the anterior descending branch of the left anterior descending coronary artery with stenotic extension of the proximal segment and chronic occlusion of the first diagonal branch of the left descending artery.

VASCULITIS GRANULOMATOSA

(Takayashu arteritis, moya-moya disease, *puls less syndrome)*

Vasculitis granulomatosa is a group of diseases (Wegener's granulomatosis, Churg-Strauss syndrome and Takayasu's arteritis), and among them the greatest significance for the collaboration of rheumatologists and cardiologists belongs to Takayasu's arteritis whose symptoms are directed precisely to the level of the central cardiovascular system. It is arteritis with segmental inflammation of the large arteries due to which their stenosis and / or aneurysm dilatation develops. In the EULAR / PRESS classifications there are criteria for angiographic abnormalities of the aorta and its branches, and there are angiographic classifications of Takayasu's arteritis from 1994 (125, 126).

Table 5. Proposed EULAR / PRES criteria for the classification of Takayasu arteritis in children

Angiographic abnormalities of the aorta or its branches (key criterion) with at least one of the following findings (124,125,126)
1. Reduction or disappearance of peripheral pulse on limbs
2. Arterial pressure difference more than 10 mmHg
3. Murmors over the aorta and its large branches
4. arterial hypertension (compared with normal values in children

The 1994 classification of Takayasu arteritis was also published (125), and according to that classification we followed our clinic in a large retrospective study on vasculitis from 2000-2012 (126).

Table 6. Angiographic classification of 1994 Takayasu arteritis

Tip	Blood vessel affected
I.	**Aortic arch branches**
IIa.	**Ascending aorta, aortic branch and its branches**
IIb.	**Ascending aorta, aortic arch and its trunks, descending aorta**
III.	**Thoracic descending aorta, abdominal aorta and/or renal arteries**
IV.	**Abdominal aorta and / or renal arteries**
V.	**Combination of types IIB and IV**

In our literature, an 11-year-old girl with changes matching the Takayasu arteritis type IIB classification; but by severe changes in the left coronary artery from sub-occlusion to complete occlusion. Coronary arteries are not mentioned in the available classifications. Extensive cardiac treatment and serious cardiac surgery in collaboration with rheumatologists and anti-inflammatory therapy of the broad spectrum (methylprednisolone pulse therapy, chronic steroid administration - decortin, basic therapy with methotrexate and biologics), undoubtedly argue that the separation of paediatric rheumatology and cardiology is impossible, in fact, that their the new connection is strengthened by recognizing new entities and a modern approach to hitherto incurable complications of rheumatic heart disease (127).

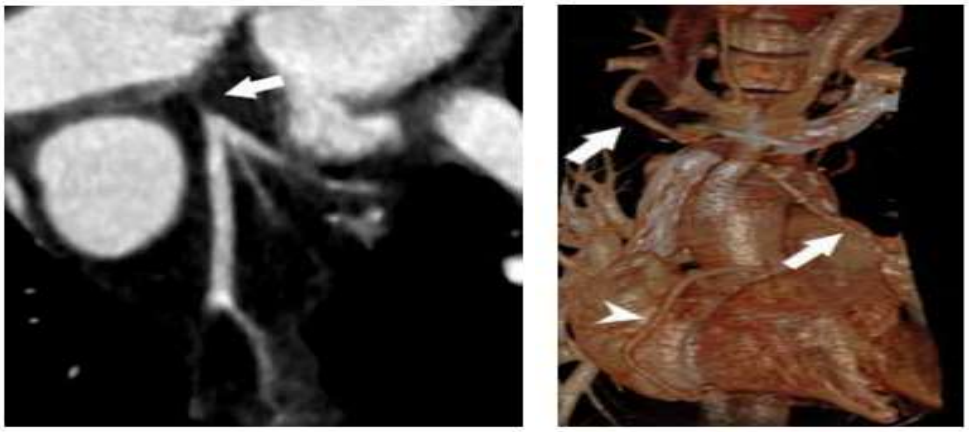

Fig 8. A. Coronary CT angiography in patients with Takayasu's arteritis type II. Occlusion of the main trunk of the left coronary artery (arrow, LM - left main). **B**. Coronary atresia (LM) bypass of the right internal mammary artery (RIMA). Properly passable right coronary artery (head arrow)

