Development of a colour Doppler ultrasound scoring system in patients of Takayasu’s arteritis and its correlation with clinical activity score (ITAS 2010)

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Abstract

Objectives. The objectives of this study were to develop a scoring system with colour Doppler ultrasound (CDUS) in patients with Takayasu’s arteritis, to correlate the CDUS score with the Indian Takayasu’s Activity Score (ITAS) and to assess the degree of agreement between CDUS and angiogram in the diagnosis of Takayasu’s arteritis.

Methods. Nineteen angiographically confirmed Takayasu’s arteritis patients fulfilling three or more of the 1990 ACR criteria were evaluated. Their ITASs were recorded. A CDUS scoring system, CDUS-Kolkata (CDUS-K), was devised based on the presence of stenosis and altered flow patterns. It was then correlated with the ITAS. An inter-rater agreement analysis was done between the CDUS-K scores and angiographic scores in selected arterial sites.

Results. We found a significant degree of correlation between the ITAS and the CDUS-K score ($r = 0.7144$, 95% CI 0.3852, 0.8823, $P = 0.0006$). A high degree of correlation was found between the CDUS-K and angiographic scores in the selected arterial sites ($k$-value = 0.725 on inter-rater agreement analysis).

Conclusion. CDUS imaging may be used as an objective tool for assessing disease severity in Takayasu’s arteritis. Development of a CDUS-K scoring system would be a supplementary tool to clinical scoring and the ITAS. CDUS imaging could be a cost-effective, non-invasive and reliable substitute for angiogram, especially for follow-up in Takayasu’s arteritis patients.

Key words: Takayasu’s arteritis, Indian Takayasu’s Activity Score, colour Doppler ultrasound scoring.

Introduction

Takayasu’s arteritis is a large vessel vasculitis of unknown aetiology that mainly affects the aorta and its major branches along with pulmonary and coronary arteries. It is more common in the eastern part of the globe [1, 2]. It is more prevalent among younger females, with a female: male ratio of 8:1 in Japan as compared with 1.58:1 in India [3]. It is considered the most common cause of renovascular hypertension in India [4]. This is due to involvement of the abdominal aorta and renal arteries [3]. The pattern of disease expression differs markedly from that of small or medium vessel vasculitides. The BVAS or Vasculitis Damage Index (VDI), which are indices designed for use in ANCA-associated vasculitis, are not suitable for use in Takayasu’s arteritis, as it involves a different pattern of clinical disease [5]. The Indian Rheumatology Association Vasculitis Group (IRAVAS) has developed an index of disease activity severity and extent that is being used for study of the disease, the Indian Takayasu’s Activity Score (ITAS 2010) (see the supplementary data available at Rheumatology Online) [2, 5]. Combining ITAS with imaging would allow us to develop a more comprehensive assessment tool. Angiogram (conventional or digital subtraction) is considered the gold standard for diagnosing Takayasu’s arteritis, but it is an invasive and costly procedure with risks of radiation- and contrast material-induced hazards [6, 7], hence it is difficult to repeat. So there are efforts to replace it with other imaging modalities such as US or CT angiography and PET imaging [7]. Colour Doppler ultrasound (CDUS) is a safe, non-invasive, repeatable and fast tool for assessing vessel anatomy and hemodynamic changes within a
vessel [8, 9]. CDUS can diagnose Takayasu’s arteritis accurately and monitor disease progression and the effects of therapy. Serial CDUS studies can reduce the need for angiographic follow-up [10]. Not only that, CDUS can also identify the affected arteries that are yet to be visualized in angiography [11, 12]. Despite such advantages of CDUS, there is no widely accepted CDUS scoring system in Takayasu’s arteritis to correlate with the disease burden. Our study was intended to develop a rational, quantitative CDUS scoring system, to study the association between the CDUS score and ITAS and to assess the degree of agreement between CDUS and angiogram in the diagnosis of Takayasu’s arteritis. The Doppler score that was developed is called the CDUS-Kolkata (CDUS-K) score.

The objectives are to use CDUS in assessing the extent of vascular involvement in Takayasu’s arteritis, develop a quantitative CDUS scoring system for the vascular involvement, study the association between the Doppler score and ITAS and assess the degree of agreement between CDUS and angiogram.

