The new frontiers of ultrasound in the complex world of vasculitides and scleroderma

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Abstract

Modern US equipment allows rheumatologists to directly visualize vascular, musculoskeletal, dermal and internal organ structure. In multisystemic and challenging diseases such as vasculitides and scleroderma, where new outcome measures are required in both clinical practice and trials, US measures promise reproducible and objective scores of disease activity and extension. US reveals early pathognonomic abnormalities and may help start early treatment.

Key words: ultrasound, systemic sclerosis, vasculitis, heart, vascular, musculoskeletal, skin, lung.

Background

In the past decade, US has been employed in the investigation of organ involvement in SSc and vasculitides. US is non-invasive, largely available, low cost, does not employ ionizing radiation [1], and could be employed in diagnosis, follow-up and prognostic stratification. Along with well-established US applications, such as echocardiography as a screening test for pulmonary hypertension (PH), new US techniques have recently entered the clinical arena. In this review, we briefly summarize some of the US applications in SSc and vasculitides.

Cardiac involvement

Cardiac involvement, which is very frequent in SSc and vasculitis, leads to a fatal outcome in a substantial percentage of patients. It is usually asymptomatic, however, and by the time it becomes clinically evident extensive damage to the myocardium has already occurred and treatment is rarely effective. In SSc, clinical evidence of cardiac involvement may be found in 20–25% of patients, while at post-mortem examination the heart is affected in up to 80% of patients. The endocardium, myocardium and pericardium, separately or concomitantly, can be affected. Echocardiography is crucial because it makes it possible to detect not only cardiac abnormalities responsible for the symptoms, but subclinical alterations as well. Echocardiography is routinely employed in SSc for the assessment of PH. Although right heart catheterization is necessary for diagnostic confirmation, US is a routine screening tool for this condition. Primary myocardial involvement, characterized by vascular alterations and fibrosis that lead to ischaemia, arrhythmias and myocardial dysfunction, could be found in SSc patients independently of PH and significant renal or pulmonary involvement. Echocardiography is also routinely employed in vasculitis, to assess valvular abnormalities, hypertension-related damage, sequelae of vasculitis-related ischaemia and, of course, systolic and diastolic function. A main limitation of echocardiography is that ejection fraction is often the only parameter provided to evaluate cardiac function, whereas more subtle myocardial dysfunction cannot be assessed.

Several studies have recently proposed novel echocardiographic techniques, such as Doppler tissue imaging (DTI) and speckle tracking-derived strain analysis, as effective tools for early detection of right and left ventricular systolic and diastolic dysfunction [2]. All studies employing these techniques consistently showed significant alterations of cardiac mechanics in SSc patients compared with controls [2, 3]. These abnormalities are independent of the presence of PH and are often detectable in asymptomatic patients with otherwise normal hearts on echocardiogram [3]. Left ventricular speckle tracking has also been reported as decreased during the acute phase of Kawasaki disease, probably due to myocardial swelling.

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caused by myocarditis. Although very promising, intervendor variability is a significant limitation of speckle tracking- and DTI-derived strain analysis; moreover, normal cut-off values are still lacking. Pulsed-wave DTI, with specific reference values, is the sole technique that has gained clinical relevance.

Three-dimensional echocardiography is another emerging US technique that could detect very early abnormalities of right and left ventricular function and assess left atrial volume. Nevertheless, its role in SSc and vasculitis patients is still to be determined.

Myocardial fibrosis, the final pathological hallmark of cardiac involvement in these patients, is reported in 50–80% of cases at necropsy. It can be imaged on a transthoracic echocardiograph by proprietary integrated backscatter, since collagen deposition determines increased myocardial echodensity. However, in spite of the promising experimental and initial clinical results [4], this technique, being technically demanding, subject to artefacts and dependent on good image quality, is not widely employed. Myocardial late enhancement detected by cardiac MRI is the current non-invasive gold standard for myocardial fibrosis assessment. Its presence has been reported in a relatively high percentage of both SSc and vasculitis patients. Future studies are needed to define the clinical additive value of cardiac MRI when combined with echocardiography.

A very promising US tool in vasculitis (especially in Kawasaki disease) is coronary artery US imaging, which showed comparable accuracy to CT in the evaluation of proximal coronary artery. On the other hand, CT provides more information for distal segments, although with a non-negligible radiation burden [5].

