ORIGINAL ARTICLE

Correlation between C-reactive Protein and Morphology of Aortic Intramural Hematoma on CT Angiography

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Objectives To investigate the morphologic characteristics of intramural hematoma (IMH) at CT angiography (CTA), and evaluate the possible correlation with serum C-reactive protein (CRP) level.

Material and Methods Forty-two patients who were initially diagnosed as IMH by aortic CTA and also had serum CRP examination on the same day of CTA were enrolled in this retrospective study, including 30 males and 12 females, with the mean age of 61 ± 14 years old (max-min: 32-91). The volumetric CT data sets were retrospectively processed and analyzed on the post-processing workstation. Based on the thickness of IMH and length-area curve, the cross-sectional area of true lumen and total vessel were measured, the hematoma-vessel ratio (HVR) was calculated. Imaging characteristics were compared between patients who had pathological elevated CRP (> 0.8 mg/dl) and those did not. Spearman correlation analyses of CRP level and morphological characteristics of IMH were performed, and the receiver operational characteristic (ROC) curve was drawn to evaluate the diagnostic validity of CRP.

Results Of all 42 IMH patients, the mean CRP was 3.94 ± 4.71 mg/dl, and the mean HVR was $46.7\% \pm 14.2\%$. HVR in patients with elevated CRP was significantly higher than that in controls ($49.7\% \pm 15.0\%$ vs. $40.7\% \pm 10.5\%$, $P = 0.030$). HVR was mildly correlated with CRP in all patients ($r = 0.48$, $P < 0.001$). CRP levels differed neither between patients with Stanford type A and B ($P = 0.207$), nor between patients with and without intimal disruption ($P = 0.230$). To discriminate $HVR > 47\%$ (the mean value), the area under curve (AUC) were 0.700 (95% CI: 0.535-0.865) for CRP at a cutoff point of 3.55 mg/dl, with a sensitivity of 54.5% and a specificity of 90.0%.

Conclusion CRP was mildly correlated with the severity of cross-sectional hematoma area of IMH, but not with Stanford types and the presence of intimal disruption.

AORTIC intramural hematoma (IMH) is a rare subtype of acute aortic syndrome (AAS), accounting for 5%-10% of AAS based on serial studies in the International Registry of Aortic Dissection (IRAD).¹⁻³ Compared to the classical acute aortic dissection (AD), IMH shares similar clinical presentation and in-hospital mortality, but is more frequently to develop complications like pericardial effusions and periaortic hematoma.² Rupture of the vasa vasorum is considered the inciting event of IMH, causing bleeding into the aortic media. Previous study reported ¹⁸F-fluorodeoxyglucose (FDG) uptake of aortic wall in a portion of IMH patients, reflecting the activation of inflammation in the process of IMH.^{1,2} Kital *et al.* suggested sustained elevated C-reactive protein (CRP), an inflammatory marker, is associated with adverse events in patients with IMH.³ However, the mechanism remains unclear. To our knowledge, little literature has investigated the correlation between inflammatory marker and morphology of IMH.

CT is the gold standards for diagnosis of IMH, especially in emergent scenario.⁴ At unenhanced CT, IMH is characterized by crescent or circular hyperdensity in the aortic wall with occasionally internal displacement of intimal calcification.^{1, 5-6} At contrast enhanced CT, IMH is confirmed by the absence of an intimal flap and direct flow communication between the true lumen and hematoma area.^{5,6} Furthermore, intimal disruption or ulcer-like projection (ULP) on CT is associated with progress of IMH.⁶⁻⁸ The development of 3-dimensional post-processing software allows quantitative measurement of the whole aorta.⁹ The purpose of this retrospective study was to evaluate the possible correlation between serum CRP and morphologic characteristics of IMH by a semi-quantitative analysis method on thoracic-abdominal CT angiography (CTA).

MATERIALS AND METHODS

Patient Selection

This retrospective study was approved by the institutional review board, and the informed consent was waived. By searching the hospital information system, 123 patients who were initially diagnosed as IMH by CTA between August 2015 and November 2017 were

acquired. We retrospectively reviewed the original images and clinical data, excluded 13 patients with complication of aortic dissection, 36 patients whose CT is actually follow-up examination since onset, and 32 patients who did not have serum CRP results or CRP examination taken over 24 hours after CTA. The threshold for pathological elevated CRP was defined as >0.8 mg/dl according to the criterion of our clinical laboratory.

