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AN EXAMINATION OF INTRACRANIAL ARTERIAL CALCIFICATION MEASUREMENTS: RELIABILITY AND CORRELATION WITH VOLUMETRIC VARIABLES

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Abstract- In this study, we found the Agatston score to be highly reproducible between observers. Agatston score correlated with both volume score and visual scales, with the advantage of containing more information than mere volumetric or qualitative analysis. VBA Agatston scores, which can be automatically segmented in 95% subjects, is good at reflecting total IAC Agatston score.Finding shows the relationship between IAC Agatston score and above quantitative variables was described by a multiple linear regression model (F=1870, P<0.001, R2=0.978), with standardized coefficient values of 0.982 for calciumvolume and 0.033 for density weighted value. In last, IAC Agatston score is highly reproducible and contains more information than mere volumetric or qualitative analysis. IAC Agatston score, especially the relatively more easily measured VBA Agatston score, may bepotential target for futurestudies.

Keywords:IAC, Agatston score, volume score, visual scales

1.1 Background

Intracranial arterial calcification is a known indicator of atherosclerosis and easily identifiable on unenhanced brain CT imaging11. Previously, our study in 490 participants showed that the prevalence of calcification in intracranial arteries were 69.4%14. Other studies have found similar high prevalence rates of IAC in White individuals14,18. Unenhanced brain CT imaging is widely available in general hospitals. However, the current methods used to evaluate severity of IAC are both diverse and inconsistent, which lead to unreproducible and inconsistent results in IAC-related clinical studies.

Currently, different qualitative and quantitative methods are available for IAC measurement on brain CT in clinical research. Visual grading systems are the most common methods, partially due to the handy and convenient procedure. Usually the slice with the heaviest calcified plaque is selected, on which grading is performed by visual inspection or with some simple measuring tools. Extent (or circumferential degree, continuity, etc.) and thickness of calcification around the vessel circumference are two main factors for evaluation, with some scales based on one of these factors14, 13, or on a more comprehensive assessment1012,

On the other hand, quantitative methods are more attractive in clinical research because they provide more objective measures of IAC. However, there are yet no specific scores for intracranial arteries. Some studies used volume score, which is the quantified calcium volume in given arteries detected on CT. But some important calcium information such as density value may be missed in this method. Some widely-used scores for coronary artery attract our attention, particularly the Agatston score. The Agatston score, which is based on the Agatston algorithm and reflects both coronary calcium volume and density information, is now a standard and validated quantitative parameter adopted to evaluate cardiovascular risk in clinicalpractice10. Typical Agatston score is calculated on 3mm-thick CT slices, using a weighted value assigned to the highest artery calcium density of each slice12.

To establish a reliable method for future research and facilitate relevant clinical studies, we verified the feasibility of IAC Agatston score on brain unenhanced CT and investigated its correlation with IAC properties reflected in other qualitative or quantitative methods.

1.2 METHODS

1.2.1 Study participants and measuredarteries

The patient series consisted of 84 men and women who were referred to our hospital for unenhanced brain CT imaging in Jan 2015, regardless of their reasons for examination. These subjects were participants of our previous study which identified the frequency and determinants of IAC2. Because the present study focused on comparisons between Agatston score and different IAC properties, subjects without IAC were not included. Calcification were defined as hyperdense foci with attenuation number ≥130 HU. Both qualitative and quantitative IAC properties were measured. Intracranial arteries were assessed for each subject, included the IICA, ACA, MCA, PCA, BA, and bilateral intracranial VA. No PCA calcification was detected in this group of subjects, so based on anatomy, the entire intracranial arteries were categorized into anterior circulation (including bilateral IICA, MCA and ACA) andVBA.

1.2.2 IMAGEACQUISITION

All scans were performed on a 16-slice multi-detector row CT system (Light speed 16 plus, General Electric, Milwaukee, WI). The unenhanced brain CT scans were acquired in axial mode with tilting along the occipito-meatal line, covering the base of the skull to vertex region and with the following parameters: 140 kVp, 170 mAs, 2 seconds per rotation. Axial images were reconstructed at 0.625 mm intervals and stored as DICOM data for analysis.