Materials and methods

The study comprised 19 angiographically proven Takayasu’s arteritis patients who visited the rheumatology outpatient clinic of the Institute of Post-Graduate Medical Education and Research (IPGME&R) Kolkata between July and December 2012. Angiogram and CDUS were done within 2 weeks of each other and no medical or surgical intervention was done in between. Necessary approval from the IPGME&R Oversight Committee (institutional ethics committee) and informed patient consent were obtained.

Angiographically proven patients fulfilling three or more of the 1990 ACR classification criteria were included. Patients with coarctation of the aorta; isolated bilateral renal artery stenosis; eccentric, localized and non-homogeneous wall thickening, which is more suggestive of atherosclerosis; and biphasic flow in common carotids and radial arteries without any changes in peak systolic velocities, as they are considered as normal variants, were excluded.

The ITAS 2010 score sheet was completed by a physician on the day of the patient’s first visit. The score sheet incorporates six domains: systemic symptoms, gastrointestinal, genito-urinary, CNS symptoms, renal (systolic and diastolic hypertension) and cardiovascular findings in the form of bruit, pulse inequality and pulse loss. Diastolic hypertension, stroke, bruit, pulse inequality, new loss of pulse, claudication and carotidopathy are ascribed 2 points each and the rest are allotted 1 point each. The maximum ITAS is 51.

The Doppler studies were done by a radiologist. It was always the same radiologist throughout the study. The study is a single-blind study, as the radiologist who did the Doppler studies was unaware of the ITAS and angiogram reports. Approximately 50 min–1 h were required to scan all 19 vascular regions in one patient. The CDUS was repeated by the same radiologist and by another radiologist, without seeing the previous report, within 1 week, for any intra-observer and inter-observer variation, respectively. Both image acquisition and reading were done by the second radiologist. The intra- and inter-observer errors for the CDUS findings were assessed in all cases. ESaote (Italy) MyLab25Gold was used for the CDUS. The angle of insonation was kept at 60° for determining flow characteristics with CDUS. For assessing vascular morphology, the probe was kept as parallel as possible to the vessel wall. An electronically focussed linear transducer (frequency range 8–12 MHz) was used for superficial arteries and a curvilinear transducer (frequency 3.5 MHz) was used for the abdominal aorta and renal arteries. Evaluated arteries were those that are included in the ITAS, i.e. common carotid artery (CCA), subclavian, brachial, radial, abdominal aorta, renal, common femoral, popliteal, posterior tibial and arteria dorsalis pedis. In B-mode the intima media thickness (IMT), visible stenosis (with its percentage) and aneurysms were evaluated, whereas peak systolic velocity, pulsatility index and spectral waveform patterns were evaluated by duplex sonogram. The cut-off level for IMT of the carotid arteries was taken as 0.8 mm. IMT was not assessed in the other arteries due to the lack of standardized IMT values for them.

Stenosis has been identified by direct visualization in B-mode along with changes in the peak systolic velocity, pulsatility index in duplex studies and/or aliasing in colour flow imaging. The term aliasing refers to the bright turbulent flow pattern appearing in CDUS often relating to vascular stenosis. A triphasic waveform (Fig. 1) is considered a normal pattern seen in high-resistance peripheral arteries, i.e. a non-continuous flow pattern, with antegrade systolic flow followed by early retrograde diastolic flow that usually ends with late antegrade diastolic flow. Loss or diminution of the late antegrade diastolic component is taken as a biphasic waveform (Fig. 2) usually seen distal to an obstruction. Monophasic flow (Fig. 3), characterized by an almost continuous flow pattern without any systolic or diastolic variations, is seen distal to a severe obstruction. We developed a scoring system for the visualized CDUS changes, such that 1 point was ascribed to stenosis, 1 to a biphasic flow pattern, 1 for a monophasic flow pattern, and 0 to a triphasic flow or biphasic flow in CCAs, internal arteries and radial arteries without any changes in peak systolic velocities or proximal stenosis. Thus the maximum score for one particular artery is 1, whereas the minimum is 0 and the total score is 19. The maximum score for any artery is 1 because one artery can show only one of the three abnormalities, i.e. stenosis, biphasic or monophasic flow.