CT angiography scan protocol

All examinations were performed on 256-slice CT scanners (Brilliance iCT, Philips Medical, Cleveland, USA) with bolus tracking mode. After plain scan, 60-80 ml (1 ml -1.5 ml/Kg,) contrast media (Ultravist 370, Shering AG, Guangzhou, China) was injected intravenously at the rate of 3.5 ml-4.5 ml/s (usually 4 ml/s, decreased in poor venous condition), followed by a 40 ml saline bolus. The scanning parameters depend on body mass index (BMI ≥ 24, tube voltage 120 kVp; BMI < 24, tube voltage 100 kVp) and findings on plain scan. If hyperdensity confined in the descending aorta without suspected signs of involving the root, ascending segment and arch of aorta, we used non-ECG-gated scan; if hyperdensity involved the root, ascending segment and arch of aorta or undetermined lesion range, we used retrospective ECG-gated scan. The Pitch and tube rotation time were 0.914 and 0.4 s respectively in non-ECG-gated scans, and 0.3 and 0.33 s respectively in retrospective ECG-gated scans. Other parameters included slice thickness 1 mm, increment 0.5 mm and matrix 512×512. Tube current modulation and iterative reconstruction were applied to all scans. Angiographic scan was triggered by the enhancement of the region of interest (ROI) reaching 150HU at the thoracoabdominal aorta junction with a delay of 5 s.

Image analyses

The volumetric CT data sets were processed on a workstation (Extended Brilliance Workspace, version V4.5.5.51035, Philips Medical). The CT attenuation values of IMH were measured on unenhanced axial images with ROI ≥ 4 mm², avoiding the area of aortic wall, plaque or artifact. The thin slice angiographic images were imported into Advanced Vessel Analysis (AVA)

module, a 3-dimensional post-processing software for vessels. After bone removal, seed points were displaced from aortic root to bifurcation of iliac arteries, covering the whole aorta. Manual adjustments of the center line and ROIs on axial images were applied, to make sure the true lumen was appropriately selected without the unnecessary aortic branches and artifact.

Morphologic characteristics of IMH were measured on curved planar reconstruction (CPR) images, including length, proximal reference area and distal reference area (**Figure 1**). The whole aorta was divided as (1) ascending aorta, (2) aortic arch, (3) descending thoracic aorta, (4) abdominal aorta superior to orifice of right renal artery, and (5) abdominal aorta inferior to orifice of right renal artery. The most severe segment was chosen by the maximum thickness of IMH on CPR images, and then the most severe cross-sectional slice was decided by the minimum area of true lumen according to the minimal point of Volume-Length curve. The most severe true lumen area and total vessel area were measured on the most severe cross-sectional slice with manual adjusted ROI. All measurements were completed by two observers with over 5 years of experience in CTA reconstruction independently [Z.X.H. (reader 1); J.X. (reader 2)], and the average of two values were used. We calculated the hematoma area, hematoma-vessel ratio (HVR) and volume index using following formulas:

Hematoma area = total vessel area – true lumen area

Hematoma-vessel ratio (HVR) = hematoma area / total vessel area

Volume index = hematoma area × length / 1000

IMH was diagnosed according to the criteria described above by two independent observers who were both state-certified radiologists [L.T. (reader 3); W.J. (reader 4)] with over 10 years of experience in CTA. The Stanford classification categorizes IMH by involvement of segments proximal to the left subclavian artery. Type A affects ascending aorta and aortic arch, while Type B does not. Intimal disruption was defined as a localized blood-filled pouch protruding into the thrombosed false lumen.^{3, 6} Localized contrast pooling in aortic wall, an imaging finding of pseudoaneurysm which was frequently connected to true lumen with very small orifice, was carefully differentiate from intimal disruption.^{7, 10} When two assessments differed, a consensus was made by a superior radiologist [Y.L. (reader 5)] with over 20 years of experience in CTA.

Statistical analysis

Categorical variable was expressed as counts and percentages, and continuous variable as mean and standard deviation. After testing normality, the student's *t* test or non-parameter test was used for continuous variables, and the correlation between morphologic characteristics and CRP levels were assessed by Pearson or Spearman correlation. The receiver operating characteristic (ROC) curve was drawn to evaluate the diagnostic validity of CRP levels, and the area under the curve (AUC), sensitivity, and specificity were calculated. The optimal cutoff point was calculated according to the maximum of Youden index. Statistical analyses were performed using SPSS software (version 21.0; IBM, Armonk, NY). *P* values less than 0.05 were considered statistically significant.

RESULTS

There were 42 eligible patients included in this study. The Demographics of this study cohort were shown in **table 1**. The mean age was 61 ± 14 (32-91) years old, and 71.4% patients were male. The most common symptom was chest and/or abdominal pain (39/41, 95.1%). History of hypertension was found in 70.7% (29/41) patients. CTA images of 34 patients were obtained within 24 hours from onset, while in 7 of 8 patients, CT images were obtained in 3 to 17 (10.6 ± 4.8) days after the onset (1 unknown). The involvement of ascending aorta was detected in 11.9% (5/42) patients, and intimal disruption was detected in 33.3% (14/42) of all patients and in 26.5% (9/34) of patients whose onset was within 24 hours.