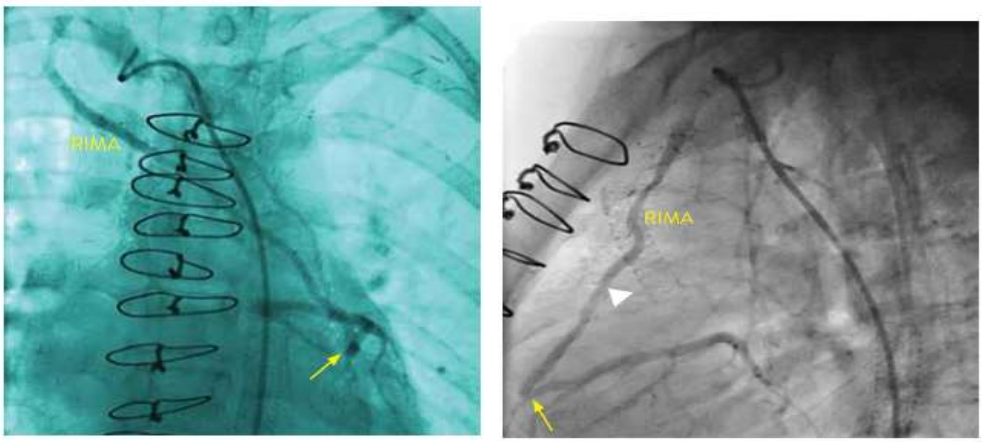

Fig 9 (posteroanterior and lateral projection). Angiographic presentation of the bypassing of the occluded main trunk of the left coronary artery (LM) using the right internal mammary artery (RIMA) to the circumflex artery (Cx) (arrow). Contrast was injected into the right subclavian artery. Regular revascularization of the entire left coronary basin by Cx retrograde is seen. A stent is also seen in the conduit from the ascending aorta to the left common carotid artery (head arrow) because sub-occlusion of the left common carotid artery.

