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Μεταπτυχιακή Διπλωματική Εργασία

"THE ROLE OF ULTRASOUND IN SYSTEMIC PRIMARY VASCULITIS: A REVIEW OF LITERATURE"

υπό

ΑΝΝΑ ΣΙΜΗΧΑΝΙΔΟΥ

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Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
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Περίληψη

Εισαγωγή: Οι συστηματικές αγγειίτιδες αποτελούν ετερογενή ομάδα νοσημάτων, η οποία χαρακτηρίζεται από μεγάλη ποικιλία αιτιολογικών, κλινικών, βιοχημικών, επιδημιολογικών και απεικονιστικών ευρημάτων. Ο στόχος της παρούσας ΜΔΕ είναι να διερευνήσει το ρόλο του υπερήχου στη διάγνωση, πρόγνωση και παρακολούθηση, καθώς και να συγκρίνει τη διαγνωστική ακρίβεια του υπερήχου με αυτή των άλλων απεικονιστικών μεθόδων.

Μεθοδολογία: Οι βάσεις δεδομένων MEDLINE και COCHRANE χρησιμοποιήθηκαν για την αναζήτηση των όρων "vasculitis" και "ultrasound" μετά την εφαρμογή φίλτρων για το χρόνο, το είδος και τις γλώσσες. Το τελικό σύνολο άρθρων τα οποία εισήχθησαν στην εφαρμογή Zotero Research Assistant (version 5.0.96.3) ήταν 1095.

Αποτελέσματα: Η διαγνωστική ακρίβεια του υπερήχου, ειδικά με τη χρήση Color και Pulsed Wave Doppler, έχει διερευνηθεί εκτενέστερα στις αγγειίτιδες μεγάλων αγγείων. Το σημείο της «άλω» εμφανίζει 68 – 77% ευαισθησία και 81 – 96% ειδικότητα για τη διάγνωση της γιγαντοκυτταρικής αρτηρίτιδας, οι οποίες ενισχύονται περαιτέρω όταν λαμβάνονται υπόψη το σημείο «συμπίεσης» και μεταβολές του αγγειακού αυλού. Η υψηλή διαγνωστική ακρίβεια του υπερήχου μείωσε την ανάγκη για βιοψία της κροταφικής αρτηρίας. Ο υπέρηχος εμφανίζει παρόμοια ευαισθησία και ειδικότητα (81% και σχεδόν 100%) στη διάγνωση της αρτηρίτιδας Takayasu συγκριτικά με κλινικά κριτήρια. Επιπροσθέτως, ποικίλες εφαρμογές του υπερηχογραφήματος και του υπερηχοκαρδιογραφήματος είναι ιδιαίτερης σημασίας για την έγκαιρη διάγνωση και την παρακολούθηση της νόσου Kawasaki, ιδίως σε παιδιατρικά περιστατικά, χάριν στην απουσία έκθεσης σε ακτινοβολία. Τέλος, ο υπέρηχος μπορεί να αναδείξει πάχυνση του τοιχώματος των κοινών μηριαίων φλεβών (> 05mm) σε περιπτώσεις νόσου Behcet's ανεξαρτήτως αγγειακής συμμετοχής, δείκτης που θα μπορούσε να χρησιμοποιηθεί διαγνωστικά και προγνωστικά. Ο ρόλος του υπερήχου στην διερεύνηση της ενδοθηλιακής δυσλειτουργίας στο οξύ και χρόνιο στάδιο όλων των τύπων συστηματικής αγγειίτιδες παραμένει αδιαμφισβήτητος.

Συζήτηση – Κατακλείδα: Η εφαρμογή των εδραιωμένων και καινούριων τεχνικών υπερηχογραφήματος μπορεί να βελτιστοποιήσει τη διάγνωση και την εκτίμηση της ενεργότητας της νόσου. Ωστόσο, περαιτέρω έρευνα είναι απαραίτητη.

Λέξεις – κλειδιά: αγγειίτιδα, υπερηχοκαρδιογράφημα, έγχρωμο Doppler υπερηχογράφημα, αρτηριίτιδα

Abstract

Introduction: Systemic vasculitides consist a heterogenous group of diseases, characterized by great variability of etiologic, clinical, biochemical, epidemiological and imaging findings. The goal of this thesis is to explore the role of ultrasound in diagnosis, prognosis and follow – up, and furthermore compare its accuracy with that of other imaging modalities.

Methods: We searched the MEDLINE and COCHRANE databases using the terms "vasculitis" and "ultrasound" after applying temporal, species and language filters. The final count of articles imported in the Zotero Research Assistant (version 5.0.96.3) was 1095.

Results: The diagnostic accuracy of ultrasound (US), especially with the use of Color and Pulsed Waved Doppler, is best established for large vessel vasculitis. The "halo" sign has 68 – 77% sensitivity and 81 – 96% specificity in the diagnosis of giant cell arteritis, that are further enhanced when "compression" sign and luminal changes are considered. The high diagnostic accuracy of US has reduced the need for temporal artery biopsies. US yields similar sensitivity and specificity (81% and almost 100%) for the diagnosis of Takayasu arteritis in comparison to clinical criteria. Additionally, various applications of US and echocardiography, such as Speckle Tracking and Tissue Doppler Imaging, are of great importance for the timely diagnosis and follow – up of Kawasaki disease, particularly for pediatric cases, because they lack radiation exposure. Finally, US may reveal increased vein wall thickness (VWT >0.5mm) in common femoral veins in patients with Behcet's disease, independently of vascular involvement, implying that VWT may serve as diagnostic and prognostic marker. The role of US in thoroughly investigating endothelial dysfunction in acute and chronic stages of all types of systemic vasculitis is indisputable.

Discussion – Conclusions: The implementation of well – established and modern techniques of ultrasound can optimize diagnosis and assessment of disease activity, although further research is required.

Keywords: vasculitis, echocardiography, color Doppler ultrasound, arteritis

1. Introduction

Vasculitis is defined as inflammation of the blood vessel wall, either as the main feature or secondary to a disease with an unrelated histopathology. The wide variability among different types of vasculitis concerns their etiology, clinical and biochemical attributes, demographic features, genetic and pathogenetic mechanisms. The 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012) divides vasculitides into infectious and non – infectious, based on whether the vessel wall is affected by pathogens, although infection may in some cases advocate inflammation. Non – infectious vasculitides are further classified mainly according to the prevailing vessel type affected and secondarily to other characteristics, such as primary or secondary involvement, single organ involvement or assumed etiology (table 1). It is important to underline that the categorization is not obsolete and that any type of vasculitis can actually affect all vessel sizes although with different frequency.(1) The diagnosis of vasculitis requires a multimodality imaging approach combined with clinical and biochemical properties. Every modality has advantages and disadvantages that must be taken into consideration during the work – up and follow – up of patients with vasculitis (table 2). The goal of the present MSc Thesis is to investigate the role of ultrasound in the diagnosis and follow – up of vasculitis by elucidating its many techniques and applications and comparing its accuracy to that of the rest imaging modalities.

Table 1: Names of vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides(1)*****
Large vessel vasculitis (LVV)
Takayasu arteritis (TAK)
Giant cell arteritis (GCA)
Medium vessel vasculitis (MVV)
Polyarteritis nodosa (PAN)
Kawasaki disease (KD)
Small vessel vasculitis (SVV)
Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
Microscopic polyangiitis (MPA)

Granulomatosis with polyangiitis (Wegener's) (GPA)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
Immune complex SVV
Anti–glomerular basement membrane (anti-GBM) disease
Cryoglobulinemic vasculitis (CV)
IgA vasculitis (Henoch – Schönlein) (IgAV)
Hypocomplementemic urticarial vasculitis (HUV) (anti – C1q vasculitis)
Variable vessel vasculitis (VVV)
Behcet's disease (BD)
Cogan's syndrome (CS)
Single – organ vasculitis (SOV)
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Others
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis C virus – associated cryoglobulinemic vasculitis
Hepatitis B virus – associated vasculitis
Syphilis – associated aortitis

Drug – associated immune complex vasculitis
Drug – associated ANCA-associated vasculitis
Cancer – associated vasculitis
Others
*From Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis & Rheumatism. 2013;65(1):1–11.

Table 2: Comparison among modalities for the diagnosis of vasculitis(2,3)		
Modality	**Advantages**	**Disadvantages**
CT/CTA	Widely available Fast image acquisition Wide vascular assessment Acquired images for "second look" analysis Minimally invasive	Radiation exposure Contraindicated if allergy to iodine or impaired renal function Low resolution for small vessels
MRI/MRA	Wide vascular assessment Acquired images for "second look" analysis No radiation exposure Minimally invasive	Expensive Limited availability Contraindicated if impaired renal function Claustrophobia Low resolution for medium/small vessels Not compatible with some metal devices Long acquisition time for wide vascular assessment
PET/PET-CT	Whole – body assessment Acquired images for "second look" analysis Minimally invasive	Expensive Limited availability Radiation exposure No standards for positivity No resolution for medium/small vessels
US	Inexpensive Wide availability No radiation exposure No nephrotoxic contrast High resolution for medium and small arteries	Long assessment time for wide vascular assessment Operator – dependent Restricted by poor acoustic window

	Dynamic examination	
DSA	Wide vascular evaluation High resolution for small vessels Therapeutic intervention	Expensive Limited availability Radiation exposure Contraindicated if allergy to iodine or if impaired renal function Invasive Operator – dependent

2. Methods

We searched the MEDLINE and COCHRANE databases using the terms “vasculitis” and “ultrasound”. A temporal filter including articles published after 2010 was applied, along with filters on species (human) and language (English, German, Modern Greek). The final count of articles included 1308 results. We excluded articles by title and abstract and we imported 998 objects in the Zotero Research Assistant (version 5.0.96.3). After deduplication, we screened the retrieved articles by text, added literature included in them and expanded our database to 1097 objects. Our last search took place at 5 December 2021. Secondary vasculitis was not included in this MSc Thesis. Single organ primary vasculitis was elaborated on, if it consisted part of the systemic primary vasculitis described each time.

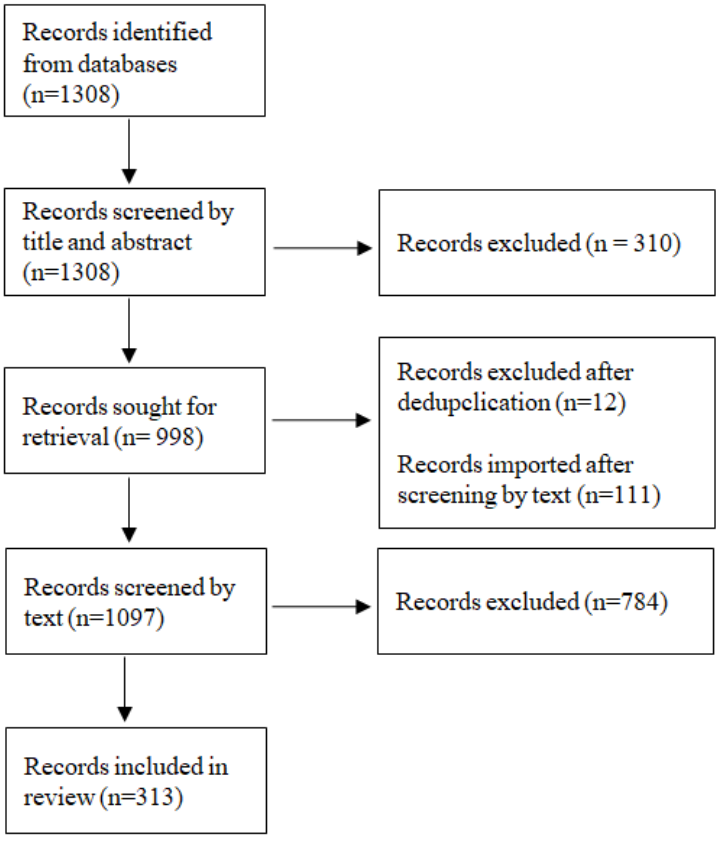


Chart 1: Flow chart of records

3. Results

3.1. Large Vessel Vasculitis (LVV)

3.1.1. Giant Cell Arteritis (GCA)

The importance of ultrasound is stated in the 2018 EULAR recommendations for imaging in LVV.(4) The first recommendation with level of evidence 1 (LE 1) is that suspected GCA cases should undergo US to confirm diagnosis, preferably before or soon after GC therapy initiation, but no longer than the first week.(4) This recommendation is imposed by the fact that high – dose GC quickly inhibit macrophage activation, reduce edema and consequently vessel wall inflammation. As a result, within the first two to four weeks imaging findings may be vague or absent.(3,5) However, treatment should not be delayed, if US in unavailable or inconclusive, in order to prevent serious complications and mainly blindness.(4)

