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FULL PAPER

Perfusion-based assessment of disease activity in untreated and treated patients with aortitis and chronic periaortitis: correlation with CT morphological, clinical and serological data

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Objective: To evaluate the role of perfusion-based assessment of inflammatory activity in patients with treated and untreated aortitis and chronic periaortitis as compared with clinical and serological markers.

Methods: 35 patients (20 females; median age 66 years) with (peri) aortitis were retrospectively evaluated. All patients had clinical symptoms prompting at the time of imaging. All patients first underwent whole-body contrast-enhanced CT and subsequently segmental volume perfusion CT for assessment of the degree of vascularization of (peri) aortitis as a surrogate marker for inflammatory activity. Blood flow, blood volume, volume transfer constant (k -trans), time to peak and mean transit time were determined. The thickness of the increased connective tissue formation was measured. Perfusion data were correlated with clinical symptoms and acute-phase inflammatory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and leukocyte number.

Results: 21 of 35 patients were untreated and 14 of 35 had previous/ongoing immunosuppression. The interobserver agreement was good ($\kappa = 0.78$) for all perfusion parameters. Average values of perfusion parameters were higher in untreated patients but remained abnormally elevated in treated patients as well. Perfusion data and ESR and CRP correlated well both in aortitis ($p < 0.05$) and in periaortitis ($p < 0.05$). In periaortitis, perfusion parameters agreed well with ESR and CRP values ($p < 0.05$) only in untreated patients.

Conclusion: Perfusion CT parameters in untreated aortitis and chronic periaortitis correlate well with serological markers with respect to disease activity assessment. However, in treated periaortitis, correlations were weak, suggesting an increased role for (perfusion-based) imaging.

Advances in knowledge: Volume perfusion CT may be used for diagnosis of aortitis/periaortitis.

INTRODUCTION

Aortitis and periaortitis are all-encompassing terms ascribed to inflammation of the aortic wall or its vicinity. Their clinical presentations vary markedly ranging from unspecific back or abdominal pain with or without fever, over weight loss and night sweats, up to symptoms related to secondary complications such as luminal stenosis, occlusion, aneurysm formation with secondary thrombosis or encasement of adjacent anatomical structures such as the ureters.¹ For the classical large vessel vasculitis, established diagnostic criteria exist but no definite criteria exist for its idiopathic variants.^{2–4} Patients with inflammatory aortic aneurysms (IAAs), perianeurysmal aortitis or Ormond's disease usually present with elevated inflammatory markers.^{5,6} Aortitis and periaortitis of autoimmune, infectious or other

causes are accompanied by inflammation, which is among others, e.g. soft tissue swelling or increased metabolism, characterized by increased angiogenesis owing to high levels of released vasoactive substances. Nevertheless, all these disorders undergo different phases of inflammatory activity mostly in form of flare-ups and degenerate later to more or less active stages of fibrosis. The latter knowingly has less oxygen demands and therefore shows less vascularization.⁷ Hence, monitoring of microvascularization (perfusion) of these disorders using modern and accurate imaging techniques such as CT perfusion could represent a good alternative for assessment of the degree of inflammatory activity. As is generally known, all these disorders are mostly incurable, exhibiting a chronic course with flare-ups and thus deserve long-term treatment. Nowadays, in clinical practice, disease activity is assessed by

means of clinical and serological [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and leukocyte count] parameters. However, these biomarkers may fail in particular in mixed disease forms with predominant fibrosis. Other imaging techniques used in the past are fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG-PET) and MRI, but their use is generally not recommended during routine check-ups essentially owing to the high examination costs. ^{18}F -FDG-PET additionally proves to sometimes be too sensitive to immunosuppression-induced metabolic changes with very early (within 24 h) normalization of glucose utilization in and/or around the aortic wall, which leads to difficulties in understanding the true course of the underlying autoimmune process. Monitoring activity of immunosuppressive agents is also mandatory for dose adaption or therapy adjustment. Moreover, new immunosuppressive drugs such as anti-interleukin-6 (anti-IL-6) knowingly, rapidly normalize serological parameters and disease activity during therapy is therefore difficult to assess.⁸

As most of these patients first undergo CT imaging for diagnosis, we thought of reinforcing standard contrast-enhanced CT (CECT) diagnosis by adding an additional perfusion measurement of the vessel wall or perivascular abnormalities for visualization and quantification of disease activity both in treated and untreated patients. This approach is meant to ensure the radiologist knows that the suspected tissue formation is active or inactive in terms of local inflammation similar to the use of ^{18}F -FDG-PET in this clinical setting.

Hence, this work evaluates the role of CT perfusion-based assessment of inflammatory activity in patients with treated and untreated aortitis or chronic periaortitis (A/CP) by comparison of established clinical and serological markers.