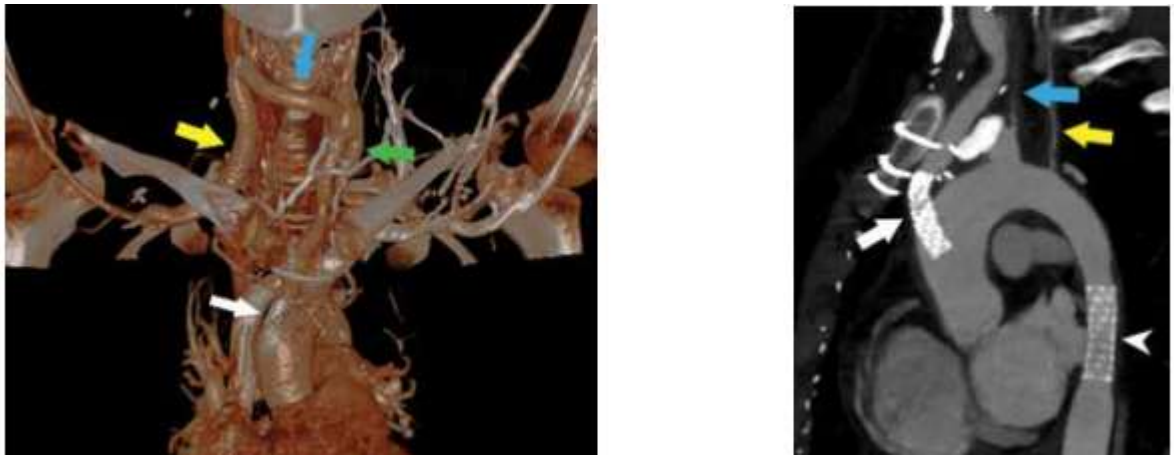

Fig 10. A. CT angiography in patients with Takayasu's arteritis type II. B; sub-occlusive stenosis ACCS. occlusion ASS, sub-occlusion ACD Condition after implantation of conductor between ascending aorta and left ACCS with stent placement at stenosis site (white arrow), by-pass between left ACCS and left axillary artery (green arrow), between ACCS and ACDx (blue arrow) and after implantation of a conductor between the right subclavian artery and the right ACC (yellow arrow). **B**. Multiplanar reconstruction of CT angiography in patients with Takayasu's arteritis type II. B with stent placed in conductor stenosis between ascending aorta and left ACCS (white arrow) and in descending aortic stenosis (arrowhead). Sub-occlusive stenosis of the left ACCs (blue arrow) and left subclavian artery (yellow arrow).

REFERENCES

[1]. Gross L. Th e cardiac lesions in Libman-Sacks disease with consideration of its relationship to acute diff use lupus erythematosus. Am J Pathol. 1940;16:375–407.

[2]. Libman E, Sacks B. A hitherto undescribed form of valvular and mural endocarditis. Arch Int Med. 1924;33:701–37.

[3]. Ansari A, Larson PH. Heart disease in systemic lupus erythematosus: diagnosis and management. Tex Heart Inst J. 1985; 12(1):9–21.

[4]. Malčić I, Senečić Irena, Dasović A, Radonić M. Prijeteća perikardijalna tamponada kao prvi simptom sistemnog eritemskog lupusa u dvoje djece. Reumatizam. 1995;42;9–22.

[5]. Cervera R, Font J, Pare C, Azqueta M, Perez-Villa F, LopezSoto A i sur. Cardiac disease in systemic lupus erythematosus: prospective study of 70 patients. Ann Rheum Dis 1992;51:156–9.

[6]. Tincani A, Rebaioli CB, Taglietti M, st al. Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. Rheumatology (Oxford). 2006; 45(Suppl 4):8–13

[7]. Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmun Rev 2006; 5: 331-7.

[8]. Mombouli J, Vanhouette PM. Endothelial dysfunction: from physiology to therapy. J Mol Cell Cardiol 1999;31:61-74.

[9]. Kharbanda R, Deanfield J. Functions of the healthy endothelium. Cor Art Dis 2001; 12: 485-491.

[10]. Abusamieh M, Ash J. Atherosclerosis and systemic lupus erythematosus. Cardiol Rev 2004;12:267-75

[11]. Agewall S. Is impaired flow-mediated dilation of the brachial artery a cardiovascular risk factor? Curr Vasc Pharmacol 2003; 1: 107-9.

[12]. Bacon PA. Endothelial cell dysfunction in systemic vasculitis: New developments and therapeutic prospects. Curr Opin Rheumatol 2005;17:49-55

[13]. Constans J, Dupuy R, Blann AD, et al. Anti-endothelial cell autoantibodies and soluble markers of endothelial cell dysfunction in systemic lupus erythematosus. J Rheumatol 2003;30:1963-6.

[14]. Mendall MA, Strachan DP, Butland BK, et al. C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. Eur Heart J 2000;21:1584-90.

[15]. Biasucci LM, Liuzzo G, Grillo RL, et al. Elevated levels of Creactive protein at discharge in patients with unstable angina predict recurrent instability. Circulation 1999;99:855-60.

[16]. Nicolo D, Monestier M. Antiphospholipid antibodies and atherosclerosis. Clin Immunol 2004;112:183-189.

[17]. Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation 2005;112:3337-47.

[18]. Zampieri S, Iaccarino L, Ghirardello A, et al. Systemic lupus erythematosus, atherosclerosis, and autoantibodies. Ann N Y Acad Sci 2005 Jun; 1051:351-61.