Of 42 patients with IMH, the mean CRP level was 3.94 ± 4.71 (0-16.6) mg/dl, while in 28 (66.7%) of these patients, the CRP level was elevated (> 0.8 mg/dl). There was no significant difference in CRP between IMH Stanford type A and B ($Z = -1.263$, $P = 0.207$), and between IMH patients with and without intimal disruption ($Z = -1.201$, $P = 0.230$).

In measurements of 42 IMHs, the mean CT attenuation value was 68.9 ± 12.6 HU, the mean length was 24.1 ± 10.0 cm, the mean true lumen area was 455.8 ± 290.6 mm², the mean hematoma area was 424.8 ± 427.3 mm², the mean volume index was 101.4 ± 94.1 and the mean HVR was $46.7 \% \pm 14.2\%$.

Correlation analyses of HVR with CRP were performed with Spearman method and the results was

Figure 1. Image analysis and measurement of morphologic characteristics of IMH in a 59-year-old man who complained about chest and back pain for 5 hours. (A) Plain scan CT image shows crescent hyperdensity (white arrow, CT value: 55.2 HU) in descending aorta. (B) (C) Oblique and coronal maximum intensity projection (MIP) images revealed Stanford type B IMH, involving from descending aorta to abdominal aorta inferior to orifice of right renal artery. (D) After adjustment of center line, the area-length curve (upper image) shows notches along the course of IMH, and the most severe cross-sectional slice is located at the descending aorta by the thickness of IMH (lower image) according to the notch of the curve. (F) Axial image shows the manual drawn ROI cover the whole cross-section of aorta. This patient received thoracic endovascular aortic repair.

presented in **Table 2**. The CRP level was mildly correlated with both HVR and hematoma area in all included patients ($r = 0.48$, $P < 0.001$; $r = 0.35$, $P = 0.03$, respectively) (**Figure 2**), and also in patients whose CTA was taken ≤ 24 h after onset ($r = 0.47$, $P = 0.005$; $r = 0.36$, $P = 0.04$, respectively). The HVR of patients with elevated CRP was significantly higher than that with normal CRP [$49.7\% \pm 15.0\%$ ($n = 28$) vs. $40.7\% \pm 10.5\%$ ($n = 14$), $t = -2.259$, $P = 0.03$].

In all IMH patients of this study cohort, to discriminate HVR $> 47\%$, which was the mean value of HVR, the area under curve (AUC) was 0.700 for CRP (95% CI: 0.535-0.865), and the optimal cutoff point was 3.55 mg/dl, with a sensitivity of 54.5% and a specificity of 90.0% (**Figure 3A**). In patients who had CTA within 24 h of onset, to discriminate HVR $> 47\%$, the AUC was 0.706 for CRP (95% CI: 0.520 – 0.892), and the optimal cutoff point was 3.55 mg/dl, with a sensitivity of 47.1% and a specificity of 100.0% (**Figure 3B**).

Table 1. Demographic and clinical information of enrolled IMH patients in this study ($n=42$)

Characteristics	Value
Age (year), mean $\pm$ SD (min - max)	61 $\pm$ 14 (32-91)
Gender (male), n (%)	30 (71.4)
Hypertension*, n (%)	29 (70.7)
Diabetes*, n (%)	4 (9.8)
Chest and/or abdominal pain*, n (%)	39 (95.1)
Smoker*, n (%)	18 (43.9)
Time between onset and CTA	
≤ 24 h, n (%)	34 (81.0)
> 24 h or unknown*, n (%)	8 (19.0)
Stanford type	
type A, n (%)	5 (11.9)
type B, n (%)	37 (88.1)
Complication	
with ULP, n (%)	14 (33.3)
without ULP, n (%)	28 (66.7)

*Clinical data were unavailable in 1 case of outpatient.

IMH, intramural hematoma; CTA, CT angiography; ULP, ulcer-like projection.