The most sensitive sonographic finding is the “halo” sign, which according to the OMERACT consensus corresponds to a homogenous, hypoechoic and usually concentric thickening of the artery wall, well delineated towards the lumen (picture 1A).(4,6) The “halo” sign probably corresponds to the typical histopathological inflammatory infiltration of the arterial wall, while when vasa vasorum type of lesions are histologically present, only rarely is a typical “halo” found in US. This discrepancy could explain false negative cases in US.(7) However a recent study correlated intimal hyperplasia and not inflammatory infiltration with thicker “halo”.(8) Several observational studies, systematic reviews and meta – analyses have reported on the diagnostic accuracy of US in comparison to clinical diagnosis and/or TAB (table 3).(9–12) According to recent meta – analyses, the “halo” sign has a 81 - 96% specificity, which may reach 100%, if found bilaterally.(10,11,13,14) It has a 63 - 77% sensitivity and therefore should be interpreted in the appropriate setting, since it may be also present in other vasculitides, infections, atherosclerosis and other situations.(4,10,13–15) US typically has lower diagnostic accuracy in large vessel GCA (LV – GCA).(16) The “compression” sign has also been reported to enhance diagnosis, especially in combination with the “halo” sign, with a sensitivity of 79% and specificity of 100% when both signs are present,(17) and a remarkable inter – and intra – observer agreement.(18,19) This sign is considered positive, when the arterial wall remains visible despite compression implemented by the US probe (picture 1B).(6) Color and pulsed wave Doppler US (CDUS and PWD,

respectively) can evaluate stenosis and occlusion.(18) However, most studies support that stenosis and occlusion – when complementary to "halo" sign – do not significantly enhance diagnostic accuracy in comparison to clinical diagnosis and TAB. (10,10,18,20,21) The opposite conclusion was also reached,(13,22) however it is believed that high – resolution (≥ 15MHz) transducers allow recognition of even minimal wall thickening and therefore stenosis does not need to be a surrogate for diagnosis.(23) According to the TABUL study inexperienced sonographers may be even confused by the presence of stenosis.(24) As a result, the OMERACT consensus stated that only "halo" and "compression" signs should be consider principal for the US diagnosis of C – GCA and LV – GCA.(6)

Table 3: Meta – analyses on the diagnostic accuracy of ultrasound in LVV

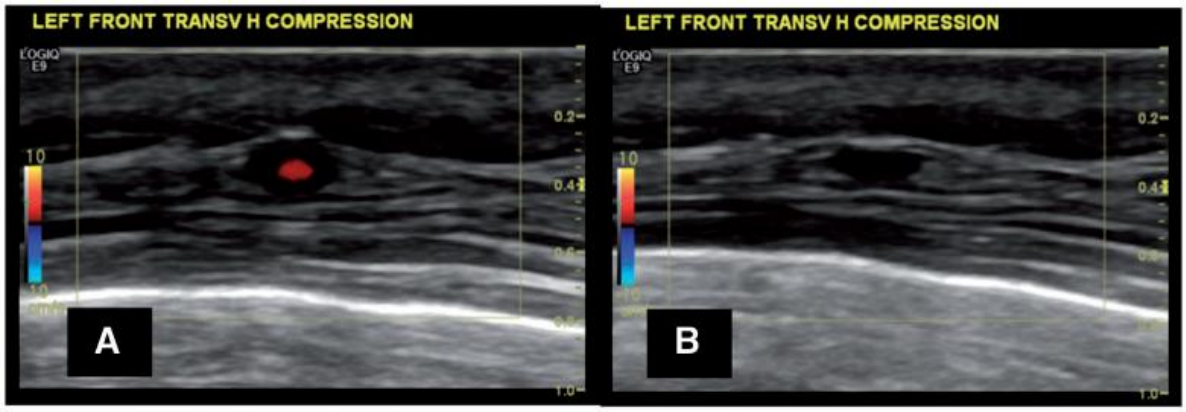
Author	**Year**	**Reference method**	**Number of studies**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Giant Cell Arteritis					
Arida et al.(11)	**2010**		**8**		
Unilateral "halo" sign		ACR criteria	8	68 (61 - 74)	91 (88 – 94)
Bilateral "halo" sign		ACR criteria	4	43 (not referred)	100 (not referred)
Ball et al.(12)	**2010**		**17**		
"Halo" sign		TAB	9	75 (67, 82)	83 (78, 88)
"Halo" sign, stenosis or occlusion		TAB	9	83 (77, 89)	82 (77, 87)
"Halo" sign		ACR criteria	6	69 (60, 77)	89 (84, 92)
"Halo" sign, stenosis or occlusion		ACR criteria	7	78 (72, 84)	88 (84, 91)
"Halo" sign, stenosis or		TAB and/or ACR criteria (no steroids	5	75 (65, 84)	88 (82, 93)

occlusion		before imaging)			
“Halo” sign, stenosis or occlusion		TAB and/or ACR criteria (steroids before imaging)	7	72 (65, 79)	87 (82, 90)
Duftner et al.(10)	**2018**		**17**		
“Halo” sign		Clinical diagnosis	8	77 (62, 87)	96 (85, 99)
“Halo” sign, stenosis or occlusion		Clinical diagnosis	3	78 (57, 90)	89 (78, 95)
“Halo” sign		TAB	7	70 (56, 81)	84 (73, 91)
“Halo” sign or stenosis		TAB	2	77 (23, 97)	91 (75, 97)
“Halo” sign, stenosis or occlusion		TAB	5	78 (48, 93)	91 (70, 98)
Rinagel et al.(13)	**2019**		**25**		
“Halo” sign		TAB	20	68 (57, 78)	81 (75, 86)
“Halo” sign, stenosis or occlusion		TAB	11	78 (64, 87)	79 (73, 85)
Sebastian et al.(14)	**2021**		**23**		
“Halo” sign		Clinical diagnosis ± TAB	18	67 (51, 80)	95 (89, 98)

"Halo" sign		TAB	15	63 (50, 75)	90 (81, 95)
"Halo" sign ± stenosis ± occlusion		Clinical diagnosis or TAB	4	52 (18, 84)	81 (64, 91)
"Halo" sign ± stenosis		Clinical diagnosis or TAB	4	43 (12, 80)	85 (66, 94)
Takayasu Arteritis					
Barra et al.(25)	**2018**				
Diagnosis (increased IMT)		Clinical diagnosis	3	81 (69, 89)	100 (not referred)

A few studies have aimed to establish cut – off values for the intima – media thickness (IMT), and by extension the "halo" thickness.(26–28) In a prospective, blinded case – control study, IMT of normal subjects did not exceed 0.6mm in any of the arteries evaluated and cut – off values for GCA were established as follows: 0.42mm in TAs, 0.34mm and 0.29mm in frontal and parietal branches, 0.37mm in facial and 1.0mm in axillary arteries. Sensitivity and specificity was 100% for TAs, their frontal branches and axillary arteries, 97.2 and 98.7% for parietal branches, 87.5% and 98.8% for facial arteries.(28) Most recently, Ješe et al. reported similar cut – off values: 0.4mm for temporal, facial and occipital, 0.7mm for vertebral and 1mm for common carotid, subclavian and axillary arteries, with sensitivity and specificity ranging from 96% to 100% for most of the arteries.(29) De Miguel et al. showed that atherosclerosis also increases IMT in TAs, especially when common carotid artery – IMT ≥ 0.9mm, and proposed a cut – off value ≥ 0.34mm for TAs when at least two branches are affected, thus increasing specificity.(30) In a similar manner, Czihal et al. suggested the combined evaluation of temporal and axillary arteries with cut – off IMT values ≥0.7/1.2mm.(27) Later, the 0.7mm cut – off was validated by compression sonography and showed high diagnostic accuracy not only in diagnosing GCA, but also in predicting ocular arterial occlusion.(31) High – resolution probes have been used to acquire more accurate IMT measurements.(30,32) 55MHz transducers can reveal the four – line pattern of IMT in thickened superficial arteries that corresponds to a histologically proven intimal thickening ≥

0.6mm.(32) According to Noumegni et al., 18 MHz and 22 MHz transducers show an acceptable level of agreement, with the latter correctly identifying slightly more cases. This study, however, only evaluated the presence of “halo” and compression signs and not an exact measurement of IMT.(18) The usefulness of high – resolution transducer requires further research.



Picture 1: (A) The "halo" sign of temporal artery in GCA; **(B)** Positive "compression" sign with remaining "halo" after compressing the temporal artery (from: Monti S, Floris A, Ponte C, Schmidt WA, Diamantopoulos AP, Pereira C, et al. The use of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. Rheumatology (Oxford). 2018 Feb 1;57(2):227–35).(44)

The “halo” sign is linked to response to treatment, prognosis and follow - up. As for all methods, when in cranial arteries, it typically reduces and disappears within the first two to three weeks of GC therapy, while even briefer or longer time periods have been reported.(3,20,33–37) Hypoechogenicity of the arterial wall has been established as a sign of active GCA, which means that remission of the “halo” sign might be a marker of response to treatment.(22,34,38) On the other hand, vasculitic changes may persist longer in large vessels than in TAs and this persistence does not always reflect undertreatment or increased rate of relapse.(20,39) The presence of an echolucent band within the thickened hypoechoic wall was described as a sign of active vasculitis in lower limb arteritis.(40) Several studies have investigated the long – term appearance of the vascular wall. Ford et al. stated that more than 70% of cases exhibited different US findings in follow – up after a median five months period. Findings resolved completely in 41% of patients, while in one third the hypoechogenicity of the vascular wall diverged into hyperechogenicity. Most subjects with

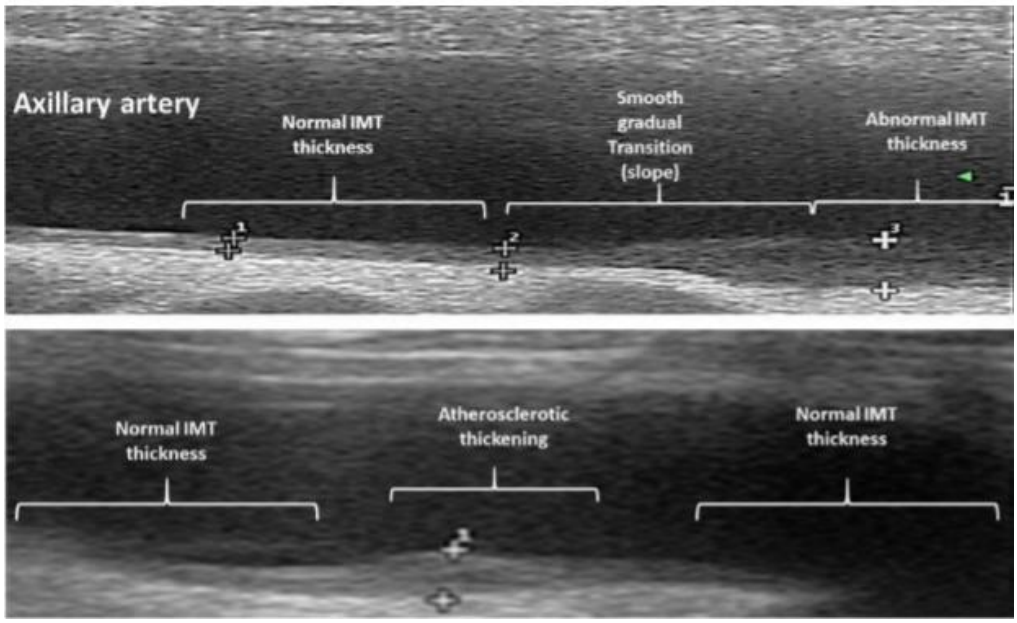
hyperechogenicity were on clinical remission at the time of follow – up.(34) This observation is consistent with other studies.(40–43) Although hyperechogenicity has been attributed to fibrosis or fine calcifications of atherosclerosis induced by vasculitis, its true pathogenesis remains unclear.(41,43)