Vascular involvement

In large-vessel vasculitides, inflamed artery walls are usually homogeneously thickened: the wall swelling is circumferential and differs from atherosclerotic lesions, which are asymmetric and inhomogeneous with calcifications. US reveals homogeneous vascular wall swelling, determines the grade of stenosis and the presence of retrograde flow or occlusion.

Linear probes with a frequency of at least 10 MHz are used to examine the common superficial temporal artery. Typical features are the hypoechoic wall swelling, turbulent flow and acute arterial occlusions (Fig. 1) [6]. Other arteries, such as the occipital and facial arteries, may be examined depending on symptoms. Two meta-analyses found sensitivities of temporal artery US for the presence of wall swelling, stenosis and/or occlusion in relation to the clinical diagnosis of temporal arteritis of 75% and 86%, and specificities of 83% and 96%, respectively [7, 8]. A third meta-analysis described a sensitivity of 68% and a specificity of 91% for the presence of wall swelling alone [9]. Diagnostic accuracy varies greatly between studies and centres and depends on the experience of the sonographer, the quality of equipment and the use of duplex ultrasonography.

Axillary arteritis is common in GCA. An intima–media complex of >=1.0 mm is suspicious for large-vessel GCA. The diagnosis is definite if the homogeneous wall swelling is >=1.5 mm [10]. The subclavian and common carotid arteries may also be involved. Temporal artery histology or US is positive in only ~60% of cases. Nearly 50% of patients with newly diagnosed GCA have large-vessel GCA in terms of proximal arm vasculitis. Experienced centres have replaced temporal artery biopsies in patients with typical US findings. Furthermore, axillary artery US results in a greater number of patients diagnosed with large-vessel vasculitis and helps in starting effective treatment early in the course of the disease. The arteries most commonly involved in Takayasu’s arteritis are the subclavian, common carotid and vertebral arteries [10].

Kawasaki’s disease is an acute self-limiting medium-sized vessel vasculitis of childhood. It is characterized by fever, polymorphous exanthema, membranous desquamation of fingertips, conjunctivitis, mucositis and cervical lymphadenopathy. Aneurysms occur in coronary arteries in ~25% of untreated cases. Transthoracic echocardiography reveals these aneurysms with a sensitivity of 95% and a specificity of 99% [11].

Application of colour Doppler US for the evaluation of medium- and large-size vessels and the detection of intima–media thickness as a marker of accelerated atherosclerosis is well known. Microvascular assessment of digital arteries in SSc patients has been elegantly described by Schmidt et al. [12] as delineating a smaller artery lumen, reduced pulsation and thickened, slightly hyperechoic artery walls in SSc digital arteries. It seems that US can even help differentiate between primary and secondary RP [12], thus enabling us to distinguish severe from mild disease, and acute from chronic vascular occlusion. US depicts the same anatomical structures as finger angiography. However, it is cheaper, faster and non-invasive.

US may also detect early renal vascular damage in SSc patients without clinical evidence of nephropathy. Doppler indices of renal vascular resistance are closely related to the duration of the disease, age and plasma renin activity and they make possible early detection of high risk of scleroderma renal crisis [13].

Pulmonary involvement

Assessment of the lung has long been considered off-limits for US, since US energy is rapidly dissipated by air. However, this is true in a normal, aerated lung, where there is no acoustic mismatch that can reflect the US beam. The presence of structures other than air, such as exudate, transudate, blood, cells or fibrotic tissue, creates an acoustic mismatch in the lung and opens the previously locked pulmonary acoustic window.

In recent years, lung US (LUS) has emerged as a new, promising technique for the evaluation of many pulmonary abnormalities. Interstitial lung disease (ILD) can be imaged by the presence of B-lines (also called US lung comets). B-lines are a sonographic sign of interstitial syndrome, originating from thickened interlobular septa. They can
be easily assessed by either a sector/cardiac, convex/abdominal or a linear/vascular probe. B-lines have been reported in different forms of diffuse parenchymal lung disease, including pulmonary fibrosis. More recently, the validity of LUS has been demonstrated by comparing this new technique with CT signs of pulmonary fibrosis in SSc patients (Fig. 2) [14]. There is good correlation between B-line number and the semi-quantitative Warrick score ($r = 0.72, P < 0.001$) [10]. Moreover, it seems very promising as a screening tool in patients at high risk of developing ILD [15]. The utility of LUS in patients with connective tissue disorders has been further confirmed by employing a simplified method, in order to maximize efficiency and underline its potential role in routine high-volume clinical practice [16].