METHODS AND MATERIALS

Patient characteristics

Since January 2010, segmental perfusion CT has been routinely included in the work-up of all patients with A/CP who gave their written informed consent to the examination for more accurately assessing the magnitude of inflammatory changes related to these disorders. Retrospective database search at our institution (University Hospital Tübingen, Tübingen, Germany) between January 2010 and March 2015 identified 35 patients [20 females and 15 males; median age: 66.8 years $\pm$ 9.05 standard deviation (SD), range 42–90 years] with A/CP.

Institutional review board approval was obtained for retrospective evaluation of imaging, clinical and laboratory data.

The underlying diseases were classified as aortitis ($n=8$), chronic periaortitis ($n=13$), IAA ($n=4$), retroperitoneal fibrosis ($n=9$) and mediastinal ($n=1$) fibrosis based on their localization and imaging features. Subsequently, we subsumed the latter three under the umbrella term periaortitis, but, for clinical purposes, we differentiated these variants of periaortitis based on CT morphological features such as main exact localization in relation to aorta. Aortitis was defined as an abnormal inflammation (wall thickening and increased enhancement) of the aortic wall not extending into the retroperitoneum, outside the aortic mural confines. As our patients with aortitis were aged

50 years or above, we considered them all as suffering from giant-cell aortitis as there was no history of inflammatory or other autoimmune diseases or infection of the large vessels. Chronic periaortitis was defined as a fibroinflammatory reaction extending from the adventitia of the abdominal aorta into the retroperitoneum, staying, however, close to the aortic wall either encasing the aorta (cuff-like) or being cap-like shaped. In case of more lateral extension of soft tissue including encasement of the ureters, we classified periaortic inflammation as retroperitoneal fibrosis (Ormond's disease). Periaortic inflammation occurring in the setting of pre-existing aortic aneurysm and characterized by an inflammatory mantle of the aneurysm wall was considered an IAA. Overall, a total of 35 CECT and volume perfusion CT (VPCT) studies were reviewed. Other perivascular differential diagnoses mimicking inflammation or fibrosis *e.g.* lymphoma, retroperitoneal carcinosis, peritonitis were excluded. Moreover, patients with malignant primary diseases were excluded owing to the potential of tumour-induced changes of the serological parameters.

Clinical data

All patients underwent clinical examination and all symptoms were registered. Disease activity at time of imaging was classified active ($n=33$) or inactive ($n=2$) depending on the presence of symptoms and serological markers of inflammation.

Laboratory data

Acute-phase inflammatory parameters like CRP (normal value $<0.5\text{ mg dl}^{-1}$), ESR (normal range: 0–15 mm) and leukocyte count (normal range: 3800–10,300 μl^{-1}) were registered in all patients. Three patients had histological proof (all three patients had retroperitoneal fibrosis).

Contrast-enhanced CT and volume perfusion CT imaging protocol

All examinations were performed on a 128-row CT scanner (Somatom® Definition AS+; Siemens Healthcare, Forchheim, Germany).

CECT imaging protocol included craniocaudal scan direction 120 kV, 200–250 mAs, slice thickness = 3.0 mm, collimation = $128 \times 0.6\text{ mm}$, tube rotation time = 0.5 s and pitch = 0.6. This examination was performed before VPCT. 100-ml contrast medium was administered intravenously using the same injection pump at a rate of 2.5 ml s^{-1} followed by 50-ml saline flush. The delay time was set at 65 s which represents a mixed arterial–late capillary perfusion phase.

VPCT imaging was performed using a scan range of up to 9.7 cm z-axis coverage was planned over the involved vascular or perivascular abnormality. Perfusion parameters were 80 kV, 60/100/120 mAs (for chest/abdominal/pelvic examinations), collimation $64 \times 0.6\text{ mm}$ with z-flying focal spot and 26 CT whole coverage of the liver tumour within a total scan time of 40 s. The mean radiation exposure for liver perfusion measurements was 7 mSv. During perfusion scanning, the patients were asked to resume shallow breathing for the entire duration of the study. 50-ml Ultravist® 370 (Bayer Vital, Leverkusen, Germany) was injected at a flow rate of 5 ml s^{-1} in an antecubital vein followed by a saline flush of 50 ml NaCl at 5 ml s^{-1} and a start delay of 7 s.

Contrast medium was administered using a dual-head pump injector (Stellant®; Medtron AG, Saarbruecken, Germany). VPCT was performed at least 15' after CECT. From the VPCT raw data, one set of axial images with a slice thickness of 3 mm for perfusion analysis was reconstructed without overlap, using a smooth tissue convolution kernel (B10f). All images were transferred to an external workstation (Multi-Modality Work-place, Siemens) for analysis.