[19]. Xu Q, Kiechl S, Mayr M, et al. Association of serum antibodies to heat-shock protein 65 with carotid atherosclerosis. Lancet 1993; 341: 255-259.
[20]. George J, Harats D, Gilburd B, Afek A, et al. Immunolocalization of _2-glycoprotein I (apolipoprotein H) to human atherosclerotic plaques: potential implications for lesion progression. Circulation 1999;99:2227-2230
[21]. Hansson GK. Mechanisms of disease: inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-1695.
[22]. Bulkley BH, Roberts WC. The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy: a study of 36 necropsy patients. Am J Med 1975;58:243-264.
[23]. Urowitz MB, Bookman AAM, Koehler BE, et al. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976;60:221-225
[24]. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513-51.
[25]. Salmon J, Roman M. Accelerated atherosclerosis in systemic lupus erythematosus: implications for patient management. Curr Opin Rheumatol 2001;13:341-344.
[26]. Frostegard J. SLE, atherosclerosis and cardiovascular disease. J Intern Med 2005 June; 257(6):485-95
[27]. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513-9.
[28]. Gladman DD, Urowitz MB. Morbidity in systemic lupus erythematosus. J Rheumatol 198714:223-6.
[29]. Badui E, Garcia-Rubi D, Robles E, et al. Cardiovascular manifestations in systemic lupus erythematosus. Prospective study of 100 patients. Angiology 1985;36:431-41
[30]. Gazarian M, Feldman BM, Benson LN, at al. Assessment of myocardial perfusion and function in childhood systemic lupus erythematosus. J Pediatr 1998;132:109- 16
[31]. Manzi S, Selzer F, Sutton-Tyrrell K, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. Arthritis Rheum 1999;42:51-60.
[32]. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992; 93: 513-9.
[33]. Doria A, Shoenfeld Y, Wu R, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2003;62:1071-7.
[34]. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-7.
[35]. Kitagawa Y, Gotoh F, Koto A, Okayasu H. Stroke in systemic lupus erythematosus. Stroke 1990;21:1533-9.
[36]. Manger K, Kusus M, Forster C, et al. Factors associated with coronary artery calcification in young female patients with SLE. Ann Rheum Dis 2003;62:846-50.
[37]. Rahman P, Gladman DD, Urowitz MB. Premature coronary artery disease in systemic lupus erythematosus in the absence of corticosteroid use. J Rheumatol 2000;27:1323-5
[38]. Borchers AT, Keen CL, Shoenfeld Y, Gershwin ME. Surviving the butterfly and the wolf: mortality trends in systemic lupus erythematosus. Autoimmun Rev 2004;3:423-53
[39]. Xu Q, Dietrich H, Steiner HJ, et al. Induction of arteriosclerosis in normocholesterolemic rabbits by immunization with heat shock protein 65. Arterioscler Thromb 1992;12:789-799
[40]. Kifer N, Sestan M, Frkovic M, et al. 2019 ACR/EULAR classification criteria and therapy in predicting organ damage accrual in patients with childhood-onset systemic lupus erythematosus: A retrospective study over the last 29 years . Lupus 2022;0/0:1-9
[41]. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* (2006);4:295–306
[42]. Shoenfeld Y, Blank M, Cervera R, Font J, Raschi E, Meroni P. Infectious origin of the antiphospholipid syndrome*. *Ann Rheum Dis.* 2006 65:2–6
[43]. Barbhaiya M, Erkan D. Primary thrombosis prophylaxis in antiphospholipid antibody-positive patients: Where do we stand? *Curr Rheumatol Rep.* 2011:13:59–69
[44]. Kaplan SD, Chartash EK, Pizzarello RA, Furie RA. Cardiac manifestations of the antiphospholipid syndrome. Am Heart J. 1992 124:1331–38.
[45]. Cervera R, Tektonidou MG, Espinosa G, at al. Task force on catastrophic antiphospholipid syndrome (APS) and Non-criteria APS Manifestations (I): catastrophic APS, APS nephropathy and heart valve lesions. Lupus. 2011;20:165–73
[46]. Tenedios F, Erkan D, Lockshin MD. Cardiac manifestations in the antiphospholipid syndrome. Rheum Dis Clin North Am. 2006;32:491–507