For the evaluation of renal arteries, renal size was estimated. The main renal artery was evaluated for the presence of stenosis and changes in peak systolic velocities. Interlobular arteries were then studied for changes in acceleration time and resistance index. These parameters are very informative for diagnosing renal artery stenosis.
The CDUS-K scores were compared with the ITAS to determine the degree of correlation between them. A correlation study was also done for the two CDUS-K scores of the same radiologist and another was done for the scores of the two radiologists.

To assess the degree of agreement between the two modalities of imaging, we selected four overlapping arterial domains, where both CDUS and angiography can document stenosis. The selected arterial territories were the bilateral common carotid, subclavian, renal arteries and abdominal aorta (a total of seven). One point was assigned to each diseased artery. The peripheral arteries were not taken into account here, as angiograms cannot give any detail of their flow character.

The data were summarized by routine descriptive statistics, i.e. mean and s.d. for numerical variables and count and percentage for categorical variables. Disease duration, being a non-parametric variable, was summarized by median and interquartile range (IQR). An approximately linear association between the ITAS and CDUS-K score was seen in a scatter plot and Pearson’s correlation coefficient $r$ was calculated. A simple linear regression analysis was also attempted to obtain a regression equation linking these two variables. Inter-rater agreement

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**Fig. 1** Triphasic waveform.

(a) Schematic representation. (b) CDUS image.

**Fig. 2** Biphasic waveform.

(a) Schematic representation. (b) CDUS image.
between the angiographic assessment and CDUS with respect to score categories was assessed by calculating Cohen’s κ (unrated). Key statistics are expressed as the 95% CI and \( P < 0.05 \) is regarded as statistically significant. Medcalc software (Mariakerke, Belgium) was used for statistical analysis.

**Results**

Of the 19 patients, 8 (42%) each were in the age groups 11–15 years and 21–30 years, 2 (11%) were between 31 and 40 years, and 1 (5%) was >40 years of age. The mean age of the patients was 22.8 years, with the minimum age being 12 years and the maximum age 43 years. Sixteen (84%) patients were female and 3 (16%) were male. The median disease duration was 11 (7.75) months. Of these 19 patients, 5 presented with systemic symptoms, most commonly headache, 14 with cardiovascular symptoms and 6 with neurological symptoms, with few patients having overlapping symptoms. Among the 14 patients who presented with cardiovascular system manifestations, 8 (57%) presented with limb claudication and 3 (21.5%) each presented with angina and hypertensive heart failure. Eight (44%) of the 19 patients were hypertensive. Of these, six had renal artery stenosis, one had supra renal aortic stenosis and one was without any stenosis. Among the CNS manifestations, syncope was the presentation in 3 (50%) patients, stroke in 2 (33%) and blurring of vision in 1 (17%) patient, which was due to retinal detachment. The ESR values (in millimetres in the first hour) of the patients at the time of CDUS were recorded (Table 1). Angiographic findings of our 19 patients showed that 16 (42%) had subclavian artery stenosis, 8 (21%) had carotid artery stenosis, 6 (16%) each had abdominal aorta and renal artery stenoses and only 2 (5%) had descending thoracic aorta stenosis. An inter-rater agreement analysis was also done to compare CDUS with the gold standard investigation, angiogram. Overall, we got a high kappa value, which signifies a very good degree of agreement between these two imaging modalities. Kappa values were the following: carotids, 0.905; subclavian, 0.638; renal, 0.882; abdominal aorta, 0.872; overall, 0.725 (Table 2). Except for the subclavian artery, CDUS-K values of the other arteries are in good agreement with angiogram values. CDUS could detect 17 of the 21 angiogram-proven subclavian lesions, 6 of 8 renal lesions and 5 of 6 abdominal aorta lesions. CDUS could detect one clinically evident carotid lesion that was undetected by angiogram. We had two patients with thoracic aorta involvement in angiography. We could not detect those lesions with CDUS, but we did not miss the diagnosis of Takayasu’s arteritis, because in both of them there were additional stenotic sites in other arteries and we could also accurately pick up the distal abnormal waveforms caused by the proximal thoracic aorta stenosis.