The clinical impact of LUS in the management of ILD could be significant, since LUS is inexpensive, largely available, has a very short learning curve and can be performed at the bedside. In the future, LUS in SSc-related ILD might help distinguish established pulmonary fibrosis from alveolitis. So far it is not possible, since both conditions may generate B-lines.

Musculoskeletal involvement

Musculoskeletal involvement is a major cause of disability in SSc. Most common signs and symptoms of joint and tendon involvement in SSc are arthralgias, reduced range of motion and flexion contractures of joints. Clinical findings typical of inflammatory arthritis are rare in SSc patients with arthralgias. Usually, no structural damage can be found on X-rays. Only a few published studies have assessed the sensitivity of musculoskeletal US in detecting synovitis and erosions in SSc. Cuomo et al. [17] reported that US examination detected a significantly higher prevalence of joint pathology compared with clinical findings in 45 patients with SSc. Effusion and/or synovial proliferation were found in 26 of 45 patients, while joint tenderness and/or swelling only in 15 of 45 ($P < 0.03$). The same study showed that US indicated a significantly higher number of joints with osteophytes than X-rays (59% vs 27%; $P < 0.005$). A pilot study using a 17 MHz US transducer to evaluate hand disability in scleroderma concluded that A1 pulley thickness, measured by US, correlates with hand mobility and disease duration [18]. Another study found strict association of tendon friction rubs with increased thickness of the retinacula, suggesting that this was the morphological basis for this clinical finding [19].

Skin involvement

Three cutaneous phases of the disease are recognized in SSc: oedematous, fibrotic and atrophic. The capacity to differentiate between these phases is crucial to tailor the correct therapeutic strategy for the patient. Usually, skin involvement is assessed by the modified Rodnan Skin Score (mRSS). However, an objective and reproducible technique that can differentiate oedema from fibrosis is still lacking in clinical practice. Despite excellent spatial resolution of high-frequency US and good interclass and
intraclass agreement in skin evaluation [20], few reports are available about its employment in SSc.

In the early phase of the disease, US can depict a dermal thickening due to oedema, and in the late phase a reduction in thickness with the evolution of fibrosis and atrophy. Dermal thickness of the dorsal aspect of the fingers measured by US did not correlate with the local mRSS, possibly meaning that mRSS is not actually measuring dermal thickness. However, a correlation with the total mRSS was found, suggesting that skin US can provide information about disease severity [20]. A significantly higher dermal thickness was found in SSc patients in comparison with the controls, both clinically involved and uninvolved areas. US showed thicker dermis in dcsSc patients, compared with lcsSc patients, except for the proximal phalanx, confirming the high sensitivity of skin US with respect to clinical evaluation [20, 21].

Another important parameter is dermal echogenicity. Longitudinal studies reported thickened and hypoechoic dermis in the early oedematous phase. Evolution towards the fibrotic and atrophic phases was associated with a progressive reduction in thickness and increased echogenicity. Nevertheless, not all the authors were able to recognize an association between different echogenicity and oedema or fibrosis [21].

Recently, US elastography has been used to evaluate the skin of the forearm of SSc patients. Less elastic dermis was found in SSc patients compared with controls, both involved and uninvolved areas. This confirmed the very high sensitivity of US elastography, which made it a very promising tool for the future use [22].

Conclusions
US is a non-invasive, low cost, rapid and repeatable method. It provides a very precise assessment of organ involvement in SSc and vasculitides. Despite significant improvement of US machines, some needs are still unmet, such as the differentiation between oedema and fibrosis in skin and lung, the evaluation of coronary arteries and the evaluation of myocardial oedema. Further data are needed to evaluate the prognostic power of US findings.

Rheumatology key messages
• US plays a crucial role in assessment of organ involvement in SSc and vasculitides.
• Further studies are needed to define the role of US in decisions about therapy and prognosis of SSc and vasculitides.

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