1.2.3 STATISTICALANALYSIS

Intra-observer and inter-observer reliabilities of Agatston score were assessed with ICC. Differences between the mean Agatston scores by each visual scale were evaluated using ANOVA with the Bonferroni comparisons. The correlation between Agatston score and different IAC variables were assessed using Spearman's rho. In order to describe the linear association between Agatston score and two exploratory variables (volume score and density weighted value), as well as between Agatston score in entire intracranial arteries and two vessel categories (anterior circulation and VBA), multiple linear regression models were developed by stepwise method. To describe association between Agatston score and different visual grading scales, several quadratic trend models were developed. The goodness of fit of the model was expressed as R2, ranging from zero to one. Besides, plot models with curved lines were performed to further reveal the quadratic trend between two variables. All data were analyzed by SPSS 16.0 software. Two-sided P values less than .05 were considered statisticallysignificant.

1.3 RESULTS

Intra-observer agreements were 0.998 for IAC Agatston score. Inter-observer agreements were 0.996 for IAC Agatston score. Clinical profile was showed in table 2. Present of anterior circulation calcification were found in all 84 patients (100%), and present of VBA calcification found in 33 patients (39.3%). Among 168 MCAs, 168 IICAs, 168 VAs and 84 BAs that were assessed, calcification were found in 4MCAs (2.4%), 159 IICAs (94.6%), 49 VAs (29.2%) and 2 BAs (2.4%) (table 3). No

ACA or PCA calcification were detected. Regarding segmentation ways in different vessel categories, anterior circulation calcification needed manual editing in 73 scans (86.9%). Meanwhile, VBA calcifications needed manual editing in 4 out of 33 scans (12.1%) with VBA calcification, or 4 out of 84 patients with or without VBA calcification (4.8%). The mean IAC Agatston score was 116.44±163.13. General IAC measurements of the study cohort are summarized in Table 3 while more specific artery measurements are presented in Table4.

Table 1. Scales for CT visual scoring

Extent score of intracranial carotid arterial calcification	
Grade 0	No calcification
1	Dot of calcification
2	Calcification <90 degrees of artery wall circumference
3	90–270 degrees circumference
4	270–360 degrees around artery circumference
Thickness score of intracranial carotid arterial calcification	
Grade 0	No calcification
1	Calcification 1 mm thick
2	Calcification 2 mm thick
3	Calcification 3 mm thick
4	Calcification >3 mm thick

Total visual grade (classified by summing of extent and thickness)	
Mild	1-3
Moderate	4-6
Severe	7-8

Table 2. Clinical information

Variable	Overall N=84
Age (years)(mean/range)	71.0 (41-94)
Sex (male), %	46 (54.8)
Hypertension, %	47(56.0)
Diabetes mellitus, %	24(28.6)
Chronic renal failure, %	4(4.8)
Hyperlipidaemia, %	13(15.5)
Ischemic heart disease, %	9(10.7)
Ischemic stroke history, %	13(15.5)
Current smoker, %	10(11.9)

Table 3. General IAC measurements and Spearman's correlation coefficients for IAC Agatston score

	Overall N=84	Correlation with IAC Agatston score	
Values for different IAC variables		Correlation coefficient	*P* value
Total visual grade (Mild/ Moderate/ Severe)	16/38/30	0.814	0.000
Extent score (median/range)	3.0 (1-4)	0.844	0.000
Thickness score (median/range)	3.0 (1-4)	0.825	0.000
Sum of extent and thickness score (median/range)	6.0 (2-8)	0.884	0.000

Table 4. Calcium volume and mean density for each intracranial artery

Calcified artery	Volume(mm^3, mean±SD)	Volume (mm^3, range)	Mean density (Hu, mean±SD)	Mean density (Hu, range)
MCA (n=4)	18.4±20.7	1.8-46.2	251.7±77.7	202.0-367.4
IICA (n=159)	129.3±165.3	0.6-970.4	292.8±97.5	137.8-529.2
VA (n=49)	33.1±87.7	0.4-594.4	219.7±77.1	141.4-475.1
BA (n=2)	77.5±41.7	48.1-107.0	326.8±91.6	262.0-391.5

Tabble 5. Agatston score by different grades of different visual scales

		IAC Agatston score		
	Grade	No.	Mean ± SD	Range
Total visual grade	Mild	16	5.0±11.4	0-46.5
	Moderate	38	51.3±43.8	0-177.0
	Severe	30	258.5±200.9^a	23.0-797.5
Extent score	1	12	6.0±13.0	0-46.5
	2	20	17.2±19.4	0-71.3
	3	33	98.9±70.9^b	14.8-310.8
	4	19	321.0±222.4^c	23.0-797.5
Thickness score	1	9	1.9±2.2	0-6.8
	2	14	17.3±23.8	0-79.5
	3	35	64.8±54.8	2.8-244.3
	4	26	279.0±206.3^c	36.5-797.5

a the mean value of severe groups were significantly different from those of other grades (P<0.001); b the mean value of group 3 was significantly different from those of grade1 and grade2 (P<0.01); c the mean value of group 4 was significantly different from those of other grades (P<0.001).