[47]. Turiel M, Sarzi-Puttini P, Peretti R, et al. Five-year follow-up by transesophageal echocardiographic studies in primary antiphospholipid syndrome. Am J Cardiol. 2005 96:574–79.
[48]. Cervera R. Recent advances in antiphospholipid antibody-related valvulopathies. J Autoimmun. 2000;15:123–25.
[49]. Amital H, Langevitz P, Levy Y, et al. Valvular deposition of antiphospholipid antibodies in the antiphospholipid syndrome: a clue to the origin of the disease. Clin Exp Rheumatol. 1999;17:99–102..
[50]. Blank M, Krause I, Magrini L, et al. Overlapping humoral autoimmunity links rheumatic fever and the antiphospholipid syndrome. Rheumatology. 2006;45:833–41.
[51]. Jara LJ, Medina G, Vera-Lastra O, Amigo MC. Accelerated atherosclerosis, immune response and autoimmune rheumatic diseases. Autoimmun Rev. 2006;5:195–201.
[52]. Roman MJ, Shanker B, Davia A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. New Engl J Med. 2003;349:2399–406.
[53]. Andrade D, Bortolotto L, Bonfa E, Borba E. Primary antiphospholipid syndrome: absence of premature atherosclerosis in patients without traditional coronary artery disease risk factors. Lupus. 2015;25:472–8.
[54]. Vlachoyiannopoulos PG. Atherosclerosis in premenopausal women with antiphospholipid syndrome and systemic lupus erythematosus: a controlled study. Rheumatology. 2003;42:645–51.
[55]. . Kobayashi K, Kishi M, Atsumi T, et al. Circulating oxidized LDL forms complexes with β 2 -glycoprotein I. J Lipid Res. 2003;44:716–26.
[56]. Vaarala O, Aho K, Palosuo T, et al. Crossreaction between antibodies to oxidised low-density lipoprotein and to cardiolipin in systemic lupus erythematosus. Lancet. 1993;341:923– 25.
[57]. Delgado Alves J, Kumar S, Isenberg DA. Cross-reactivity between anti-cardiolipin, anti-high-density lipoprotein and anti-apolipoprotein A-I IgG antibodies in patients with systemic lupus erythematosus and primary antiphospholipid syndrome. Rheumatology.2003;42:893– 99.
[58]. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002;46:1019–27
[59]. Osula S, Bell GM, Hornung RS. Acute myocardial infarction in young adults, causes and management. Postgrad Med J.2002;78:27–30
[60]. Correia AF, Oliveira DC, Sanctos M. Coronary artery thromboses, stent thrombosis and antiphospholipid antibody syndrome: case report. Cardiol Res. 2018;9:129–32.
[61]. Cervera R, Serrano R, Pons-Estel GJ, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2015;74:1011–8.
[62]. Gualtierotti R, Biggioggero M, Meroni PL. Cutting-edge issues in coronary disease and the primary antiphospholipid syndrome. Clin Rev Allergy Immunol. 2013; 44:51–6.
[63]. Nazir S, Tachamo N, Lohani S, Hingorani R, Poudel DR, Donato A. Acute myocardial infarction and antiphospholipid antibody syndrome: a systematic review. Coron Artery Dis. 2017;28:332–5.
[64]. Urbanus RT, Siegerink B, Roest M, et al. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. Lancet Neurol. 2009;8:998–1005.
[65]. Lauwerys BR, Lambert M, Vanoverschelde JL, Cosyns JP, Houssiau FA. Myocardial microangiopathy associated with antiphospholipid antibodies. Lupus. 2001;10:123–5.
[66]. Azeem T, Vassallo M, Samani NJ. Images in cardiology. endomyocardial fibrosis associated with antiphospholipid syndrome. Heart. 2000;84:156-73.
[67]. Laskin CA, Clark CA, Spitzer KA. Antiphospholipid syndrome in systemic lupus erythematosus: is the whole greater than the sum of its parts? Rheum Dis Clin North Am. 2005;31:255–72.
[68]. Kampolis C, Tektonidou M, Moyssakis I, et al. Evolution of cardiac dysfunction in patients with antiphospholipid antibodies and/or antiphospholipid syndrome: A 10-year follow-up study. Semin Arthritis Rheum. 2014;43:558–65.
[69]. Tektonidou MG, Ioannidis JP, Moyssakis I, et al. Right ventricular diastolic dysfunction in patients with anticardiolipin antibodies and antiphospholipid syndrome. Ann Rheum Dis. 2001;60:43–8.
[70]. Roldan CA. Valvular and coronary heart disease in systemic inflammatory diseases: systemic disorders in heart disease. Heart. 2008;94:1089–101.
[71]. Vaccaro F, Caccavo D, Roumpedaki E, et al. Dilated cardiomyopathy due to thrombotic microangiopathy as the only manifestation of antiphospholipid syndrome: a case report. Int J Immunopathol Pharmacol. 2008;21:237–41.
[72]. Chaouat A, Weitzenblum E, Higenbottam T. The role of thrombosis in severe pulmonary hypertension. ERJ. 1996;9:356–63.