In terms of prognosis and follow – up, Soares et al. reported that "halo" sign might be used as a marker of more severe and/or disseminated disease,(45) although it was shown that "halo" was not predictive of ischemic complications. (20) In two consecutive studies, Ponte et al. supported the use of CDUS in assessing disease activity and response to treatment.(20,46) The number of TA segments with "halo" and the maximum "halo" IMT were significantly correlated to acute phase reactants. "Halo" sign was present in 94% of relapses, but with less affected segments and lower IMT. (46) Contrarily, other studies observed that the thickness of "halo" in TAs is similar in acute phase and relapse and thinner during remission.(37,47) Another study reported that a "halo" sign in more than four segments was present in new or flared cases and tended to decrease in number during follow – up.(37) US is important in monitoring patients receiving IL – 6 inhibitors, since in those patients CRP and ESR remain low even in undertreated disease or relapse and cannot be used to follow – up disease activity.(20,48) For the time being, EULAR recommendations (LE 5) suggest that imaging could be utilized to follow – up structural disturbances, such as stenosis, occlusion, dilation and aneurysms. If relapse is suspected, imaging might be used to confirm it, but in cases of clinical and biochemical remission, it is not routinely recommended.(4)

Another recommendation (LE 1) states that US of TAs should be performed in patients suspected for C – GCA as a first – line imaging modality. Furthermore, if US findings of the TAs are normal but clinical suspicion of GCA remains high, other intra – and extra – cranial arteries, especially axillary, should be evaluated.(4) Several studies are consistent with this recommendation. According to one study, US sensitivity is 96% when only TAs are assessed and rises to 98% and 100% respectively when axillary and both axillary and common carotid arteries (CCAs) are added at baseline CDUS in patients with high suspicion of GCA.(49) A remarkable increase of sensitivity was reported when both temporal and axillary arteries were evaluated at initial US.(50) A recent study, concluded that US of the axillary artery is competent enough to be the first – line approach in LV – GCA compared to fluorodeoxyglucose positron emission tomography/ computed tomography (FDG –

PET/CT).(51) The “slope” sign was proposed as specific of axillary involvement; it represents the homogenous mural thickening that gradually transitions to normal thickness, in comparison to atheromatosis that appears to be more abrupt (picture 2). Further investigation on this sign is required.(52) Distal subclavian and axillary arteries are the most common site of extra – cranial involvement in GCA, especially in younger age.(53) Occipital arteries present lesions in almost 70% of patients.(3) In patients with C – GCA and/or LV – GCA, “halo” sign was found in occipital arteries in 31%, facial arteries in 41% and both in 19% of cases, even in patients with spared TAs.(54) When posterior circulation ischemic strokes occur, GCA must be considered in the differential diagnosis and conversely, if GCA is suspected in such patients a US protocol that includes carotid, vertebral, axillary, subclavian, occipital and temporal arteries plus a transcranial Doppler (TCD) of cerebral arteries should be implemented.(55) The “spot” sign is a hyperechoic spot in the head of the optic nerve suggestive of embolism of central retinal artery can be assessed by orbital color – coded sonography (OCCS) to differentiate embolic from vasculitic cause of vision loss.(56) Low flow velocities in retrobulbar arteries without occlusion may be found in GCA.(57) Other sites that may be involved include the proximal and distal arteries of the upper and lower limb.(3,58) In limb restricted GCA (LR – GCA), in 86% of cases only the upper limb is affected, in 9% only the lower limb and in 5% both.(58) One study suggested that a bilateral “halo” sign in femoropopliteal arteries should be considered typical for GCA.(43) Last but not least, the aorta might also be impaired; in almost one third of GCA patients aorta and major supra – aortic branches exhibit a “halo” sign, although cranial arteries may appear intact.(59) Only the proximal 4cm of the ascending aorta can be assessed by transthoracic echocardiography (TTE) for dilation or aneurysm, aortic valve insufficiency or myocardial dysfunction.(23,60) Transesophageal echocardiography (TEE), although usually not preferred, can reveal aneurysms, acute aortic complications,(60) aortic thrombosis(23,61,62) and findings of aortitis in the distal part of thoracic aorta. (63–65) US can evaluate the abdominal aorta for wall inflammation and periaortitis, however it might be limited by the patient’s physique and the presence of bowel gas.(23) Aortitis as an isolated expression of GCA may exist, although usually indistinguishable from other causes, such as infection and other vasculitides.(1,66) The “double barrel” sign in TEE, that corresponds to focal echolucent abscess cavities adjacent to the aortic lumen, can help distinguishing infectious aortitis.(60) Multimodality imaging is necessary in suspected aortic involvement.(4) The

extent of the disease should be exhaustively investigated, since it has been related to treatment response and prognosis. Czihal et al. showed that upper limb involvement has a good prognosis with resolution of sonographic findings in 32% of the subjects at least six months after diagnosis. Bilateral, unilateral and right – sided GCA and subclavian artery involvement correlate with worse prognosis.(67) Another study found that lower limb critical ischemia could rapidly evolve within weeks in contrast to upper limb, where collateral vessels typically stave this complication off.(43,67) On the other hand, long – term lesions of the artery wall are more prone to completely resolve in TAs than in subclavian and/or axillary arteries.(34) Simultaneous intra – and extra – cranial involvement in baseline US was related to inadequate treatment response and more frequent relapses. Contrarily, normal baseline US or involvement of one vascular bed had better prognosis.(68) As much as 76% of patients developing stroke within the first week of GCA diagnosis had a posterior circulation infarct strongly associated with vertebral "halo" sign.(45,69–71) Aortitis is accompanied by increased risk of aneurysm formation, a complication that develops at least three to five years from diagnosis.(66,72) Since aneurysms are usually silent and may be lethal, close monitoring should be implied (LE 5).(66,73)



Picture 2: The "slope" sign, proposed by Dasgupta et al., represents the gradual thickening of the wall of axillary arteries in GCA, compared to the discrete, irregular thickening in atherosclerosis (from: Dasgupta B, Smith K, Khan AAS, Coath F, Wakefield RJ. "Slope sign": a feature of large vessel vasculitis? Ann Rheum Dis. 2019 Dec;78(12):1738).(52)

TA biopsy (TAB) is considered the golden standard for GCA diagnosis, despite its invasive character and low sensitivity, that originates from the segmental wall involvement.(3,10) Since cranial arteries are spared in up to 40% of cases and extra – cranial arteries are often not accessible for biopsy, diagnosis is based upon clinical, laboratory and imaging findings.(10) US allows the assessment of the full length of most vessels, does not require cessation of anticoagulants, has lower cost and the results are immediately available.(22) A few meta – analyses compared the diagnostic accuracy of US with that of clinical diagnosis and/or TAB(9–12) and reported diagnostic accuracy for the "halo" sign as equally high as that of TAB.(10) Sommer et al. found that TAB had a 97.3% sensitivity in patients with elevated ESR and CRP serum levels and a positive US, suggesting that in such cases TAB might not be necessary.(74) Luqmani et al. proposed a strategy of conducting US in all patients and proceed to TAB only in those with negative US by conducting a prospective study. The authors concluded that US is more cost – effective than TAB both with or without clinical correlation.(24) Both high positive and negative prognostic values for temporal arteritis have been reported.(75,76) Last but not least, some investigators tried to enhance the accuracy of TAB by guiding the procedure through US, however results were ambiguous.(36,77) The aforementioned and several more studies converge, at a different degree, to the hypothesis that a negative result in US can exclude diagnosis, if clinical suspicion is low, and a positive US can rule in the diagnosis, if clinical suspicion is high. This way the need for TAB may decrease, reducing interventions and preventing unnecessary GC therapy. (24,75,76,78–84) This conclusion was implemented by the 2018 EULAR recommendations, in which however it is stated that the role of TAB should not be undermined.(73)

In compliance to this recommendation, several studies have attempted to develop pre – test probability scores.(85–89) Two retrospective studies introduced the concept of "fast – track clinics", consisting of clinical and US evaluation within short time (24 hours and one week respectively) and referral to a specialized team within 24 hours. Both studies, reported lower incidence of irreversible visual impairment, more scarce complications of prolonged GC administration and restriction of hospitalization expenses, which lead to a better cost – effectiveness ratio.(85,86) Laskou et al. developed a GCA probability score (GCAPS), which took clinical and biochemical parameters into consideration. According to GCAPS, suspected cases were divided into three categories – low, intermediate and high risk for GCA. A US was conducted within two days and based on the result, low – risk patients with negative US were

further categorized as “GCA unlikely”, while high – risk patients with positive US as “treat as GCA”. For both categories, no necessity for further evaluation was considered, while for the two intermediate categories – “GCA uncertain” and “treat as GCA with additional test” – additional tests and clinical re – evaluation were assigned. A cut – off value of 9.5 (≤ 9 not GCA, ≥ 10: GCA) yielded 95.7% sensitivity and 86.7% specificity.(87) Higher diagnostic accuracy of US compared to prior literature was showcased when GCAPS was implemented in diagnosis.(88)

Since US is operator – dependent, a few researchers reported results after specific and constructed trainings of sonographers, that usually lead to excellent inter – and intra – observer agreement.(24,90,91) EULAR also recommends that imaging should be performed by trained specialists (LE 5).(4) Deep learning using convolutional neural networks had promising results in avoiding operator – dependency.(92) Some researchers tried to quantify US findings by creating scores.(93) Van der Geest et al. created a Halo Score (HS) by grading wall thickness in TAs, their branches and axillary arteries bilaterally. HS was higher in GCA patients and when HS ≥ 10 (0 – 48), specificity reached 95%. HS was positively correlated to a positive TAB(84), an observation validated again recently.(8) As mentioned before, the same study related high HS with intimal hyperplasia, and suggested that a positive TAB with high HS is predictive of ocular ischemia.(8) Including subclavian arteries in a modified HS was not found to raise accuracy, however it better correlated with inflammatory markers, an aspect that could assist evaluation of disease activity and response to treatment.(94,95) A temporal compression sonography (TCS) score based on HS was suggested, without any effect on diagnostic accuracy.(31)

Contrast – enhanced US (CEUS) has recently started to be investigated. A pilot study reported enhancement of the proximal CCA wall in patients with LVV, which allowed better visualization of the lumen – wall interface. The degree of the enhancement corresponded to the severity of neovascularization and was considered to be a possible indicator of disease activity, although this assumption requires further and larger studies.(96) A semi – quantitative method for assessing CCA mural enhancement by CEUS in patients with LVV defined three grades of severity and concluded that CEUS could be a more reliable marker of disease activity than clinical diagnosis and inflammatory markers. Severe degree was accompanied by a C – IMT > 1mm and was predominantly present in active disease. Last but

not least, CEUS had a sensitivity of approximately 100%, when compared to FDG – PET/CT, but not as high specificity due to post – inflammatory neoangiogenesis that lead to enhancement despite the regression of inflammation.(97)