Figure 1. Semi-automatic segmentation of IAC. The colour-overlay images show semi-automatic segmentation of calcification in bilateral IICA and left VA by software (green, orange andred).

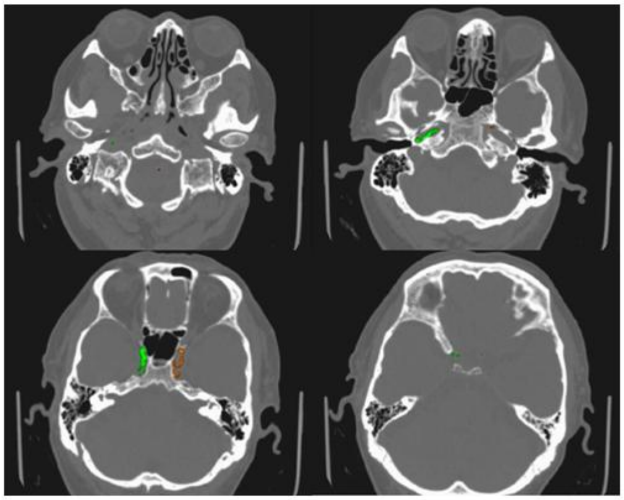
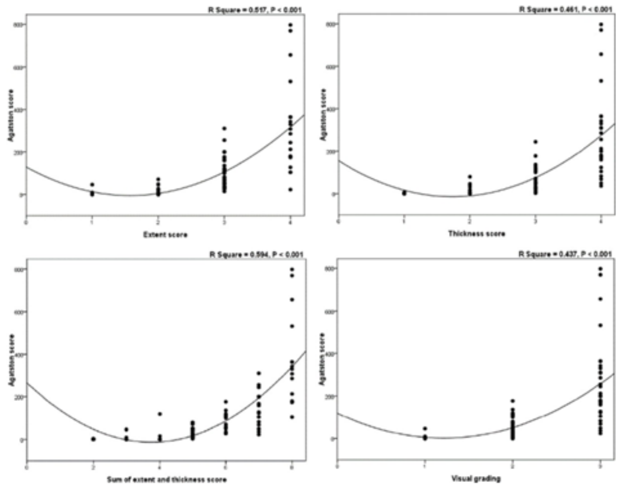


Figure 2. Plot models of quadratic curve estimation between Agatston score and visual grading variables.



Correlations between IAC Agatston score and two quantitative variables (volume score and density weighted value) are shown in table 4-3. Agatston score correlated well with volume score, with Spearman's correlation coefficient of 0.988, which was highest among all IAC variables. The density weighted value was positively correlated with Agatston score and volume score, but only moderately, with correlations of 0.545 and 0.436, respectively. The higher correlation of density weighted value with the Agatston score reflects the density upweighting of the Agatston score. The relationship between IAC Agatston score and above quantitative variables was described by a multiple linear regression model (F=1870, P<0.001, R2=0.978), with standardized coefficient values of 0.982 for calciumvolume and0.033 for density weighted value.

The results indicated that Agatston score was affected by both calcium volume and calcium density. Calcium volume had bigger effect on Agatston score according to the value of standardized coefficients. R2 suggested that these two variables could explain 97.8% variation of Agatston score.

For relationship between IAC Agatston score and qualitative variables, the grades of 3 visual grading scales all significantly correlated with Agatston scores, with Spearman's correlation matrix of 0.814 for total visual grade, 0.844 for extent score and 0.825 for thickness score (P<0.001) (table 3). ANOVA showed that there were significantly different mean Agatston scores among different total visual grades (table 5). Higher total visual grades were generally associated with a greater range of Agatston score: 0 to 46.5 for mild, 0 to 177.0 for moderate, 23.0 to 797.5 forsevere. The results for extent score and thickness score were similar to those of total visual grades. However, post-hoc comparisons indicated that the qualitative methods only partially reflected the differences of mean Agatston scores in different grades (table 5). For total visual grades, mean Agatston scores were not significantly different between the grades (P>0.05) when comparing between mild and moderate groups. For extent score, mean Agatston scores were not significantly different when comparing grade 2 with the other grades. For thickness score, mean Agatston scores were not significantly different between the grades (P>0.05) except when comparing grade 4 with the other grades. In quadratic models with measured Agatston scores, the R2 values were 0.437 for total visual grade, 0.517 for extent score and 0.461 for thickness score (P<0.001), which suggested that these variables could only explain around half of variation of Agatston scores. Scatter plots and curved lines for the three visual grading scales with Agatston score are shown in figure 3.