[73]. Atsumi T, Khamashta MA, Haworth RS, et al. Arterial disease and thrombosis in the antiphospholipid syndrome: a pathogenic role for endothelin 1. Arthritis Rheum. 1998;41:800–7
[74]. Krause I, Lev S, Fraser A, Blank M, et al, Close association between valvular heart disease and central nervous system manifestations in antiphospholipid syndrome. Ann Rheum Dis. 2005;7:P12.
[75]. Martinuzzo ME, Pombo G, Forastiero RR, Cerrato GS, Colorio CC, Carreras LO. Lupus anticoagulant, high levels of anticardiolipin, and anti-beta2- glycoprotein I antibodies are associated with chronic thromboembolic pulmonary hypertension. J Rheumatol. 1998;25:1313–9
[76]. Abanador-Kamper N, Wolfertz J, Kamper L, et al. Disseminated intracardiac thrombosis: a rare manifestation of antiphospholipid syndrome. Eur Heart J Cardiovasc Imag. 2012;13:537.
[77]. Onea R, Germain P, Zimmermann A. Coronary microvasculopathy and intracardiac thrombosis in antiphospholipid syndrome. Arch Cardiovasc Dis. 2012;105:461–2.
[78]. Brucato A, Jonzon A, Friedman D, et. Al. Proposal for a new defi nition of congenital complete block. Lupus. 2003;12:427–35.
[79]. Reichlin M, Brucato A, Frank MB, et al. Maternal connective tissue disease and congenital heart block (letter). N Engl J Med. 1985;312:1328–9
[80]. Alspaugh MA, Maddison P. Resolution of the identity of certain antigen-antibody systems in systemic lupus erythematosus and Sjögren's syndrome: an interlaboratory collaboration. Arthritis Rheum. 1979;22:796–8.
[81]. Dörner T, Chaoui R, Feist E, et al. Signifi cantly increased maternal and foetal IgG autoantibody levels to 52 kD Ro (SS-A) and La (SS-B) in complete congenital heart block. J Autoimmun. 1995;8:675–84.
[82]. Schmidt KG, Ulmer HE, Silverman NH, et al. Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. J Am Coll Cardiol. 1991;17:1360–6.
[83]. Miranda ME, Tseng CE, Rashbaum W, et al. Accessibility of SSA/Ro and SSB/La antigens to maternal autoantibodies in apoptotic human foetal cardiac myocytes. J Immunol. 1998;161:5061–9.
[84]. Tincani A, Rebaioli CB, Taglietti M, Shoenfeld Y. Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. Rheumatology 2006;45:iv8–iv13.
[85]. Malčić I, Kniewald H, Benjak V, Dorner S. Kongenitalni atrioventrikularni blok – neonatalni lupusni sindrom. Congenital Heart AV-Block – Neonatal lupus syndrome. Pediatr Croat. 2004;48;121–5.