Finally, US has a role in evaluating articular and extra – articular inflammation in order to diagnose and monitor disease activity PMR.(98) The most typical findings are subacromial/ subdeltoid bursitis, followed by tenosynovitis of the long head of the biceps, while hip synovitis, interspinous bursitis and other sites of inflammation can be recognized.(98,99) These findings may assist the diagnosis of PMR and might even be more sensitive in revealing residual disease after therapy in comparison to acute phase reactants and clinical evaluation.(98) US also plays an important role in the differential diagnosis of PMR.(99)

EULAR recommends (LE 5) that conventional angiography should be saved for interventional purposes, such as revascularization of ischemic tissues.(3,4,23) Other imaging modalities to evaluate vascular inflammation and its complications include MRI, CT and PET. MRI should be used to assess active mural inflammation in cranial arteries, when US is inconclusive or unavailable (LE 2).(4) MRI and MR angiography (MRA) can determine the extent of the disease, vascular complications, such as stenosis, occlusion or dilation of the arteries, infarcts in target organs, as well as PMR.(4,99) Cardiac MRI (CMRI) is useful in suspected cardiac involvement.(38)For medium – size arteries, especially for carotid, ophthalmic and vertebral, MRA is often preferred over other methods.(3) MRI, preferably using a 3T scanner, has similar diagnostic accuracy in comparison to US (sensitivity: MRI 69%, US 77%, specificity: 91% both).(4,100) The value of MRI in assessing disease activity is not well – established.(101) MRI – MRA should be conducted early, within the first five days, from GC initiation.(5,9)

Computed Tomography (CT) is recommended to evaluate LV – GCA, but not C - GCA, according to the EULAR (LE 3 and LE 5, respectively).(4) CT angiography (CTA) can visualize wall thickening and contrast – enhancement in early stages of inflammation and mural hyperdensity and calcifications in later stages and enables accurate measurements of luminar lesions.(38) Venous and portal venous phases allow the investigation of parenchymal organs.(2) The role of CT - CTA in long – term follow – up of disease activity is not yet established.(101)

FDG – PET and FDG – PET/CT are not appropriate for cranial arteries, especially for TAs, due to low spatial resolution and increased uptake of FDG from the brain, that obscures adjacent vessels.(9) FDG – PET has a sensitivity of 80% and specificity of 90% and FDG – PET/CT 90% and 98% respectively, and presents a higher diagnostic accuracy for LV – GCA compared to MR and CT. Some studies reported higher diagnostic accuracy of US in the presence of a "halo" sign in the axillary and subclavian arteries, however not for the aorta.(50,102) Imfeld et al. concluded that the two modalities are complementary,(103) while Seifert et al. experimented with fused PET/US, combining the metabolic properties of PET and the morphologic findings of US.(104) The accuracy of FDG – PET/CT remains high within the first three days of GC therapy and declines abruptly after ten days, while liver uptake increases, imposing difficulties in assessing disease activity.(3) Although, the role of FDG – PET is still ambiguous, it remains quite promising for detecting remissions in the future.(3) It may also reveal an alternative diagnosis and designate findings suggestive of PMR or conversely exclude vasculitis in patients with PMR.(3,9,99)

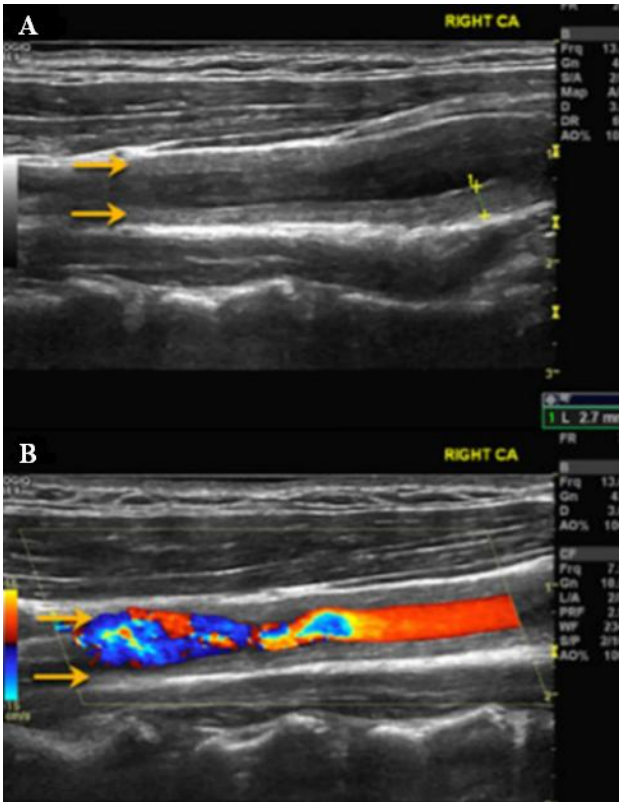
3.1.2. Takayasu Arteritis (TAK)

The 2018 EULAR recommendations state that in suspected TAK, contrast enhanced MRI should be the imaging method of choice (LE 3). This recommendation stems mainly from two factors. Mural inflammation and luminal changes, including stenosis, occlusion, dilation and aneurysm, are depicted with a sensitivity and specificity that may reach 100% and furthermore radiation exposure of the typically young TAK patients is avoided. Other modalities should be used when MRI is not readily available (LE 3 for CT, LE 5 for PET and US). (4) Imaging should be reserved for suspected relapses, as adjunctive to inconclusive clinical and biochemical markers, and not as routine follow – up during remission or in otherwise confirmed relapses (LE 5). Long – term luminal changes should be followed – up frequently, with modality and chronic intervals being chosen individually (LE 5).(4) Conventional angiography should be spared for interventional purposes (LE 5). Diagnostic accuracy of all imaging modalities declines during treatment, although specific time intervals after treatment initiation are not well – established.(3)

The extent is similar to GCA, but TAK more commonly affects the left CCA and subclavian, the vertebral and mesenteric arteries and never the TAs.(3,101) A cluster analysis reported that TAK lesions are symmetrical, in contrast to prior literature supporting asymmetrical involvement.(105) Typically, arteries affected by TAK are inaccessible for biopsy.(3) Therefore in suspected cases, CDUS of the aforementioned arteries and the abdominal aorta should be performed as soon as possible,(101) despite the lack of fast – track clinics' evidence.(73) Isolated aortitis may rarely occur.(106) If claudication or hypertension exist, limb and renal arteries should be assessed, respectively.(4,101) Retrobulbar, namely ophthalmic and central retinal arteries should be periodically evaluated by CDUS, since increased time after disease onset was significantly correlated to reduced blood flow velocities and increase RI, predisposing vision disturbances.(107)

According to a recent meta – analysis, US yields a 81% pooled sensitivity and 100% specificity for TAK when compared to clinical diagnosis, while the pooled concordance of US and angiography was 86%.(25) The most typical finding is the concentric, usually mid – echoic, thickening of the arterial wall in early stages, due to inflammation and edema, known as the "macaroni" sign (picture 3).(108,109) IMT has been suggested as an indicator of active disease, since it significantly declines after treatment and increases during

relapses.(25,108,110) Barra et al. in their meta – analysis reported that C – IMT was 0.56mm greater in TAK against healthy controls.(25) Thickening may persist in later stages, echogenicity usually increases and luminal changes and collateral vessels arise.(108,109) The hyperechogenicity after treatment has long been proposed to be a marker of disease activity.(101,109) Svensson et al. found that in active, newly diagnosed TAK, IMT was increased, the wall was low to moderately echogenic and intramural arteries were present. During remission, mild increase of IMT and echogenicity with fibrous mural stripes were observed. The combination of maximal reliable IMT measurements of various arteries were used in a Takayasu ultrasound index, in order to quantify the total inflammatory burden of the arteries. All parameters, including the index, were higher in TAK patients compared to healthy controls, especially during early disease.(111) Fan et al. assessed the progression of wall thickening and outer diameter of carotid arteries and reported that both remained unchanged during follow – up, in patients that would subsequently relapse, while in those in remission they declined.(112) Decreased brachial FMD has been reported as marker of endothelial dysfunction in TAK, although not in correlation to disease activity or acute phase reactants.(113)



Picture 3: (A) The "macaroni" sign and **(B)** the consequent stenosis, as revealed by Color Doppler, in a common carotid artery of a patient with Takayasu arteritis (from: Barreira SC, Melo AT, Ponte C, Khmelinskii N. Macaroni sign and carotid occlusion in Takayasu's arteritis. Rheumatology (Oxford). 2021 Apr 6;60(4):2029–30).(114)

The role of CEUS in assessing disease activity during follow – up has been investigated thoroughly. Many studies designated increased mural enhancement as predictive of active TAK and restricted vascularization during remission after treatment.(110,115,116) Schinkel et al. suggested a semi – quantitative method of grading CEUS in carotid arteries and showed that the grade of neovascularization, ranging 0 – 2, corresponded to the severity of inflammation and activity of TAK.(96) Ma et al. compared active and inactive cases of TAK and concluded that mural thickness is greater in the active stage, while luminal stenosis and occlusion are more common in the inactive stage. Severe vascularization was found in almost 62% of active and in an estimable 24% of inactive cases. Both wall thickening and neovascularization declined after three months of therapy.(117) Residual enhancement during inactive disease could be attributed to remaining neovessels, despite clinical and biochemical absence of inflammation.(97,116,117) Accordingly, CEUS might be more sensitive in detecting even subtle inflammation unnoticed by clinical and laboratory markers, further supporting its importance in follow up. (97,117,118) Li et al. proposed a semi – quantitative method with four visual grades of carotid arterial wall neovascularization and concluded that grades ≥2 corresponded to clinically active or undertreated cases, even if acute phase reactants remained low. CEUS exhibited good correlation with clinical diagnosis and a 100% sensitivity and 80% specificity compared to FDG – PET/CT. In this study, CEUS correctly classified active or inactive disease in 96.8% of cases.(118) More recently, Ma et al. utilized carotid wall thickness and clinical factors, to predict US progression within one – year follow – up. Increased mural thickness and grade 2 neovascularization at baseline predicted imaging progression.(119) Neovascularization grade ≥2 as highly specific of active disease was also reported by Lottspiech et al., who investigated all three carotid, subclavian and axillary arteries. Grade 0 was highly specific of inactive disease, while grade 1 remained equivocal and could correspond to either remodeling or lurking inflammation. Weighing grade 1 cases by maximum IMT seemed promising in increasing diagnostic accuracy and recognizing patients with smoldering disease.(120) A new application of US, the superb microvascular imaging (SMI), allows extremely low flow within arterial wall to be detected. SMI revealed neovascularization in an active TAK case, that consecutively receded after six months follow – up.(121)

Stenosis is evaluated with greater sensitivity by CDUS in comparison to conventional angiography, MRA or CTA.(4,25) Sinha et al. created a scoring system of CDUS based on

stenosis and abnormal blood flow parameters in various arteries. This scoring system yielded high inter – and intra – observer agreement and a high degree of correlation with the Indian Takayasu Clinical Activity Score (ITAS2010), a result that supports utilizing CDUS in evaluating disease activity.(122) In case of CCA stenosis or occlusion, if peak systolic velocity (PSV) in external carotid artery (ECA) is retained, so does in internal (ICA), despite the fact that PSV typically appears reduced in TAK. Such findings enable an indirect assessment of blood flow adequacy in the brain.(123) Apart from typical luminal lesions, rare cases of dissection have been described, most often in the aorta and secondarily in CCA. Dissection commonly involves short arterial segments, with a thick, rigid intimal flap without apparent movement, while seldom multiple dissections might occur in the same segment and must be differentiated by collateral vessels.(124)