On analysing the CDUS-K score and ITAS (Table 3) we found a significant degree of correlation between the two (correlation coefficient \( r = 0.714, \) 95% CI 0.385, 0.882, 0.725).
angiographic scoring and CDUS-K scoring et al. and progression in Takayasu’s arteritis, Direskeneli through the ITAS. In a study assessing disease activity patients and showed improvement in disease activity effective immunosuppressant in 20 Takayasu’s arteritis 2000 www.rheumatology.oxfordjournals.org Goel et al. vessel arteritis and used the ITAS to follow-up patients. et al. [13] assessed the efficacy of tocilizumab in large tion and response to therapy and prognosis. Salvarani of severity, detection of flares and assessment of selec- tion of the number of angiographically active disease. The reproducibility in group use variability equivalent to the BVAS [5]. The wide range of the ITAS in Takayasu’s arteritis closely reflects the number of cardiovascular system items and thus allows for grading of severity, detection of flares and assessment of selection and response to therapy and prognosis. Salvarani et al. [13] assessed the efficacy of tocilizumab in large vessel arteritis and used the ITAS to follow-up patients. Goel et al. [14] evaluated the use of mycophenolate as an effective immunosuppressant in 20 Takayasu’s arteritis patients and showed improvement in disease activity through the ITAS. In a study assessing disease activity and progression in Takayasu’s arteritis, Direskeneli et al. [15] also found that the ITAS seems to be helpful in assessing disease activity and damage in Takayasu’s arteritis.

**TABLE 2** Inter-rater agreement assessment of angiographic scoring and CDUS-K scoring

<table>
<thead>
<tr>
<th>Individual arteries</th>
<th>( k )-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid</td>
<td>0.905</td>
<td>0.782, 1.000</td>
</tr>
<tr>
<td>Subclavian</td>
<td>0.638</td>
<td>0.324, 0.952</td>
</tr>
<tr>
<td>Renal</td>
<td>0.882</td>
<td>0.660, 1.000</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>0.872</td>
<td>0.631, 1.000</td>
</tr>
<tr>
<td>Four sites together</td>
<td>0.725</td>
<td>0.488, 0.961</td>
</tr>
</tbody>
</table>

\( P = 0.001 \). The above finding was also supported by regression analysis \( (R^2 = 0.510, P = 0.001) \) (Fig. 4).

There was no intra-observer variation in CDUS-K scor- ing. Reassessment CDUS-K scoring, done by another radiologist, also correlated well with the primary scores \( (P < 0.001, r = 0.986) \). The results varied in only four arterial sites, two of which were due to variations in visualization of renal artery stenosis, one due to differences in docu- mentation of a subclavian artery stenosis and the last due to triphasic flow seen by the second radiologist vs biphasic flow seen by the first radiologist in a femoral artery distal to an abdominal aorta stenosis.

In two of our patients we found a diffuse and homoge- neous increase of the carotid IMT (mean carotid IMT of the right CCA of patient 1 was 1.1 mm and that of patient 2 was 1.2 mm; mean carotid IMT is the average of three values taken from the proximal, mid and distal portions of the CCA) without any demonstrable increase in peak systolic velocity or pulsatility indices. These were neither assigned any score in our CDUS-K scoring system nor documented clinically or angiographically, but were sug- gestive of early vessel wall involvement of Takayasu’s arteritis.

**Discussion**

The ITAS 2010 is convenient for clinicians and has been extensively evaluated by the IRAVAS. The convergent val- idity of the ITAS showed a significant correlation with the BVAS, particularly in patients with recent onset and clin- ically active disease. The reproducibility in group use scoring live patients was excellent, with inter-rater vari- ability equivalent to the BVAS [5]. The wide range of the ITAS in Takayasu’s arteritis closely reflects the number of vascular changes in Takayasu’s arteritis patients and documented clinically or angiographically, but was sug- gestive of early vessel wall involvement of Takayasu’s arteritis.