[86]. Buyon JP, Kim MY, Copel JA, Friedman DM. Anti-Ro/SSA antibodies and congenital heart block: necessary but not suffi - cient. Arthritis Rheum. 2001;44(8):1723–7.
[87]. Tseng CE, Buyon JP. Neonatal lupus syndromes. Rheum Dis Clin North Am. 1997;23:31
[88]. Brucato A, Franceschini F, Buyon JP. Neonatal lupus: long term outcomes of mothers and children and recurrence rate. Clin Exp Rheumatol. 1997;15:467–73.
[89]. Malčić I, Škrablin-Kučić S. Fetal and neonatal cardiology (cro-Fetalna i neonatalna kardiologija, Manualia universitatis studiorum zagrebiensis: Medicinska naklada; Zagreb, 2011
[90]. Follansbee WP. Th e cardiovascular manifestations of systemic sclerosis (scleroderma). Curr Probl Cardiol. 1986;11:241–98
[91]. Follansbee WP, Miller TR, Curtiss EI et al. A controlled clinicopathologic study of myocardial fi brosis in systemic sclerosis (scleroderma). J Rheumatol. 1990;17:656.
[92]. Deswal A, Follansbee WP. Cardiac involvement in scleroderma. Rheum Dis Clin North Am. 1996;22:841–60.
[93]. Bissel L-A, Yusof Y, Buch M. Primary myocardial comprehensive review of the literature to inform the UK Systemic Sclerosis Study Group cardiac working group. Rheumatology 2017;65:882-895.
[94]. Medsger TA Jr, Bombardieri S, Czirjak L et al. Assessment of disease severity and prognosis. Clin Exp Rheumatol 2003;21:S426.
[95]. Geirsson AJ, Wollheim FA, Akesson A. Disease severity of 100 patients with systemic sclerosis over a period of 14 years: using a modified Medsger scale. Ann Rheum Dis 2001;60:111722.26
[96]. Caramaschi P, Canestrini S, Martinelli N et al. Scleroderma patients nailfold videocapillaroscopic patterns are associated with disease subset and disease severity. Rheumatology 2007;46:15669.26
[97]. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;43:24374426
[98]. Jiang S-J, Chen S-L, Su LD. Systemic scleroderma: a clinical and immunological study. Chin Med J 1986;99:885-92.
[99]. Akesson A, Wollheim FA. Organ manifestations in 100 patients with progressive systemic sclerosis: a comparison between the CREST syndrome and diffuse scleroderma. Br J Rheumatol 1989;28:281-5
[100]. Arias-Nunez MC, Llorca J, Vazquez-Rodriguez TR et al. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. Medicine 2008;87:272-80.
[101]. 1 Schade L, Paiva ES, Muller CS. Skeletal and heart muscle involvement in SSc. Rheumatology 2012;51:61