TTE also plays a pivotal role for the diagnosis and follow – up of TAK. TTE is of limited value for the thoracic aorta,(4,106) apart from its proximal ascending segment.(101) According to Nishigami et al., the echocardiographic appearance of the aorta depends on the segment. The descending aorta and the aortic arch appear wavy and scalloped and later calcified, the so – called “porcelain aorta”. Smooth tapering or focal stenosis involve the descending thoracic and abdominal aorta, creating a “pseudo – coarctation”, while rarely chronic occlusion may occur.(125,126) Smooth – walled dilation or aneurysms of the ascending aorta may appear in later stages. Collateral vessels may be present in the setting of chronic stenosis.(126) TEE might provide useful information on thoracic aorta and coronary arteries (CAs) morphology and flow, especially in the orifices of CAs.(106,126,127) TTE and TEE can evaluate valvular abnormalities, usually aortic and mitral insufficiency, and in almost two thirds of patients, simultaneous involvement of multiple valves.(128–130) Pulmonary hypertension (PH) may affect as much as half of TAK patients and has been related to an 13 – fold increased risk for future valvular intervention,(130) underlining the importance of assessing pulmonary arteries.(130,131) A study found that the right pulmonary artery is involved in more than 90% of cases, exhibiting the “macaroni” sign, luminal stenosis, medium to high echogenicity occlusion and gradual stenosis of distal vessels that corresponds to the CTPA “rat – tail” sign.(131) Pericardial effusion, although not very frequent, may also be revealed by TTE.(101,132) Last but not least, TTE and TEE allows inspection of ventricular dimensions and function, cardiomyopathy and heart

failure.(101,133–135) Wang et al. used aortic valve involvement and pulmonary hypertension evaluated by TTE to create a risk assessment model that predicts heart failure.(136)

More sporadic applications of US are also described in literature. Intravascular ultrasound (IVUS) can detect subtle wall changes, requires however larger studies.(126,137,138) Aortic stiffness deduced by echocardiography through carotid – femoral pulsed wave velocity, is found to be increased in TAK compared to healthy controls.(139) In a case report, TCD was used to assess ophthalmic artery and anterior circulation blood flow, both pre – and post – revascularization of an occluded CCA in a patient with TAK and retinal ischemia.(140) It is important to underline that in pregnant women pre – delivery echocardiography should be performed, since TAK may complicate pregnancy with hypertension, pre – eclampsia, and valvular dysfunction, predominantly aortic regurgitation.(141,142)

MRI is the method of choice for evaluating aorta and its large branches. Circumferential wall thickening ≥0.6mm with a high T2 – signal and post – contrast enhancement are typical early findings.(2,101) Long – term luminal changes are detected by MRA with high diagnostic accuracy, comparable to angiography.(101,108) Concerning disease activity, especially after treatment initiation, the role of MRI/MRA is under investigation. Edema may overlap over chronic lesions even during remission, while mural inflammation and fibrosis cannot be differentiated by gadolinium enhancement. Recently, gadofosveset was suggested as an alternative, since it does not enhance fibrotic tissue. Cardiac MRI is quite accurate in revealing even subtle myocardial ischemia.(101)

CT/CTA has 95% sensitivity and 100% specificity in diagnosing TAK in early stages, before severe remodeling occurs.(101,108) Early findings include mural thickening and hyperdensity in pre – contrast images and a double – ring sign in venous phase.(101,143) Later, moderate wall thickening, calcifications, luminal changes and overlapping chronic lesions might be found.(108,143) CT is particularly useful in differentiating TAK from atherosclerosis, since in TAK calcifications are typically transmural, circumferential and extended.(108,144) CTCA may reveal asymptomatic coronary lesions in up to 55% of patients and should be utilized in the non – acute stage of disease, if coronary or ascending aorta involvement are suspected.(101,108) The ability of CT/CTA to determine disease activity and treatment success remains unclear.(101)

LVVs share similar advantages and limitations in FDG – PET/ FDG – PET/CT.(38) FDG – PET/CT sensitivity is 87% and specificity 73% for TAK. Active, untreated vasculitis shows an uptake greater than that of the liver, however specific cut – off values are not validated yet. Diagnostic accuracy declines quickly after treatment implementation.(101) Although considered by some to be the best option, the role of FDG – PET in assessing disease activity and follow - up is not fully elucidated.(145)

3.2. Medium Vessel Vasculitis (MVV)

3.2.1. Kawasaki Disease (KD)

Timely diagnosis in KD is crucial, since up to 25% of untreated and 5% of intravenous immunoglobulin (IVIG) treated cases will develop coronary artery aneurysms (CA aneurysms, CAAs).(146) TTE is the primary method for initial diagnosis. Its high resolution enables assessment of the CAs diameters, which must be measured from intima to intima and not in proximity to branching points, where they normally tend to be ectatic (picture 4). The number, distribution and maximal diameter of aneurysms must be carefully evaluated, since they are related to disease severity and prognosis.(38,147) Both Japanese Coronary Society (JCS) and American Heart Association (AHA) have established classification systems according to the degree of CA dilation (table 4). The advantage of the latter is that it normalizes the dimensions of CAs as Z – scores (standard deviation units from the mean) and corrects them by body surface area (BSA), namely by height and weight, since the normal size of the arteries depends on the size of the child.(147) The pitfall of this method is that only small deviations in diameter may result in large deviations in z – score, a disproportion that becomes even more prominent in large aneurysms.(148) However, a recent study showed that JCS criteria might underestimate CAs dimensions and therefore the prevalence of CAAs. (149)

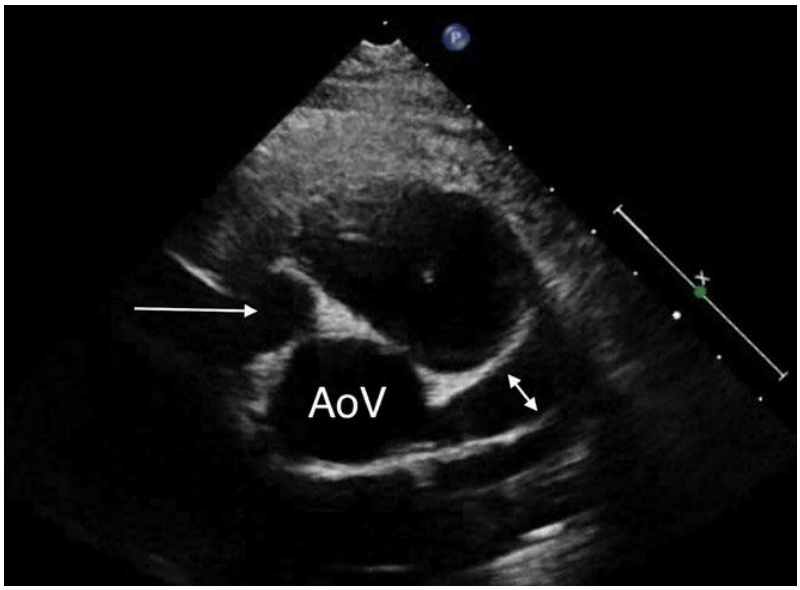
Table 4: Classification of coronary arteries dilation in Kawasaki Disease(147,150)

Japanese Cardiology Society Joint Working Group (2008)		
Aneurysm size	**Internal diameter OR dilation (mm)**	**Number of times internal diameter is larger than that of an adjacent segment (if child is ≥ 5 years of age)**
Small	< 4	≤ 1.5
Medium	>4 and ≤ 8 mm	1.5–4
Large	> 8 mm	> 4

American Heart Association (2017)	
Aneurysm Size	**Z-score**
No involvement	Always < 2
Dilation only	≥ 2 and < 2.5 **OR** if initially <2, a decrease in Z-score during follow-up ≥ 1, suggesting that CA was dilated during acute stage although diameter was within normal standards and the diameter has regressed on follow-up
Small	≥ 2.5 and < 5
Medium	≥ 5 and < 10 **AND** absolute dimension < 8 mm
Large or giant	≥ 10 **OR** absolute dimension ≥ 8 mm

In the acute stage (1st week of fever), coronal abnormalities might be absent; however, TTE must always be performed, since even in this stage, it can reveal myocarditis, valve regurgitation, pericarditis and pericardial effusion.(147,151) Coronary abnormalities typically occur after the acute stage; however the earlier they emerge, the worse the prognosis and, according to some authors, the response to IVIG treatment.(38,152) Very recently, Tsuda et al. reported that CAAs with a maximum internal diameter ≥6.0 mm or Z – score ≥7.5 at two months after KD onset showed persisting CAAs in adolescence, with a maximum follow – up of 15 years, whereas normal CAs should be expected for CAAs with maximal internal diameter ≤3.0 mm or a Z – score ≤2.5 at two months.(153) Large CAAs are more commonly complicated with stenosis, thrombosis or rupture, and may result to myocardial ischemia and death, while in later stages, they typically appear heavily calcified.(154) Mitral and, more seldom, aortic valve regurgitation, as well as aortic root enlargement can be appreciated by echocardiography.(151) In ambivalent cases, if TTE findings are typical of KD in the acute febrile phase, the diagnosis of incomplete KD can be established.(147) In a cohort study the diagnosis of incomplete KD was set during first TTE in 61% of total cases, whereas another

32% were detected by serial TTE.(155) In accordance to these results, Satoh et al. suggested TTE as a screening method along with serum NT – proBNP in infants younger than three months with fever persisting for more than two days, even if no other indicative findings of KD are present.(156)



Picture 4: Transthoracic echocardiography revealed fusiform aneurysms of the right (arrow) and left anterior descending coronary artery (double arrow). AoV: aortic valve (from: Cameron SA, Robinson JD, Carr MR, Patel A. Giant coronary artery aneurysms in an infant with Kawasaki disease: Evaluation by echocardiography and computed tomographic angiography. Echocardiography. 2018 Oct;35(10):1692–4).(157)

Myocardial function should be evaluated in all stages through measurement of end – systolic and end – diastolic dimensions of left ventricle (LV), ejection fraction (EF), fractional shortening (FS), LV systolic dyssycnhrony, myocardial performance index (MPI) and by assessing ventricular wall motion,(147,151) for most of which 2D – and 3D – echocardiography (2DE and 3DE, respectively) can be implemented(158–163). In addition, speckle tracking echocardiography (STE) can be utilized for quantitative assessment of myocardial strain in order to demonstrate even subtle myocardial dysfunction.(164,165) Several studies have reported decreased global strain (GS) and global strain rate (GSR) in 2D – and 3D – STE for pediatric and adult populations (166–169) and a few correlated the degree of decrease to the presence of coronary artery lesions (CALs).(168,170) Myocardial deformation and LV function were found by Sanchez et al. to be more restricted in the chronic phase of KD, although within normal range, (171) in contradiction to a study by Xu et al., in which global longitudinal strain (GLS) was significantly decreased during the acute phase, but restored in the chronic stage, regardless of the presence of CAAs.(172) Another

study showed that LV dysfunction and dyssynchrony was transient in CAA – negative patients, but persistent in patients with CAAs in the convalescent stage, thus imposing long – term follow up.(173) One study established an increase of GS and GLS after treatment, while another was able to predict IVIG – resistance in children with KD, since they showed more severe LV systolic dysfunction in comparison to IVIG – responsive and healthy controls. These results suggest that STE can be an important prognostic tool for responsiveness to treatment.(174) In most studies, EF was typically preserved, despite LV dysfunction. Diastolic dysfunction in KD was observed within the first 30 days from IVIG initiation; it continued even longer for patients with CA dilation.(175) Transient dilation of the pulmonary artery and RV dysfunction were observed in the acute phase and typically improved after IVIG.(176)

Tissue Doppler Imaging (TDI) is another application of echocardiography that allows elaboration on myocardial function through direct measurement of systolic and diastolic velocities in various myocardial segments.(177) LV dyssynchrony and impaired myocardial deformation assessed with STE and TDI were observed in the acute stage and remained in convalescent stages only in patients with CAAs.(173) Before treatment, myocardial velocities may be lower compared to healthy controls and may be improved, but not normalized, after therapy.(178) A significant compression of diastolic function was described for IVIG – resistant patients, underlining the utility of TDI in foreseeing refractory disease.(177)