Angiography has been accepted as the procedure of choice for the diagnosis of Takayasu’s arteritis, with the added advantage of performing interventional procedures like angioplasty or stenting of diseased vessels. It may be difficult to perform in patients with long-segment stenoses and it cannot differentiate vascular narrowing due to acute mural inflammation from stenosis due to chronic trans- mural fibrosis. Concurrently there is an increased fre- quency of ischemic complications of angiography in Takayasu’s arteritis patients [6]. Importantly, angiography does not detect changes in vascular wall architecture and gives only luminal data, so there is the possibility that early vessel wall thickening in Takayasu’s arteritis may give a false negative result in angiography [7]. It has limited value in follow-up of Takayasu’s arteritis patients as well [7]. Early changes in the vessel wall before the occurrence of clinically significant stenosis can be picked up by both CT and MR angiogram [16, 17]. MR angiograms are costly, but have the advantages of being free from the hazards of ionizing radiation and contrast material in- jection that are seen with CT angiogram [6, 18]. There is the possibility of inaccurate results in MR angiogram at vascular branch points with a false impression of stenosis or accentuation of the degree of stenosis [6]. CT angiog- raphy is also not feasible for follow-ups, due to radiation hazards [6].

CDUS is a non-invasive, cost-effective, radiation-free modality for assessing peripheral vessels without any need for contrast material. Sonography reveals homogeneous circumferential thickening of affected ves- sels, vascular occlusions and dilatations and changes in flow velocity and flow pattern in stenotic and post-stenotic segments in Takayasu’s arteritis patients [11, 19]. It can also be helpful in detecting submillimetre changes in wall thickness of the carotid arteries and in differentiating Takayasu’s arteritis from atherosclerotic disease based on minimal plaque content, concentric and long segmental involvement and the location of the lesion [18].

Schmidt et al. [8] showed that sonography can detect early Takayasu’s arteritis in the carotid and subclavian arteries and is effective in monitoring and therapeutic planning [8]. CDUS has an advantage over angiography in estimating stenosis of the carotid artery in Takayasu’s arteritis [20]. Pipitone et al. [21] showed that abnormal findings on US were noted in 83% of the CCAs, whereas only 39% of the CCAs showed angiographically detect- able alterations. The drawbacks of CDUS are poor visu- alization of the root of the great vessels and abdominal vasculature due to bowel gas and technical limitations in obese patients, and it is not applicable for imaging the thoracic aorta.

We adopted a CDUS-K scoring system for assessing vascular changes in Takayasu’s arteritis patients and compared it with the ITAS. We found that our CDUS-K score correlated significantly with the ITAS. As most of these arteries are easily accessible by CDUS, changes in flow velocities and flow patterns in them as a result of proximal occlusion are also reflected in CDUS more.
accurately than angiogram, resulting in good correlation between the CDUS-K score and ITAS. That means CDUS can be used as an objective indicator of clinical disease activity and may become supplementary for a disease activity scoring system.

There is a very good degree of agreement between CDUS and angiogram in our study when we compared them for detecting lesions in overlapping arterial territories. That means CDUS can be used as a supplementary imaging modality with angiogram in Takayasu’s arteritis, especially for follow-up purposes. However, large-scale serial follow-up studies with CDUS in Takayasu’s arteritis are necessary to verify that CDUS can be used as a substitute for angiography.

The reason for the decreased rate of detection of the subclavian artery can be explained by the anatomically echo-poor location of the artery and its proximity to the rib cage and pulmonary air. The decreased rate of detection of renal artery stenosis may be due to a failure to trace the whole segment of renal artery due to bowel gas. Previous prospective comparison of CDUS and MR angiography in patients with renal artery stenosis revealed equal specificity (93% each) of CDUS and MR angiography in diagnosing stenoses, the degree of which was at least 50%, but MR angiography has a better sensitivity in depicting renal arterial stenoses [22].

### Rheumatology key messages

- CDUS may be used as an objective tool for assessing disease activity in Takayasu’s arteritis.
- The CDUS-Kolkata scoring system is likely to be a supplementary tool to the ITAS (clinical scoring).
- CDUS can be a useful, cost-effective substitute for angiography in the follow-up of Takayasu’s arteritis.

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### Supplementary data

Supplementary data are available at *Rheumatology* Online.

### References