[102]. Eloranta M-L, Franck-Larsson K, Lovgren T et al. Type I interferon system activation and association with disease manifestations in systemic sclerosis. Ann Rheum Dis 2010;69:1396-402.
[103]. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet 1999;353:89-92.
[104]. Laing TJ, Gillespie BW, Toth MB et al. Racial differences in scleroderma among women in Michigan. Arthritis Rheum 1997;40:7344227
[105]. Low AHL, Johnson SR, Lee P. Ethnic influence on disease manifestations and autoantibodies in Chinese-descent patients with systemic sclerosis. J Rheumatol 2009;36:787-93.
[106]. 27 Schmajuk G, Bush TM, Burkham J,et al. Characterizing systemic sclerosis in northern California: focus on Asian and Hispanic patients. Clin Exp Rheumatol 2009;27(3 Suppl 54):S225
[107]. Duarte R, Cisneros S, Fernandez G et al. Kawasaki disease: a review with emphasis on cardivascular complications. Insights Imaging 2010;1:223-231.
[108]. . Newburger JW, Takahashi M, Gerber MA, et al (2004) Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 110:2747– 2771.
[109]. Burns JC, Kushner HI, Bastian JF, et al. Kawasaki disease: a brief history. Pediatrics 2000;106:E27
[110]. Burns JC The riddle of Kawasaki disease. N Engl J Med 2007;356:659–661
[111]. Suzuki A, Kamiya T, Yasuo O, Kuroe K Extended long term follow-up study of coronary arterial lesions in Kawasaki disease. J Am Coll Cardiol 1991;17:33A
[112]. Petrunić M, Drinković N, Stern-Padovan R, et al. (2009) Thoracoabdominal and coronary arterial aneurysms in a young man with a history of Kawasaki disease. J Vasc Surg 2009;50:1173–1176.
[113]. Khositseth A, Siripornpitak S, Pornkulr R, Wanitkun S (2008) Giant coronary aneurysm caused by Kawasaki disease: follow-up with echocardiography and multidetector CT angiography. Br J Radiol 2008;81:106–109
[114]. Gidding SSLate onset valvular dysfunction in Kawasaki disease. Prog Clin Biol Res 1987;250:305–309
[115]. Burns JC The riddle of Kawasaki disease. N Engl J Med 2007;356:659–661
[116]. Kato H, Sugimura T, Akagi T, et al., Long-term consequences of Kawasaki disease. A 10- to 21- year follow up study of 594 patients. Circulation 1996; 94:1379–1385
[117]. Rowley AH, Shulman ST (1998) Kawasaki syndrome. Clin Microbiol Rev 11:405–414
[118]. . Kennedy JW, Baxley WA, Bunnel IL, et al Mortality related to cardiac catheterization and angiography. Catheter Cardiovasc Diagn 1982;8:323–340
[119]. Malčić I: Kawasaki disease (p 241-243, p 342) Pediatric cardiology in the image from foetal to adulthood , University textbooks and manualias Universistatis Zzagrebiensis, Medicinska naklada, Zagreb, 2019.
[120]. Jelušić M, Malčić I et al. Pedijatrijska reumatologija (Pediatri rheumatology), Sistemski veskulitisi, pp 245-275, textbook (on croatian language), Medicinska naklada, Zagreb 2014.
[121]. Huang H, Gong Y, Li Guo and Zhang Z. Insidious coronary artery disease in a young patient with polyarteritis nodosa: a case report and literature revie. BMC Cardiovasc Disord 2021; 21:115
[122]. Malčić I, Dasović Buljević A, Marasović D, et al. Various clinical presentation of polyartheritis nodosa (PN): Revue du Rheumatisme. Suppl 1997; 10:224S.
[123]. Viktorija Ana Buljević VA, Trbušić M , Diana Delić-Brkljačić D , Malčić I. Myocardial infarction as a consequence of childhood polyarteritis nodosa- case report.Reumatizam 2016;63(2):15–20
[124]. Ozen S, Pistorio A, Iusan SM. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classifi cation criteria. Ann Rheum Dis. 2010;69:798–806
[125]. Jennette JC, Falk RJ, Andrassy K. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37:187–92.
[126]. Jelušić M, Kostić L, Frković M, Davidović M, Malčić I. Vaskulitisi u dječjoj dobi: retrospektivna studija u razdoblju od 2002. do 2012. godine u Klinici za pedijatriju Kliničkog bolničkog centra Zagreb. Reumatizam. 2015;62:6–10
[127]. Malčić I., Pasini AM, Hrabak Paar M, Mueller H, Mair R, Perkov D, Marić K, Jelušić M Girl with Takayasu arteritis – progressive cours of the disease and multiple surgical interventions. Acta Med Croatica, 74 (2020) 169-173.

Correspondence address: Prof. Dr. Sci. Ivan Malčić, MD, PhD
Clinical Hospital Centre Zagreb and Medical Faculty Zagreb, Clinic for Pediatrics, Department of Pediatric Cardiology, Reference Centre for Pediatric Cardiology of the Republic of Croatia,