Image analysis and quantitative perfusion assessment with volume perfusion CT

Data evaluation was performed by two experienced radiologists with 20 and 4 years' experience (MH and GB, respectively) in consensus. All data sets were transferred to a dedicated workstation (syngo® MMWP, v. VE 36A; Siemens Healthcare), and quantitative data evaluation was performed with a commercial software (syngo Volume Perfusion CT Body, Siemens Healthcare). CT perfusion analysis software is based on the maximum slope model using time–density curves to determine perfusion.

Automated motion correction and four-dimensional noise reduction of the data sets were applied by using an integrated motion correction algorithm with non-rigid deformable registration for anatomical alignment. For suppression of intravascular (e.g. aorta) enhancement as well as for eliminating aortic wall calcification, a threshold of 150 HU was set, displaying only lower perfusion values. Volumes of interest (VOIs) were set in the aortic wall, around the aorta and periaortic region, and at the same time, intravascular contrast was suppressed by using adequate thresholds. Quantitative perfusion parameters blood flow (BF), blood volume (BV), volume transfer constant (k -trans) and time to peak (TTP) were obtained in the measured volume. This was performed by drawing a volume of interest (VOI); an automatic pixel-based recognition algorithm allowed for encompassing whole tumour volume along the z -axis (VOI_{average} = average perfusion value inside the defined volume of interest). Subsequently, a separate VOI was drawn encompassing the maximum perfused site (VOI_{max} = volume of interest over the maximally perfused site) within the tumour which was visually determined using the BF colour-coded map. BF and k -trans are indicated as millilitres per 100 ml of tissue per minute, BV as millilitres per 100 g of tissue. We noted all mean and maximum values of these perfusion parameters including SD and the measured tissue volume. Different kinetic modelling techniques were used for quantification. A one-compartment analysis of short-duration scans during the initial phase after contrast injection permitted the calculation of perfusion (BF) and TTP indicating the time interval from arterial enhancement to peak density in the tissue. A two-compartment (Patlak) analysis, quantifying exchanges between intravascular and extravascular spaces, is used in the interstitial phase to calculate BV (excluding stagnant blood) and the k -trans (defined as the sum of the flow within the microvasculature and capillary permeability).

Finally, the maximum thickness of the aortic wall or periaortic tissue was registered. A mural thickening (i.e. $>2\text{--}3\text{ mm}$) was considered abnormal and suggestive for aortitis in particular if enhanced on CECT or accompanied by inflammatory periaortic soft-tissue changes, such as fat stranding. If the aortic wall showed only thrombotic layering and/or calcification (considering also the

age of the patient), arteriosclerosis was diagnosed, and the patients did not undergo perfusion CT. Abnormal tissue formation around the mediastinal or retroperitoneal aorta was considered suggestive of fibrosis if other causes (e.g. tumour, infection) were excluded. Finally, a thickened, enhancing wall of an aortic aneurysm was considered suspicious of IAA. At first, we scored all aortic and periaortic findings on CECT as follows: normal vs abnormal. Only the abnormal cases underwent perfusion CT.

Based on the absolute perfusion values measured, we classified our patients as clinically active (higher BF as that in the back musculature), also supported by corresponding imaging abnormalities, and inactive (lower BF as that in the back musculature).⁹ The mean value and SD of BF (musculature) was $5.9 \pm 2.63\text{ ml } 100\text{ ml}^{-1}\text{ min}^{-1}$.

Statistical analyses

Statistical analysis was performed using JMP® 11.2 statistical software (SAS Institute Inc., Cary, NC).

Regarding the VPCT analysis parameters, potential differences between the various disease entities as well as between clinical symptoms and BF vs BF (musculature) were tested by using the Mann–Whitney U test.

Since an influence of the extent of wall thickening along x -, y - and z -axis on the systemic inflammatory parameter measures has to be expected, for VOI_{average} values, a multivariate analysis using Spearman's ρ (r) was performed to test for potential correlation with the laboratory parameters (CRP, ESR and leucocyte count) weighted by the total included volume of wall thickening (in cubic centimetres).

Interobserver agreement for the assessment of VPCT values was assessed by weighted kappa (κ). For all tests, p -values <0.05 were considered statistically significant.

RESULTS

Clinical data

The underlying disorders analysed in this retrospective study were aortitis ($n = 8$), periaortitis ($n = 13$), IAA ($n = 4$), retroperitoneal fibrosis ($n = 9$) and mediastinal fibrosis ($n = 1$). The leading symptoms were exhaustion ($n = 8$; 22.9%), abdominal pain ($n = 6$; 17.1%), urinary obstruction ($n = 6$; 17.1%), weight loss ($n = 5$; 14.3%), night sweats ($n = 3$; 8.6%), back pain ($n = 2$; 5.7%), fever ($n = 2$; 5.7%), myalgia ($n = 1$; 2.9%), anaemia ($n = 1$; 2.9%) and thoracic pain ($n = 1$; 2.9%). Treated patients under maintenance therapy received methotrexate 15 ($n = 1$), prednisolone [sustained dose ($n = 4$)], prednisolone 10 + azathioprine 150 ($n = 1$), prednisolone 5 + methotrexate 15 ($n = 1$), prednisolone 7.5 + methotrexate 15 ($n = 1$), prednisolone 7.5 + leflunomide 10 ($n = 1$), prednisolone 5 + methotrexate 7.5 ($n = 1$), prednisolone 5 + methotrexate 15 + leflunomide 10 ($n = 1$). Two patients were evaluated after acute cortisol injection therapy and one after cyclophosphamide injection with subsequent prednisolone 50.