For different vessel categories, among total 84 participants, VBA Agatston score was moderately-to-highly (rs =0.731, P < 0.001) correlated with entire IAC Agatston score (table 3). However, after excluding the 51 participants with zero calcification in VBA, VBA Agatston score was highly correlated with entire IAC Agatston score (rs=0.957, P < 0.001). The results of multiple linear regression indicated that entire IAC Agatston score was affected by both anterior circulation and VBA calcification (R2 =1.000, P < 0.001), and the latter had bigger effect on total Agatston score according to the value of standardized coefficients (0.500 vs0.607).

1.4 DISCUSSION

In this study, we found the Agatston score to be highly reproducible between observers. Agatston score correlated with both volume score and visual scales, with the advantage of containing more information than mere volumetric or qualitative analysis. VBA Agatston scores, which can be automatically segmented in 95% subjects, is good at reflecting total IAC Agatston score.

Calcification is the only observable and direct sign of atherosclerosis onunenhanced CT brain. However, study results on IAC are inconsistent, likely from lack of feasible and reproducible measuring tools1. The situation has been changed in the cardiology field, in which Agatston score measured on coronary CT has been found of high predictive value in incident cardiovascular events and of important role in patient stratification. Brain CT as a noninvasive and indispensable tool in diagnosis of acute cerebrovascular diseases, is commonly available for IAC inspection. In the present study, we adopt the Agatston score for IAC, detecting calcification ≥130HU and measured on 3mm thick CT slices as suggested when the method was first introduced and validated in coronary artery. Reliability analysis showed excellent reproducibility between two observers, which is similar to a recent study in IICA Agatston score (ICC=0.99) and guaranteeing feasibility of this method for future use64. As the clinical data concerning IAC Agatston score is limited, we intend to determine its clinical significance in a series ofstudies.

The amount of calcification reflects plaque burden in arteries. Based on the imaging characteristics of calcification, volume and density (or intensity, hardness) are two factors that were continuously measured. In our study, multiple linear regression model showed that volume and density information both influenced IAC Agatston score, with volume information having a much bigger effect on IAC Agatston score according to the standardized coefficients. The IAC Agatston score is weighted upward for either greater calcium volume or greater calcium density, as shown in Spearman's correlation analysis, which is consistent with that measured in coronary artery. Since Agatston score accurately reflects the change of IAC in different dimensions, it would be a feasible parameter to indicate atherosclerotic burden.

Visual scales are common but diverse in IAC-related researches[19]. Variations exist in the obtained results depending on which factors are considered and which grading criteria are applied. With the aim to evaluate how well Agatston score reflects IAC visual characteristics, we used the qualitative method suggested by Babiarz, in which the extent and thickness information are both separately andcomprehensively evaluated[14]. In our results, extent score, thickness score, summed score of both factors, and total visual grades were all positively correlated with Agatston score, with moderate-to-high correlation strength. When setting Agatston score as “gold standard”, qualitative variables only explain 44% to 59% of the variations of Agatston score in quadratic models. The extensive range in R squares reflects large inconsistency between different visual scales, and risks in hindering real differences in studies if different scales are used. In addition, the relatively low R square metrics in quadratic models and similar mean Agatston scores between different grades show that the visual scales poorly reflect real changes in calcification, at least in calcium volume and density. There are some explanations. First, it is subjective to visually select the IAC plaque slice that is to be graded. Second, real volume and density information are not considered when grading the selected slice. Third, the calcification in a single slice is not enough to represent the slice-to-slice degree of lesion in whole cerebral arteries. Therefore, visual scales are inferior methods in reflecting calcificationchanges.

The limitation of this study is the lack of clinical data to support exact predictive value of IAC Agatston score. However, establishment of a feasible and reliable measurement is essential to clinical validation studies. We have shown that the Agatston method is an appropriate tool to measure IAC in CT brain, which will facilitate our future studies on its clinical validation.

In summary, IAC Agatston score is highly reproducible and contains more information than mere volumetric or qualitative analysis. IAC Agatston score, especially the relatively more easily measured VBA Agatston score, may bepotential target for futurestudies.

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