Calibrated integrated backscatter analysis (CIB analysis) is an established echocardiographic method that quantifies echogenicity; if tissue edema, cell infiltration, collagen deposition exist, CIB values increase. A study investigated the presence of myocardial fibrosis in various stages of disease and found increased CIB values in patients in comparison to healthy controls, especially in those with CAAs,(179) while another study found no difference regarding CALs a year after disease onset.(180) Nagata et al. performed measurements of CA wall, mitral valve, papillary muscle and ascending aorta wall and reported higher CIB values in KD, that declined over time, although less excessively in IVIG – resistant cases.(181) In similar conclusions came also Abe et al., according to whom coronary artery wall exhibits higher echogenicity in patients with KD, especially in those receiving IVIG and having coronary enlargement in the acute stage.(182) On the other hand, two studies – one through

CIB – found no significant difference in perivascular brightness between patients and controls, underlining its little value in diagnosing incomplete KD.(183,184)(184)

Echocardiography is the major imaging method during follow up therefore AHA recommended, that if initial TTE in normal or shows only CA dilation (Z-score <2), follow – up should be performed after 2 and 4 – 6 weeks, since after that period of time thrombosis is considered unlikely. This recommendation is consistent with the results of various studies that suggest that even borderline z – scores may lapse into CAAs, that may persist even a year after disease onset.(185,186). In cases complicated by evolving lesions, especially large or giant aneurysms, follow – up TTE must be performed twice a week, until lesion growth stops and then once per week for the first 45 days from the disease onset.(147,187) For long – term follow up TTE reliability declines, since middle and especially distal segments of CAs cannot be evaluated, because the thickness of the thoracic wall increases as the child grows.(147,151,187) Moreover, vessel wall changes that occur in later stages – including small calcifications and fibrofatty changes – may cause the artery to appear of normal diameter, although ongoing pathology exists and may produce myocardial ischemia in the appropriate setting. In both cases, further imaging is needed, to assess both vessel anatomy and myocardial function.(151)

Noto et al. utilized a wall motion score index (WMSI) of several segments and concluded that a WMSI $\geq$ 1.125 was positively correlated to a major adverse coronary effect, e.g. an acute myocardial infarct, within a 15 – year follow – up.(188) Stress echocardiography can assist a concealed coronary stenosis emerge, because the increased oxygen demands will not be fulfilled, thus provoke ischemia reflected as wall motion abnormalities.(151,187) Various studies demonstrated the high sensitivity (>90%) and specificity (even reaching 100%) of dobutamine stress echocardiography and its superiority to exercise stress echocardiography.(187) The latter has limitations in children, since their heart rate quickly retreats to normal, minimizing examination time, and also treadmill may not be ideal for younger children.(147)

Intravascular ultrasound (IVUS) can be employed during selective angiography to depict atherosclerotic lesions in CA wall in long – term follow – up.(154) IVUS facilitates the inspection of stenosis or/ and atheromatosis, by measuring intima – media thickness (IMT) and plaque morphology.(187) A retrospective study employed virtual histology IVUS to

correlate the consistency and progression of atherosclerotic – like CALs in KD after one and ten years of disease, however results could not be histologically proven.(189) It has been proposed that intracoronary infusion of acetylcholine and isoborbide dinitrate can be implemented to test vessel response; increased vasoconstriction and reduced vasodilation are indicative of chronic wall changes due to aneurysms, atheromatosis and stenosis.(187)

Ultrasonography is not confined to the heart and CAs. CDUS can efficiently showcase aneurysms in other medium – size arteries, although they are usually rare and not demanding treatment. However, aneurysms in systematic arteries should raise suspicion for CAAs and lead to further investigation.(38) Moreover, several studies have deduced that increased arterial stiffness of the aorta exists in the setting of KD and can be investigated by shear wave elastography (SWE), another application of US.(190–194)

Endothelial dysfunction in the acute phase and atherosclerotic changes in later follow – up stages are typically evaluated in peripheral arteries (table 5), although increased IMT values have also been described for left coronary artery (LCA).(195) According to Wu et al., C – IMT is increased in the acute phase of KD in comparison to other acute infectious diseases, a characteristic that could be helpful in incomplete cases.(196) Increased C – IMT is reported by several studies to be an important index for atheromatosis and prognosis,(146,197–199) perhaps correlated with CALs,(198,199) however contradictive evidence also exists.(200,201) In a meta – analysis of patients at least six months after disease onset, to avoid impingement due to inflammation, mean C – IMT in KD patients and in particular in patients with CAAs was not found to be significantly greater, although a tendency to increased C – IMT was noted.(146,202) Another, more recent, meta – analysis confirms that C – IMT is significantly increased and FMD decreased in KD patients compared to controls.(203) Atherosclerotic changes in CCAs were evaluated by a method combining TCI and STE and found to be significant even in early stages of the disease.(204)

Table 5: Carotid intima – media thickness (C – IMT) in Kawasaki disease

Acute phase			
Author (year)	**Kawasaki disease (mm)**	**Healthy controls (mm)**	**p - value**
Wu et al. (2019)(196)	0.550 (0.440 – 0.690)	0.483 (0.430 – 0.560)	0.01

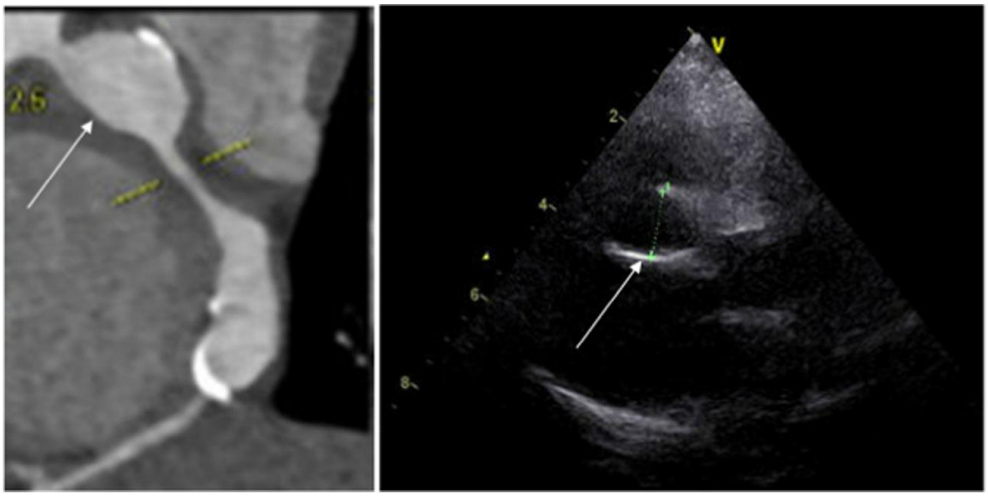
Chronic phase			
Gopalan et al. (2018)(197)	0.540 (0.453 – 0.627)	0.420 (0.384 – 0.456)	<0.001
Parihar et al. (2017)(201)	0.360 (0.345 – 0.375)	0.350 (0.274 – 0.426)	0.791
Chen et al. (2017)(198)			
Total	0.490 (0.440 – 0.540)	0.480 (0.420 – 0.540)	0.800
No CAAs	0.490 (0.430 – 0.550)		0.800
CAAs	0.490 (0.440 – 0.540)		0.900
Dietz et al. (2016)(199)	0.375 (0.372 – 0.378)	0.363 (0.358 – 0.368)	<0.001
No CAAs	0.373 (0.369 – 0.376)		<0.01
Small–medium CAAs	0.374 (0.367 – 0.382)		<0.05
Giant CAAs	0.381 (0.370 – 0.392)		<0.01
Shah et al. (2015)(205)			
RCCA (total)	0.470 (0.390 – 0.580)	0.470 (0.400 – 0.600)	0.770
RCCA (no CCAs)	0.470 (0.390 – 0.580)		0.590
RCCA (CAAs)	0.470 (0.390 – 0.580)		0.920
LCCA (total)	0.460 (0.370 – 0.580)	0.460 (0.410 – 0.600)	0.970
LCCA (no CCAs)	0.470 (0.370 – 0.530)		0.990

LCCA (CAAs)	0.460 (0.390 – 0.580)		0.950
Dietz et al. (2015)(206)	0.378 (0.358 – 0.408)	0.360 (0.333 – 0.387)	<0.0001
Laurito et al. (2014)(207)	0.500 (0.400 – 0.600)	0.500 (0.400 – 0.600)	0.930
Ishikawa and Iwashima (2013)(208)		0.430 (0.390 – 0.370)	0.906
CAAs	0.450 (0.447 – 0.453)		NR
No CAAs	0.430 (0.428 – 0.432)		NR
Selamet Tierney et al. (2013)(175)			
RCCA	0.428 (0.424 – 0.452)	0.432 (0.403 – 0.461)	0.35
LCCA	0.438 (0.404 – 0.472)	0.434 (0.406 – 0.462)	0.42
Oguri et al. (2013)(204)	0.400 (0.370 – 0.430)	0.390 (0.386 – 0.394)	0.15
Noto et al. (2012)(209)	0.540(0.460 – 0.620)	0.42 (0.38 – 0.46)	<0.001
CAAs: coronary artery aneurysms; RCCA: right common carotid artery; LCCA: left common carotid artery; NR: not referred.			

Flow – mediated dilation (FMD) is also a marker of endothelial dysfunction that was found reduced in KD by several studies.(146) Dietz et al. in their meta – analysis reported that FMD is significantly decreased in patients with CAAs in the setting of KD,(202) however results are contradicting for the correlation of FMD and CAAs.(201,202,210) Some authors related the duration of the acute inflammatory phase with lower FMD values and thus indirectly with

endothelial dysfunction.(146,208,211) Nitroglycerin induced dilation (NID) does not seem to provoke any differences between KD patients and healthy controls, regardless of CAAs.(201,202) Noto et al. conducted CEUS of the carotid arteries in adults with KD having giant CAAs. A higher mean C – IMT and a significantly increased density of adventitial vasa vasorum comparatively to healthy individuals were reported, probably reflecting the inflammatory infiltration and myofibroblast migration of the adventitial vessels.(146)

US can assess implications of parenchymal organs and their vasculature. For example, Chen et al. reported that sonographic gallbladder abnormalities, specifically hydrops and aculculus cholecystitis, may have a prognostic value, since they were more often in non – responders to IVIG treatment.(212) Moreover, US can assist differential diagnosis between bacterial lymphadenitis and lymphadenopathy in KD. Bacterial lymphadenitis is characterized by one prominent enlarged cervical lymph node of altered shape and ill – defined margins, with a hypoechoic, probably necrotic, center. On the contrary, KD lymph nodes are multiple, unilateral and have a beaded appearance (“cluster – of – grapes”) with preservation of their shape, well – defined margins and echogenic hilum.(147,213,214) Furthermore, SWE can assist differential diagnosis in cases presenting with fever and cervical lymphadenopathy as first symptoms, since stiffness is greater in bacterial lymphadenopathy.(213)