Laboratory data

Disease activity at time of imaging was classified active or inactive, depending on the presence of symptoms and serological markers for inflammation. All patients were positive for inflammatory

reactants with mean CRP 3.5 mg dl^{-1} (SD 4.6 mg dl^{-1} , range $0.04\text{--}17.43 \text{ mg dl}^{-1}$), mean ESR 45.32 mm h^{-1} (SD 32.0 mm h^{-1} , range $6\text{--}112 \text{ mm h}^{-1}$) and mean leukocyte number 8862 (SD 4049.6, range 4070–22,550) at the time of imaging. All patients showed a higher BF-value in comparison with the back musculature, the mean BF ratio [BF/BF (musculature)] was 9.82 ± 7.95 . This difference was considered statistically significant ($p < 0.0001$).

The mean values for ESR, CRP and leukocyte number were higher in untreated vs treated patients as shown on Figure 1. There was no significant difference regarding ESR ($p = 0.2$), CRP ($p = 0.21$) and leukocyte number ($p = 0.58$) as well.

Imaging data

Mean $\text{VOI}_{\text{average}}$ and VOI_{max} values of perfusion parameters are tabulated (Tables 1 and 2). The mean aortic wall thickness was 4.8 mm (SD 2.6 mm), and the mean diameter of periaortic fibrosis and inflammation was 6.29 mm (SD 1.98 mm) for aortitis and 9.97 mm (SD 5.81 mm) for periaortitis.

Interobserver agreement

There was strong agreement among the two readers about the presence or absence of abnormal imaging findings. Regarding the VOI evaluation ($\text{VOI}_{\text{average}}$), κ values for blood flow (BF)

and $k\text{-trans}$ showed almost perfect ($\kappa = 0.81\text{--}1.0$) agreement among reviewers, whereas BV, TTP and $k\text{-trans}$ showed substantial ($\kappa = 0.61\text{--}0.80$) agreement.

Regarding the VOI which was drawn encompassing the maximum perfused site (VOI_{max}), the interreader agreement analysis yielded an almost perfect agreement for $k\text{-trans}$ ($\kappa = 0.85$) and substantial agreement ($\kappa = 0.61\text{--}0.80$) for BF, BV and TTP. The overall interobserver agreement was 0.78.

Imaging and clinical findings in comparison and correlations

To assess the value of the above-mentioned perfusion-based imaging findings in supporting the clinical diagnostic process, we performed correlations with clinical data.

Patients with symptomatic aortitis showed significantly higher values for CRP ($p = 0.040$), BF ($p = 0.021$) and $k\text{-trans}$ ($p = 0.040$; Figure 2), whereas there were no significant VPCT value differences between symptomatic and asymptomatic patients with IAA, chronic periaortitis or retroperitoneal/mediastinal fibrosis.

Looking at specific symptoms themselves, $k\text{-trans}$ was significantly different in patients with weight loss ($p = 0.010$). Otherwise, no

Figure 1. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and leukocyte number of treated vs untreated patients. The difference was not statistically significant ($p > 0.05$).

Table 1. Mean values ($VOI_{average}$) for blood flow (BF), blood volume (BV), time to peak (TTP) and volume transfer constant (k -trans) with standard deviation (SD)

Entity	BF	BF SD	BV	BV SD	TTP	TTP SD	k -trans	k -trans SD
Aortitis	45.44	12.42	10.16	2.43	12.99	1.49	5.12	2.66
Periaortitis	67.02	21.08	12.61	4.33	13.43	2.25	5.55	4.23
Inflammatory aortic aneurysm	40.15	28.33	8.02	5.08	12.41	2.35	8.64	8.04
Retroperitoneal fibrosis	36.23	17.47	8.11	3.21	13.96	2.81	7.55	6.76
Mediastinal fibrosis	58.69	33.9	12.24	7.71	11.3	1.48	3.49	3.08

symptom-specific correlations or differences were found. No correlations were found between age, sex and any clinical or imaging criterion.

Imaging and serological findings in comparison and correlations

Correlations between the measured perfusion parameters, given both as mean and maximum values, and the corresponding serological markers for both aortitis and periaortitis (as the sum of all other variants) are tabulated on [Tables 3](#) and [4](#).