Table 2. Spearman correlation analyses between morphologic characteristics of IMH and CRP

Morphologic characteristics of IMH	All patients (n=42)		Patients with CTA ≤ 24 h (n=34)	
	r	P	r	P
Length	0.09	0.56	0.08	0.66
True lumen area	-0.20	0.20	-0.20	0.26
Hematoma area	0.35	0.03*	0.36	0.04*
Total vessel area	0.19	0.22	0.27	0.12
Reference area*	-0.08	0.62	-0.01	0.95
Stenosis rate [#]	0.04	0.79	0.15	0.40
Hematoma-vessel ratio [†]	0.48	<0.001*	0.47	0.005*
Volume index [‡]	0.31	0.04*	0.30	0.09

* $P < 0.05$. *Reference area = (proximal reference area - distal reference area)/2; [#]stenosis rate = true lumen area / reference area; [†]hematoma-vessel ratio = hematoma area / total vessel area; [‡]volume index = hematoma area × length/1000

Figure 2. Scatter diagram of CRP and hematoma-vessel ratio in 42 patients with IMH.

DISCUSSION

Our study demonstrated that CRP of patients with emergent onset of IMH is correlated with the cross-sectional HVR, a geometric character of IMH, in the most severe segment of aorta. Aortic geometry is considered as an important determinant for predicting AAS.^{9, 11-12} Previous studies have discussed the correlation of hematoma thickness with aortic events in the progression of IMH.¹³⁻¹⁶ In the current study, we found that high CRP level was associated with high HVR, which may represent the prominent intimal separation and the increased aortic wall stress prone to aortic events. Our results suggest a potential mechanism of CPR in predicting prognosis of IMH.

Figure 3. The ROC curves of CRP in discriminating HVR > 47%. Diagonal line represents AUC of 0.50.

in all patients (n=42); B. in patients with CTA taken within 24 h after onset (n=34).

CRP is an acute phase reactant plasma protein which increases during inflammation and after tissue damage. Elevated CRP levels detected in patients with acute aortic aneurysm or dissection was considered to be associated with poor prognosis,^{18,19} and sustained elevation or re-elevated CRP level was considered as an independent factor of aortic events in medically treated IMH patients.^{3, 20} In our study, pathological elevated CRP was detected in 66.7% IMH patients, confirming the inflammatory activation in the process of IMH, and indicating anti-inflammatory therapy may be a choice for patients with IMH.

IMH was firstly described as "dissections without intimal tears" in 1920s.¹³ However, recent studies have described cases of IMH with intimal disruption, which was also referred to as "ULP", "localized intimal defect" or "focal intimal disruption", which conflicts with the conventional definition.^{6-8, 21} ULP is another independent risk factor of aortic events in patients with IMH. Moral *et al.* suggested that intimal disruption in acute

phase (within 2 weeks) of type B IMH was associated with a poor prognosis, while chronic intimal disruption was not.⁸ Some authors believe that IMH should be referred to as an acute AD with closed and thrombosed false lumen due to the high incidence of intimal disruption at the early stage.^{7, 21-22} Comparable with previous studies, intimal disruption was observed in 26.5% (9/34) IMH patients within 1 day after disease onset in our study.^{7, 22} Furthermore, our results suggested CRP levels did not differ in patients with and without intimal disruption, indicating the heterogeneous etiology that inflammation and intimal disruption may reflect different pathology of IMH and different prognosis as well.

CT has been the choice of imaging modality in acute scenario of AAS.^{23,24} Measurements of aortic diameter are suggested to be perpendicular to the axis of blood flow, and detection of intimal disruption is recommended to be based on CT images with slice thickness ≤ 5 mm.^{7, 24} With computer-assisted analysis software, it is feasible to evaluate the areas of true lumen and hematoma perpendicular to the center line on CPR images, which runs along the direction of blood flow. The maximal diameter of hematoma area may vary depending on the position of the affected aorta.³ HVR, we believe, is more accurate than hematoma thickness in evaluation of IMH.

Although CTA is recommended for acute aortic disease, there are still some patients who cannot tolerate contrast-enhanced CT scan in emergency room because of a variety of conditions, such as advanced age, poor venous condition, and allergy to contrast media. Serum CRP level may play an additional role in risk stratification for serial examinations.

This study has several limitations. First, although in the study design we defined the time interval between CRP and CTA examinations within the same day, the two examinations were not performed precisely at the onset of IMH in all enrolled cases. As there was a mild correlation in this study, our result should be testified on larger sample size and with more strict time control. Second, there exists inevitable sampling bias. The in-hospital mortality of enrolled patients in this study was zero, which we believe, was mainly because most (88.1%) of cases were Stanford type B, a subtype with better prognosis. Third, CRP, as a nonspecific inflammatory marker, may be affected by concomitant inflammatory diseases such as pneumonia and pericardial effusion, which was not controlled in this study. These limitations may weaken the results power of this

study.

Our study revealed a possible association between CRP and the morphologic characteristics of IMH. Higher CRP indicates higher HVR, a feature reflecting the severity of IMH, we believed. The prognostic value of HVR still need be evaluated in further study.

Conflicts of interest statement

All authors declared no conflict of interests.

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