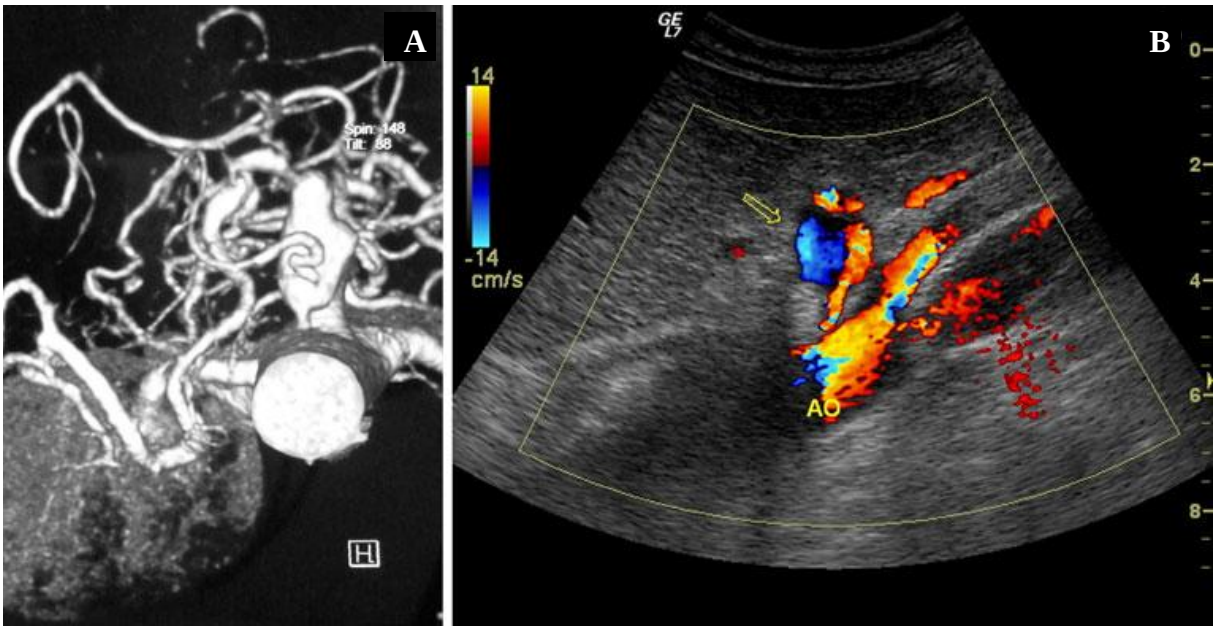


Picture 5: Aneurysm of the proximal segment of right coronary artery detected by both CTCA and echocardiography. A more distally located aneurysm and calcifications were also revealed by CTCA (from: van Stijn-Bringas Dimitriades D, Planken RN, Groenink M, Streekstra GJ, Kuijpers TW, Kuipers IM. Coronary artery assessment in Kawasaki disease with dual-source CT angiography to uncover vascular pathology. Eur Radiol. 2020 Jan;30(1):432–41).(215)

Regarding other imaging methods, selective coronary angiography remains the method of choice for the evaluation of the degree of stenosis, however due to its invasive character, it is replaced by other modalities. CT coronary angiography (CTCA) can effectively estimate the diameter and size of CAAs. While some authors suggest that CTCA and TTE are equivalent, a recent study reported that the first one established twice the amount of CAAs in the long term follow – up.(215) CTCA is particularly superior in assessing the middle and distal segments, especially with progression of age, as well as thrombi, segmental stenosis and calcifications (picture 5).(38,154) Calcium scoring can be applied to quantify the calcification load in arterial wall. In KD patients, it can evaluate small calcifications and the subsequent stenosis they may cause in CAs, that otherwise appear of normal diameter.(206) A major drawback of CTCA is its inability to establish the degree of stenosis when excessive calcification exists.(148,154) Another one is that CTCA uses ionizing radiation, although low – dose protocols, such as CTCA with prospective ECG – triggering, can be implemented.(206) MR coronary angiography (MRCA) has no ionizing radiation, displays however lower spatial resolution, prolonged scanning times that may require long sedation in children, unavailability and need for specialized personnel to conduct and interpret.(148,154) CMRI including perfusion and late gadolinium enhancement sequences, as well as adenosine stress protocol, can be utilized to assess myocardial ischemia and fibrosis, respectively.(147,154,206) Myocardial perfusion can also be assessed by scintigraphy and PET with thallium or technetium.(147)

3.2.2. Polyarteritis Nodosa (PAN)

US as a diagnostic tool has long been considered of little help for PAN, although it might be used as first approach in young patients.(216) The most indicative finding is multiple microaneurysms (1 – 5mm diameter), either saccular of fusiform, that alternate with stenosis.(217) Furthermore, thickening, irregular morphology and aneurysms in various visceral arteries and perivascular edema of the intrahepatic branches of the hepatic artery presenting as halo have been described.(216) Mainly case reports underlining the importance of US have been published, describing aneurysms most typically in hepatic, renal, mesenteric, cystic and testicular arteries and more rarely in celiac trunk, iliac, carotid and CAs.(216–219) Wang et al. reported the rare case of an arteriovenous fistula between renal artery and vein diagnosed by CDUS, CDUS and CTA yielded similar results in a follow – up period of five years (picture 6).(218) Furthermore, arterial stenosis and occlusion can also be sonographically revealed, such as in a case of occlusion of radial and ulnar arteries in the setting of hand localized PAN.(220) In another case report, the thickened wall and consecutive aneurysmal dilatations of the radial artery set the suspicion of vasculitis.(221) In both cases, and the diagnosis of PAN was confirmed by angiography.(220,221)



Picture 6: (A) An aneurysm of the celiac trunk was shown by 3D CTA reconstruction. **(B)** CDUS revealed stenosis proximally, as well as the known aneurysm in which swirling flow was detected (from: Wang H, Li J, Jiang Y, Dai Q, Jiang Y, Hou Y, et al. Polyarteritis nodosa with multiple aneurysms and renal arteriovenous fistula successfully diagnosed by color Doppler sonography. Clin Rheumatol. 2013 Mar;32 Suppl 1:S89-92).(218)

US may help assess other organs, mainly the gallbladder, testis and kidneys, particularly for ischemic complications.(216) Epididymoorchitis or mass – like testicular lesions, particularly in the setting of multisystemic inflammation, should orientate towards the diagnosis of vasculitis.(222) Single – organ PAN of the testis is described in literature and CDUS can assist differential diagnosis from mechanical causes, such as torsion (222,223). Last but not least, US was reported to evaluate peripheral nerves in the setting of PAN, in a case of non – localizing axonal neuropathy.(224)

Angiography of visceral arteries is the imaging method of choice, especially when biopsy cannot be obtained, since it is highly sensitive for microaneurysms. CTA and MRA are also utilized for diagnosis and follow – up. FDG - PET may particularly assist in cases of ambiguity. Increased uptake by muscular connective tissue is pathognomonic for PAN(225), while the leopard skin appearance produced by hot foci in muscle and subcutaneous tissues throughout the body is often described in literature.(225,226)

3.3. Small Vessel Vasculitis (SVV)

According to CHCC2012, SVV affects small arteries, arterioles, capillaries and venules of parenchymal organs, while medium size arteries and veins might also be involved.(1) Evidence on the role of US in SVV remains limited.

Multimodality imaging is important in assessing aortitis in the setting of SVV, with findings indistinguishable from those of other causes. TTE and TEE may reveal thickening, hypoechogenicity due to edema, aneurysm, stenosis and other lesions of the aortic root.(227) High prevalence of cardiac involvement characterizes SVV, especially GPA and EGPA; systolic and diastolic myocardial dysfunction evident as wall motion abnormalities, high – grade valvular dysfunction, CALs, pericardial effusion, myocarditis and ventricular masses, typically eosinophilic, may be detected even in asymptomatic patients. Echocardiography plus STE and TDI are first line in cardiac assessment.(228–234) Rare cases of aneurysms of multiple visceral arteries in ANCA – associated vasculitis (AAV) may evident by US.(235) SVV is also associated to thromboemoblic events, due to endothelial damage and hypercoagulabitlity, for the diagnosis of which CDUS remains the method of choice.(236,237)

The main use of US is the assessment of the extent of SVV in parenchymal organs, such as kidneys, lungs, testis, breast, bowel.(238–246) Multimodality imaging is implemented according to suspected underlying pathology in order to verify diagnosis.(38)

5.4. Variable Vessel Vasculitis (VVV)

5.4.1. Behcet's disease (BD)

Ultrasound has a multi – purpose role in the diagnosis, prognosis and follow – up of BD. Venous lesions consist 70% of vascular involvement and typically occur as deep venous thrombosis (DVT) of the lower limbs veins, superior and inferior vena cava (SVC and IVC, respectively).(247) DVT appears symmetrically in lower extremities, contiguously progressing from the common femoral vein proximally and distally in both deep and superficial veins.(248) Increased vein wall thickness (VWT) has been proposed as a diagnostic marker (table 6).(249–251) Alibaz – Oner et al. validated over two studies that VWT $\geq$ 0.75mm indicated BD with high probability in suspected cases. Moreover, VWT was significantly increased in BD, contrarily to other systematic inflammatory diseases except for ankylosing spondylitis.(251)

VWT was also proposed as a prognostic marker. The mean VWT was found significantly increased in BD patients regardless of DVT history compared to healthy controls, implying that thickening might be indicative of inflammation or even future DVT. Further research is needed to validate the proposed cut – off values, that may indicate patients in danger of DVT, so as to reconsider management.(249) Another promising prognostic marker could be the degree of recanalization after DVT, since it was reported that recanalization is more often incomplete and with more excessive collaterals in BD in comparison to DVT from other causes.(248) In a prospective follow – up study of patients presenting with lower limb DVT as the first symptom of BD, poor recanalization was found to be the only significant predictor of recurrence, though further validation is required.(252) Last but not least, concerning the prevalence of venous disease in BD without overt venous symptoms, one study reported no episodes of thrombosis, while another described subacute – chronic thrombosis of only the popliteal veins. Thrombotic events in upper limbs were not observed. Venous insufficiency was significantly more frequent in BD than in healthy controls in both studies. (253,254)

Most common arterial lesions are aneurysms, a major mortality cause due to risk of rupture. Usually the abdominal aorta and less regularly other arteries are affected. Stenosis, occlusion and less frequently pseudoaneurysms are described.(247,255) The risk of arterial thrombosis increases with underlying aneurysms, since reportedly 40% of patients with aneurysm have

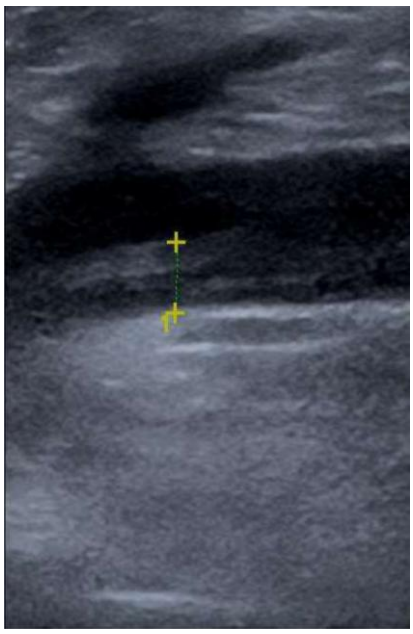
undergone a thrombotic episode. Routine examination was suggested for possible thrombosis in such cases, although the value of CDUS is unknown.(256) US may be important in the post – operative follow up of arterial lesions and their complications, although a constructed protocol has not yet been suggested.(255)

Table 6: Ultrasonographic cut – off values of vein wall thickness (VWT) in Behcet's disease (compared to healthy subjects)

Author (Year)	**Vein**	**VWT cut – off (mm)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**AUC**
Seyahi et al. (2019)(248)							
	CFV	0.617	72	90	87.8	76.3	0.833
	FV	0.557	74	94	92.5	78.3	0.859
	GSV	0.447	82	66	70.7	78.6	0.805
Alibaz – Oner et al. (2019)(250)							
	RT CFV	0.490	81	78.4	85.7	72.5	0.858
	LT CFV	0.480	82.8	81.1	87.5	75	0.852
Alibaz - Oner et al. (2021)(251)							
	RT CFV	0.500	90.7	94.5	84.3	75.4	0.941
	LT CFV	0.500	90.7	95.1	86.3	75.9	0.937

P – values were < 0.001 for all comparisons.
PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; CFV: common femoral vein; FV: femoral vein; GSV: great saphenous vein; RT: right; LT: left.