Taking the three morphological variants (periaortitis and IAA, and retroperitoneal fibrosis and mediastinal fibrosis) separately, we found the following correlations.

For untreated periaortitis and IAA ([Figure 3](#)), there was good to strong correlation for mean BF (r , 0.65; p = 0.046), TTP (r , -0.70; p = 0.038), MTT (r , 0.69; p = 0.040), with ESR, BV (r , 0.75; p = 0.010) with CRP and leukocyte number (r , 0.80; p < 0.001). For VOI_{max} values, we calculated the following correlations: BF (r , 0.73; p = 0.045), BV (r , -0.62; p = 0.045) with ESR, BF (r , 0.75; p = 0.045), BV (r , 0.66; p = 0.036), MTT (r , 0.60; p = 0.041) with CRP and k -trans (r , 0.82; p = 0.041) with the leukocyte number.

For treated chronic periaortitis and IAA, there was no correlation between the magnitude of perfusion parameters and that of corresponding ESR and CRP.

For untreated retroperitoneal and mediastinal fibrosis, there was good to strong correlation for mean BF (r , 0.74; p = 0.045), BV (r , -0.78; p < 0.001), TTP (r , -0.65; p = 0.039), MTT (r , 0.97; p = 0.004), with ESR and BF (r , 0.78; p = 0.010), BV (r , -0.75; p < 0.001), TTP (r , -0.70; p = 0.018), MTT (r , 0.98; p = 0.002)

with CRP and no significant correlation with the leukocyte count. For VOI_{max} values we calculated following correlations: BF (r , 0.81; p < 0.0001), BV (r , -0.04; p < 0.0001), k -trans (r , -0.94; p < 0.0001) with ESR; BF (r , 0.52; p < 0.04), BV (r , 0.63; p < 0.036), k -trans (r , 0.73; p < 0.04) with CRP; and BF (r , 0.80; p < 0.019), BV (r , 0.78; p < 0.021), k -trans (r , 0.91; p < 0.008) with the leukocyte number.

For treated retroperitoneal and mediastinal fibrosis ([Figure 4](#)), there was good to strong correlation with ESR and CRP only for mean BV (r , -0.78; p < 0.0001). There was no significant correlation between maximum values of perfusion parameters and serological markers in treated patients.

DISCUSSION

Our study shows that there is a good agreement between serological markers of inflammation and perfusion-based imaging parameters for assessment of the disease activity in patients with untreated aortitis as well as periaortitis (A/CP). However, this does not hold true for treated patients. The magnitude of tissue perfusion in treated patients was found to be always abnormally increased, which qualifies perfusion parameters as reliable follow-up biomarkers with the potential to overcome limitations related to laboratory data. Based on the good reviewer agreement in this study, we believe that the routine use of this technique should be encouraged.

Aortitis as well as chronic periaortitis are inflammatory disorders of different causes with different clinical manifestations and prognoses. Nevertheless, they all have something in common which is the presence of fibroinflammatory tissue in the vessel wall or surrounding the aorta or other arteries. The extent of these mural or perivascular abnormalities dictates the sensitivity of morphological imaging (e.g. CECT, MRI, ultrasound)

Table 2. Mean values in the area of the maximum blood flow (VOI_{max}) for blood flow (BF), blood volume (BV), time to peak (TTP) and volume transfer constant (k -trans) with standard deviation (SD)

Entity	BF	BF SD	BV	BV SD	TTP	TTP SD	k -trans	k -trans SD
Aortitis	73.38	9.9	16.43	1.91	11.98	0.44	23.26	3.26
Periaortitis	66.26	11.02	13.38	2.33	12.26	0.63	20.43	4.66
Inflammatory aortic aneurysm	61.03	19.5	12.11	3.42	10.96	1.18	26	6.01
Retroperitoneal fibrosis	47.73	10.83	9.61	1.87	11.79	1.37	22.8	4
Mediastinal fibrosis	85.87	12.04	13.14	2.34	10.31	0.17	19.16	8.46

Figure 2. Coronal volume perfusion CT image set [maximum intensity projection (MIP), blood flow (BF), blood volume (BV) and time to peak (TTP)] of a 72-year-old, untreated male patient (height: 179 cm; weight: 75 kg) with abdominal aortitis. The patient presented with anaemia, weight loss, exhaustion and abdominal pain. Erythrocyte sedimentation rate at the time of the CT examination was 59 mm h^{-1} , CRP 8.43 mg dl^{-1} with $13,040 \text{ leukocytes } \mu\text{l}^{-1}$. $\text{VOI}_{\text{average}}$ values were $\text{BF} = 32.26 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$, $\text{BV} = 9.71 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$ and $\text{TTP} = 10.63 \text{ s}$.

implied in the diagnosis. It is in particular aortitis which may present with mild vessel wall thickening and thus elude morphological CT and or MRI. Therefore, functional imaging has

been increasingly advocated, lately by the use of ^{18}F -FDG-PET.^{10–14} The sensitivity of imaging techniques for detection and activity assessment in patients with A/CP depends on the stage

Table 3. Correlation (r) between serological and volume perfusion CT (VPCT) parameters and statistical significance (p) for untreated patients with aortitis

Serological parameters	VPCT parameters	Maximum values (VOI_{max})		Average values ($\text{VOI}_{\text{average}}$)	
		r	p	r	p
ESR	BF	0.916	0.084	0.984	0.002
	BV	0.762	0.238	0.964	0.008
	TTP	−0.887	0.113	−0.992	0.045
	MTT	−0.860	0.139	0.761	0.130
	k -trans	0.961	0.038	0.967	0.134
CRP	BF	0.901	0.010	0.986	0.002
	BV	0.560	0.400	0.914	0.030
	TTP	−0.970	0.029	−0.945	0.016
	MTT	−0.716	0.283	0.829	0.082
	k -trans	0.967	0.033	0.978	0.004
Leukocyte number	BF	−0.292	0.708	0.710	0.179
	BV	−0.509	0.490	0.734	0.158
	TTP	0.109	0.890	−0.458	0.437
	MTT	0.375	0.624	0.672	0.214
	k -trans	0.303	0.686	0.627	0.257

BF, blood flow; BV, blood volume; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; k -trans, volume transfer constant; MTT, mean transit time; TTP, time to peak.

Owing to the low n -number ($n = 3$), treated aortitis patients were not included in the statistical analysis.

Table 4. Correlation (r) between serological and volume perfusion CT (VPCT) parameters and statistical significance (p) for periaortitis

Serological parameters	VPCT parameters	Maximum values (VOI_{max})				Average values ($VOI_{average}$)			
		No therapy		Under therapy		No therapy		Under therapy	
		r	p	r	p	r	p	r	p
ESR	BF	0.619	0.0104	-0.029	0.957	0.571	0.026	-0.20	0.606
	BV	0.552	0.020	-0.452	0.265	0.596	0.028	-0.267	0.487
	TTP	-0.634	0.001	-0.086	0.818	-0.592	0.029	0.083	0.831
	MTT	0.223	0.677	-0.771	0.007	-0.253	0.362	0.236	0.511
	k -trans	0.507	0.045	-0.371	0.458	0.389	0.152	-0.216	0.575
CRP	BF	0.529	0.038	0.086	0.872	0.637	0.019	-0.345	0.328
	BV	0.821	<0.001	-0.600	0.020	0.511	0.021	-0.478	0.162
	TTP	-0.722	0.001	-0.371	0.468	-0.527	0.020	0.224	0.533
	MTT	-0.041	0.895	-0.600	0.020	-0.089	0.751	0.236	0.511
	k -trans	0.204	0.504	-0.429	0.397	-0.014	0.959	0.030	0.931
Leukocyte number	BF	0.014	0.965	0.543	0.026	0.061	0.829	-0.164	0.651
	BV	-0.020	0.948	0.314	0.544	0.132	0.638	-0.127	0.726
	TTP	-0.206	0.500	0.143	0.787	0.193	0.491	0.478	0.162
	MTT	-0.228	0.454	-0.371	0.469	-0.175	0.532	-0.006	0.987
	k -trans	0.061	0.821	-0.143	0.787	0.539	0.038	0.139	0.701

BF, blood flow; BV, blood volume; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; k -trans, volume transfer constant; MTT, mean transit time; TTP, time to peak.

of the disease being higher in the acute inflammatory stage vs the chronic “burned-out” stage.¹⁵ CECT was used up to now in particular as a non-invasive surrogate for angiography for highlighting stenosis, occlusion or aneurysms caused by aortitis

and its variants. In this respect, sensitivity and specificity of CECT was found to be very high (95% and 100%, respectively).¹⁶ In A/CP, the location, extent and relation to other anatomical structures in the vicinity is usually well defined by

Figure 3. Sagittal volume perfusion CT image set [maximum intensity projection (MIP), blood flow (BF), blood volume (BV) and time to peak (TTP)] of a 73-year-old, untreated female patient (height: 162 cm; weight: 81 kg) with chronic thoracoabdominal periaortitis. The patient presented with abdominal pain. Erythrocyte sedimentation rate at the time of the CT examination was 99 mm h^{-1} , CRP 2.79 mg dl^{-1} with $6480 \text{ leukocytes } \mu\text{l}^{-1}$. $VOI_{average}$ values were $BF = 39.22 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$, $BV = 9.05 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$ and $TTP = 13.76 \text{ s}$.