Several studies have addressed markers of endothelial dysfunction designated by US, highlighting its prognostic value. Contradicting evidence exists on the difference of C- IMT between BD patients and healthy controls, (257–263), a discrepancy reflected in a meta – analysis, in which C – IMT was found to be increased in BD, however significant study heterogeneity was underlined.(263) Two studies positively correlated the duration of disease with IMT, one in femoral arteries in patients without known vascular involvement(259) and the other with C – IMT in patients with ocular BD. The latter study also showed that every 0.1mm increase of C – IMT independently enhances the probability of BD by 26 times.(264) One study investigated if the carotid extra – medial thickness (C – EMT), defined as the distance between the carotid media – adventitia interface and jugular intima – lumen interface, could provide prognostic information, however it was not significantly different between active BD and healthy subjects.(260) Serial carotid CDUS may reveal reduction of the C – IMT over long – term follow – up, an assumption that requires further research.(265)



Picture 7: Increased vein wall thickness in the posterior wall of a common femoral vein of a patient with Behcet's disease and prior thrombotic episodes (from: Seyahi E, Ucgul A, Cebi Olgun D, Ugurlu S, Akman C, Tutar O, et al. Aortic and coronary calcifications in Takayasu arteritis. Semin Arthritis Rheum. 2013 Aug;43(1):96–104.).(249)

Ozisler and Kaplanoglu, evaluated C – IMT and arterial stiffness in patients with BD by ultrasound radiofrequency (US RF) technology. US RF combines the morphological data acquired by US and the RF data of wall movement to provide less operator – dependent and more precise measurements. Stiffness indices were significantly higher in the vast majority, while all distensibility (DC) and compliance coefficients (CC) were significantly lower, signifying increased arterial stiffness in the patient group, although C – IMT was not

different. The non – significant difference of C – IMT could be attributed to the fact that arterial stiffness is detected earlier than an increase of C – IMT.(257) SWE also showed significantly higher CCA stiffness in BD patients compared to healthy controls, however no statistically significant difference was observed concerning neuro – BD (NBD).(262)

Brachial FMD was validated as significantly decreased in BD patients by several studies, (263,266,267) and some even correlated it negatively to disease activity and duration.(266,268) NID was found to be impaired by Merashli et al., despite the increased heterogeneity.(263) Last but not least, epicardial fat thickness (EFT) was suggested as a novel risk factor, due to its relation with visceral adipose tissue and pro – inflammatory cytokines. EFT was found by TTE to be significantly increased in BD.(264,268) Tasolar et al. also established a positive correlation of EFT with the activity and duration of BD.(268)

Cardiac manifestations consist a leading morbidity and mortality cause in BD and include pulmonary artery aneurysms (PAAs), intracardiac thrombus (ICT), aortic root aortitis and aneurysms, endomyocardial fibrosis, ventricular and valvular dysfunction, valvulitis and sporadically endocarditis, myocarditis, pericarditis, dilated cardiomyopathy, acute myocardial infarction, ventricular aneurysms and acute heart failure.(60,247,269,270) The incidence of cardiac involvement is not fully elucidated and therefore, despite their lethal outcomes, present data do not suggest TTE as a screening method in asymptomatic patients.(270)

The most frequent cardiac complications, up to almost 50% of BD patients, are aortitis with subsequent dilation and aneurysm of the aortic root. Aortitis may appear at TTE and TEE with hypoechoic mural thickening in the acute phase and increased echogenicity with stenotic segments due to fibrosis in later stages.(227,271) The sinus of Valsalva is the most common site of aneurysms and may be associated with other arterial aneurysms, such as CAAs. In the setting of an aortic root aneurysm, chronic or acute aortic regurgitation may arise.(269) Pathognomonic TTE findings for aortic regurgitation are prolapsed cusps, thinned, aneurysmal aortic leaflets, mobile mass – like lesions, echo free spaces within the annulus and annular dilation. Aortic regurgitation usually requires surgical root replacement accompanied by perioperative immunosuppressive therapy.(269,271) Surgery might be accompanied by early postoperative complications and regurgitation recurrence,(269,271) especially in patients not properly diagnosed pre – operatively.(272) Complications and mortality decreased after pathognomonic TTE findings were introduced, underlining the pivotal role of

echocardiography in the early diagnosis of BD.(273) Song et al. suggested a scoring system that consisted of pre – operative TEE findings and adequately predicted recurrence (69% sensitivity, 89% specificity).(274) Further research should investigate the appropriateness of echocardiography for the follow – up of post – operative complications of the aortic root.(275,276)

Coronary abnormalities are rarely reported.(277) Aneurysms, pseudoaneurysms and stenoses are the most common lesions and may be associated with acute coronary or other cardiac events.(271,277–281) A few cases of enlarged CAAs diagnosed by TTE and IVUS have been reported.(278,281–284). CDUS could be the cornerstone in assessing vessels that might be convenient as coronary by – pass grafts, in order to rule out vasculitic changes and reduce post – operative complications.(277)

BD is the most frequent cause of PAAs, most commonly affecting male patients. They usually are pseudoaneurysms with a mural thrombus of various sizes. They can be complicated by total thrombosis and subsequent pulmonary infarction or by bronchopulmonary fistulas or aneurysm rupture within a bronchus followed by pulmonary hemorrhage and hemoptysis. Only trunk and main pulmonary arteries are accessible by echocardiography. This location is common, although the right lower lobe vessels are affected most frequently. After implementation of therapy stabilization and deterioration may be evident by TTE.(269) In situ pulmonary artery thrombosis may be provoked by PAAs and pulmonary vasculitis,(247,285) while pulmonary embolism is not that typical, since thrombi are strongly adherent to the venous wall.(285)

Endothelial inflammation, ischemia and probably endomyocardial fibrosis contribute to ICT formation, another serious complication most frequently affecting young men around the Mediterranean Sea and in Middle East.(269,270) ICT can be adequately recognized sonographically as a heterogenous, moderate – to – high echogenic, moderately mobile material with a broad attachment within the ventricles. Thrombi may be multiple and typically involve the right ventricle (RV) and scarcely the LV and atria.(269,286) ICT may be misdiagnosed as cardiac tumor or endocardiac vegetations, however diagnosis is crucial, in order to avoid unnecessary interventions and prevent complications, such as valvular and myocardial dysfunction or thromboembolic events.(287) Spontaneous echocardiographic contrast (SEC) phenomenon, which represents a hyperechoic whirling pattern noticed

sonographically as “smoke”, can assist, since it appears only in thrombotic events.(287,288) In case of ICT at presentation, especially in young men from endemic areas, further diagnostic workup for BD should follow.(287) The extent of thrombosis may inflict on treatment: an isolated RV ICT may require only aggressive anti – inflammatory therapy, while a thrombosis extending to SVC and/or IVC further requires anti – coagulants and GC. It is important to discriminate between the two situations, since a high percentage of BD cases with ICT receiving anti – coagulants are complicated with fatal hemorrhagic events.(289) ICT typically shrinks and resolves during successful therapy and thus echocardiography may provide information about the adequacy of treatment.(286)

Clinically apparent systolic ventricular dysfunction is not typical in BD. Subclinical systolic dysfunction has been reported by several studies.(277,290) The GLS deduced by 2D – STE was significantly decreased in BD patients in comparison to healthy controls in many studies, despite normal TTE and TDI findings in some of them and no correlation to disease activity. (290–292) Yurdakul et al. utilized TDI variables, such as peak myocardial isovolumetric ventricular velocity and acceleration (IVV and IVA, respectively), as well as velocity vector imaging (VVI). IVV, IVA, as well as GS and GSR in VVI, were significantly lower in BD patients compared to healthy subjects for both ventricles, strongly suggesting systolic dysfunction.(267)

Diastolic dysfunction remains ambiguous, with more studies supporting the presence of LV diastolic dysfunction. Both deceleration time (DT) and isovolumetric relaxation time (IVRT) were found considerably longer in BD patients, the ratio of peak early to peak end diastolic velocity (E/A for CDUS and Em/Am for TDE) and the E/Em ratio was significantly increased in several studies (293–297) Hidayet et al. deduced lower GLS and global area strain (GAS) in BD patients using real time 3D – STE, particularly in patients with fragmented QRS complex in electrocardiogram (ECG). This implies that the low – cost ECG and TTE may effectively predict subclinical myocardial dysfunction early in the disease course.(298) Real – time 3D – STE revealed an almost universal augmentation of left atrium volume and systolic function to be a highly sensitive, indirect marker of LV diastolic dysfunction.(296) Atrial electromechanical delay (EMD) was also investigated by TDI in two studies, since structural and electrophysiological changes of the ventricular and atrial myocardium may provoke conduction disturbances.(293,297,299) Atrial conduction times were significantly prolonged

and positively correlated to inflammatory markers, disease activity and the risk of atrial fibrillation.(293,297,299)

Apart from vascular BD, US can provide valuable information on ocular, articular, gastrointestinal and CNS forms of BD. Akcar et al. found significantly decreased flow velocities in the retrobulbar vessels and ICA in patients with ocular BD in opposition to non – ocular BD and healthy controls. Nasal posterior ciliary arteries' flow velocities were significantly lower in active uveitis and could therefore be used in the follow-up of those patients.(300) In NBD, TCD was able to reveal low PSV and resistivity index (RI) in cerebral arteries and similar flow abnormalities were found in BD patients without neurological symptoms and MR findings, a property of TCD that may be helpful to pre – symptomatically recognize NBD. The imprint of such recognition is yet to be clarified.(301) Moreover, CDUS of the vertebral arteries revealed reduced total flow volume (TFV) and flow velocities in BD patients. Mean velocity (MV) was significantly lower in the NBD patients and since it is considered a more accurate marker of tissue perfusion, its early detection might facilitate diagnosis and prognosis of NBD.(302) US was used to diagnose erosive metacarpophalangeal joint arthritis and subclinical enthesitis, while it may allow the differential diagnosis between BD and other causes of inflammatory arthritis and osteoarthritis.(303–305) Last but not least, in cases of abdominal aortic stent placement ovarian arterial supply might be irreversibly impaired causing infertility and early menopause. CDUS might have a role in assessing ovarian vasculature post – operatively.(306)

CTA/CTV is preferred to evaluate deep vessels for aortitis or DVT, while CT pulmonary angiography (CTPA) is the golden standard for pulmonary arteries (101) and CTCA for CALs.(60) FDG – PET and MRI/MRA are also useful in imaging aortitis.(60,307) CMRI may be able to distinguish ICT from cardiac tumors, mainly based on the absence of late gadolinium enhancement of ICT. Although rim enhancement of endocardiac vegetation has been reported, ICT and vegetations may be extremely hard to discern.(308,309) Non – contrast enhanced MR venography (MRV) was superior in assessing the extent of collateral vessels in lower limbs compared to CDUS, a property that may facilitate therapeutic decisions.(310)

3.4.2. Cogan's syndrome (CS)

CS is a rare disorder with primary ocular and audio-vestibular disturbances.(311) CS may encompass vasculitis of medium – and large – size vessels, including aortitis, aortic and mitral valvulitis and insufficiency, aneurysms, CALs, thrombosis and others.(38,60,311) The role of imaging in CS is not well – established and typically follows the imaging patterns of the rest vasculitides.(60,311–313)

4. Discussion - Conclusions

After meticulously searching and reviewing existing literature, one can confidently conclude that the contribution of US in the diagnosis, prognosis and follow – up of systemic vasculitis has been and remains fundamental. Apart from entrenched applications, such as Color and Pulsed Wave Doppler, novel possibilities arise with the introduction of contrast – enhanced ultrasound, calibrated integrated backscatter analysis and, especially regarding echocardiography, Speckle Tracking Echocardiography and Tissue Doppler Imaging. The advantages and disadvantages of US are well – established, the implementation however of more modern techniques can optimize the US potential, particularly in assessing disease activity and success of treatment, two domains for which the role of imaging remains vague.

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