Figure 4. Coronal volume perfusion CT image set [maximum intensity projection (MIP), blood flow (BF), blood volume (BV) and time to peak (TTP)] of a 52-year-old, untreated female patient (height: 165 cm; weight: 69 kg) with retroperitoneal fibrosis. The patient presented with abdominal pain and bilateral urinary obstruction. Erythrocyte sedimentation rate at the time of the CT examination was 105 mm h^{-1} , CRP 2.92 mg dl^{-1} with $7540 \text{ leukocytes } \mu\text{l}^{-1}$. $\text{VOI}_{\text{average}}$ values were $\text{BF} = 63.19 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$, $\text{BV} = 10.93 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$ and $\text{TTP} = 8.69 \text{ s}$.

CECT which is, in most cases, first used for diagnosis owing to its widespread availability. Complementary, avid enhancement on CECT (increase about 20–60 HU after contrast administration) is generally considered typical for acute stages of the disease, whereas little or no enhancement is expected in the late fibrous stage.⁷ A “double ring” appearance on CECT caused by thickening of the aortic wall is considered typical for the early stages of Takayasu aortitis according to specialist literature.¹⁷ The periaortic soft-tissue distribution was even used to differentiate between benign and malignant retroperitoneal fibrosis.¹⁸ Similarly, in idiopathic IAA a wall thickening sparing mostly the posterior wall, exhibiting delayed enhancement of the soft-tissue component has been reported to be of great diagnostic value. Accordingly, CECT has been reported to have a sensitivity and specificity of 83% and 100%, respectively.¹⁹ However, the finding of a thickened aortic wall or periaortic soft-tissue formation alone cannot distinguish active inflammation from chronic fibrotic lesion. Therefore, contrary to MRI and ^{18}F -FDG-PET, CECT is considered to be less sensitive for assessment of disease activity. MRI is known for its better tissue contrast, and the presence of hyperintense signal intensity on T_2 weighted (oedema) imaging knowingly represents oedema joining inflammation.²⁰ However, its sensitivity and specificity in acute aortitis seem to be both low, as oedema is often missing and/or has been reported also in patients with inactive disease.²¹ Correspondingly, increased contrast enhancement on post-contrast fat-suppressed T_1 weighted images reflects increased vascularity and or excessive leakage of contrast out of the vasa vasorum and is considered as an equivalent for inflammation and thus for disease activity. Nonetheless, a true quantification of contrast enhancement is not possible, and this can be essential for differentiation between contrast enhancements related to inflammation *vs* enhancement in scarred (fibrotic)

tissue as for instance in burned-out lesions. Both VPCT and MRI similarly allow excellent visualization of the arterial wall and vascular lumen, with multiplanar and 3-dimensional reformation. Maximum intensity projection (MIP) and multiplanar reformations can render an “angiographic” view suitable for measurement of luminal calibre and characterization of ectasia, dilation, stenosis and occlusion of the aorta and its branches. MR characterizes mural oedema with T_2 sequences, and gadolinium contrast-enhanced MR identifies mural fibrosis. Nonetheless, the degree of mural perfusion calculated by VPCT is expected to correlate with inflammation so that fibrosis as a late stage of inactive (burned-out) disease could be as well as such characterized.

Recently, the use of ^{18}F -FDG-PET was advocated because of its potential for quantification or at least semi-quantification (*e.g.* in relation to liver uptake).²² Hence, tramline uptake suggests an active inflammatory process either in the aortic wall or periaortic region as by CP or IAA.²¹ Nevertheless, differences in ^{18}F -FDG uptake have been reported with in part very low cut-off values as in retroperitoneal fibrosis and at the same time differential diagnostic challenges for exclusion of active atherosclerosis.²³ Adding information such as scores of contrast enhancement on CECT, as part of a hybrid ^{18}F -FDG-PET/CT examination, to ^{18}F -FDG uptake has been shown to increase accuracy (93.9%) for discrimination between active and inactive disease.²⁴ In patients with IAA, positive ^{18}F -FDG uptake in the aneurysmal wall is regarded as helpful for monitoring progression as well as a predictive tool for evaluating rupture risk.²⁵ With the advance of new immunosuppressive drugs such as anti-IL-6, which rapidly normalize serological parameters and disease activity, it is difficult to follow-up so that diagnosis and response monitoring of A/CP

might be challenging. Moreover, the otherwise highly sensitive metabolic information might fail to confirm persistence of the autoimmune process as soon as the inflammatory component is resolving. ^{18}F -FDG-PET and MRI data have shown that early on during ongoing immunosuppressive therapy (e.g. steroids), these methods show no more glucose uptake or abnormal signal intensity which is beneficial for early response monitoring purposes but not for delayed diagnosis and confirmation of the disease.

All in all, modern and more sophisticated imaging techniques claiming to supply additional functional data are not widespread and consistently cause an increase of diagnostic costs.

Inflammatory markers are routinely included in the diagnostic test for vasculitides. However, they are not always concordant with the clinical activity of the disease, in particular, in cases of Takayasu aortitis, and they are also non-specific.²⁶

At this point, we added a short multiphase contrast-enhanced measurement of the CT morphologically most prominent soft-tissue proliferations either in the vessel (aortic) wall or perivascular, aiming to quantify inflammation-related increased vascularity as a measure of disease activity. For statistical purposes, we first classified these disorders in aortitis and periaortitis, whereas the latter represents an umbrella term encompassing morphologically slightly different soft-tissue proliferations next or in the vicinity of the aorta such as periaortitis, retroperitoneal fibrosis or mediastinal fibrosis and IAA. Whereas in aortitis, most average perfusion values correlated with ESR and CRP in untreated and in part also in treated patients; in periaortitis, we found good agreement between these parameters only in untreated patients. This means that during or after therapy, serological markers often fail to evaluate residual activity of the underlying disorder. By comparison, CT-based perfusion evaluation still showed markedly elevated perfusion values which are, in our opinion, prone to monitor disease activity. The maximum and mean values of assessed perfusion parameters were significantly higher in aortitis *vs* periaortitis emphasizing the different pathophysiological processes behind these diseases. Hence, the inflammatory substrate in aortitis was responsible for a shorter TTP and MTT compared with periaortitis. The former represents a granulomatous vasculitis closely related to polymyalgia rheumatic, which is characterized in its acute phase by dense inflammatory cellular infiltrates with multinucleated giant cells and lymphocytes and a high degree of vascularization.²⁷ On the contrary, in periaortitis, a mix of fibrous tissue and inflammatory infiltrates is found. The fibrous component consists of an abundant matrix composed of Type I collagen and spindle-shaped cells, whereas the inflammatory component is composed of plasma cells and macrophages organized in a perivascular fashion.²⁸ Interestingly, *k*-trans values were significantly higher in periaortitis than in aortitis. This might represent a characteristic of periaortitis in which a vasculitis of the adventitial vasa vasorum and periaortic retroperitoneal small vessels with different degrees of fibrinoid necrosis of vessel walls has been reported, but further research is needed to support this thesis.⁵ Notably, higher perfusion parameters were found in patients with symptomatic aortitis but not in patients with symptomatic periaortitis.

As many of these disorders may occur and even progress subclinically, the use of functional information that is more confident than serological markers could significantly improve quality in the management of affected patients. Discrepancies between ^{18}F -FDG-PET results and the acute-phase reactant levels have already been reported.¹³ Thus, up to 22% of patients with giant-cell arteritis and 40% of patients with Takayasu arteritis may present with normal acute-phase reactant levels despite still active disease thus advocating the use of more sensitive diagnostic methods.²⁹ A great drawback of the currently most often used imaging technique (^{18}F -FDG-PET), both for diagnosis of aortitis and periaortitis, is its limited use in patients already undergoing immunosuppressive (e.g. steroid) therapy.³⁰ At this point, perfusion CT with accurate quantification of perfusion parameters could represent a widely available highly sensitive technique that could be implemented in a normal CT-examination protocol in patients examined in this clinical setting as it highlights another facet of these diseases (vascularization) that seems to be less sensitive to early treatment-induced effects.

The main concern regarding the use of VPCT is radiation exposure in particular in younger patients. Depending on the CT scanner generation, scan length, the anatomical region to be examined as well as the patient gender, our protocol is expected to result in a patient dose between 3 and 7 mSv. In addition to a lower spatial resolution than CT and CT angiography, the drawbacks of MR include scan times that are often in excess of 45 min requiring multiple breath-hold, artefacts and safety concerns related to implanted cardiovascular devices, overestimation of the degree of branch point stenosis, poor performance in distal branches and suboptimal visualization of calcium. Moreover, we think that the findings of our study may also serve as a basis for further MR perfusion studies on vasculitis. However, further studies to show the potential benefit of VPCT and maybe MR perfusion in aortitis/periaortitis may be useful to underpin its relevance for the diagnosis and follow-up of this infrequently but important disease entity.

Our study has several limitations. First, we did not have histological proof in most of our patients, which is knowingly difficult to perform in patients with aortitis or periaortitis. Second, our series consisted of histologically different diseases which hampered optimal comparison of results. Third, the kind and intensity of immunosuppressive therapy differed within our cohort as well as the time point of examination related to the time of onset of treatment.

CONCLUSION

To our knowledge, we report for the first time about the benefit of using VPCT for diagnosis and assessment of disease activity in patients with treated and untreated aortitis or periaortitis. Our results showed good correlation of perfusion parameters with serological markers in terms of disease activity assessment in untreated aortitis and periaortitis, whereas in treated periaortitis, correlations with serological parameters were weak or inexistent, suggesting an increased role for (perfusion-based) imaging.

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