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ABSTRACT

BACKGROUND AND PURPOSE: Carotid artery plaque types can be categorized with CT according to their HU values. The purpose of this work was to analyze carotid artery plaque characteristics by using multienergy imaging.

METHODS AND MATERIALS: Thirty-two consecutive patients (23 men; median age, 70 years) were retrospectively analyzed. Carotid arteries were studied with a multienergy CT scanner. All patients received a 15-mL timing bolus of contrast medium to synchronize the data acquisition followed by an injection of 60 mL of contrast medium at a 5-mL/s flow rate. Plaque analysis in 64 carotid arteries was performed, and datasets were reconstructed by using a dedicated workstation. For each plaque, the HU value was quantified with a 2-mm-square region of interest at monoenergy values of 66, 70, 77, and 86 keV. The Wilcoxon test was used to test the differences in HU values in the plaques at different kiloelectron volts.

RESULTS: Four carotid arteries were excluded due to the absence of plaque, and another 7, because of the presence of calcified plaques. In the remaining 53 carotid arteries, Wilcoxon analysis showed a statistically significant difference in HU values among the monoenergy values of 66, 70, 77, and 86 keV ($P = .0001$). In particular, we found that with the increase in monochromatic kiloelectron volt values, there is a statistically significant reduction in the HU value of the plaque.

CONCLUSIONS: Results of this study suggest that the HU values of plaque may significantly change according to the selected kiloelectron volt; therefore, the HU-based plaque type (fatty, mixed, calcified) should be classified according to the energy level applied.

ABBREVIATIONS: CI = confidence interval; HU = Hounsfield unit

Ischemic stroke caused by atherosclerotic disease of the carotid arteries represents one of the leading causes of disability and mortality in the Western World.[1] Prior investigations have demonstrated that CT values of attenuation of the carotid artery plaque, measured in HU, may be a reliable indicator of the so-called "vulnerable plaque," which increases the risk of ischemic stroke.[2,3]

The attenuation of the carotid artery plaque varies according to the histologic composition of the plaque, with lipid core and intraplaque hemorrhage associated with low HU values and calcified elements associated with high HU values.[4,5] In CT clinical use, there are thresholds in attenuation that distinguish plaques as fatty, mixed, or calcified; and according to the inclusion of a plaque in a specific category, there is a different risk stratification.[6,7]

In past years, a new type of CT scanner has been introduced: dual-energy CT. With this technology, it is possible to obtain, during a single examination, the attenuation value of a tissue at multiple energy levels and to postprocess the dataset to evaluate the tissue attenuation determined by only 1 specific kiloelectron volt value.[8,9]

We hypothesized that the energy level used in CT may significantly change the attenuation of the carotid artery plaques, and the purpose of this work was to analyze carotid artery plaque characteristics by using multienergy imaging.

MATERIALS AND METHODS

Study Design and Patient Population

In this retrospective study, 32 consecutive (23 men, 9 women; median age, 70 years ± 10.4) patients studied in the Azienda Ospedaliera Brotzu-Cagliari from November 2011 to February 2012 were included. The inclusion criteria for performing CT of carotid arteries were the presence of a sonographic examination that showed a pathologic stenosis or a plaque alteration (irregular

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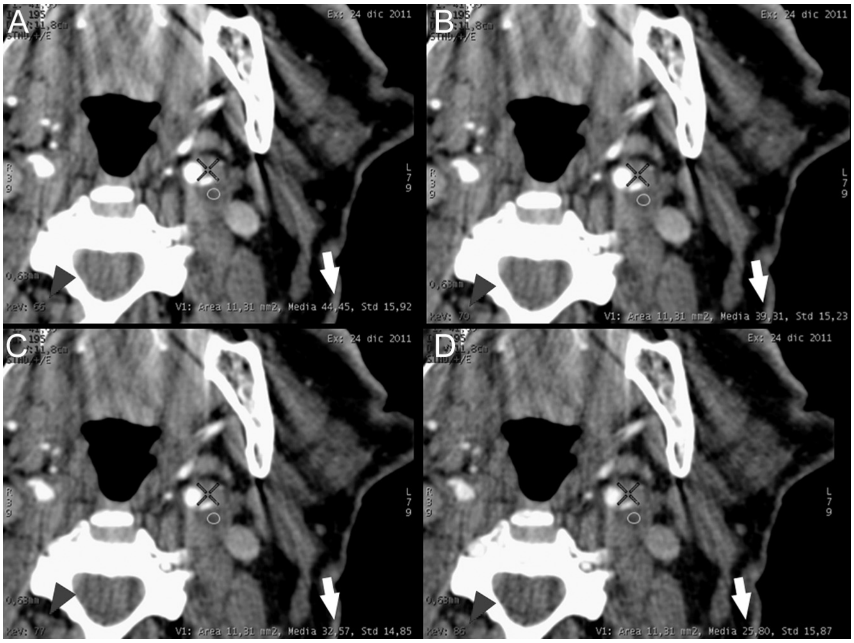

FIG 1. An 83-year-old male patient. In the 4 panels, the HU value (*white arrows*) is visible at the different monochromatic energy levels (*gray arrowheads*): 66 (*A*), 70 (*B*), 77 (*C*), and 86 keV (*D*). This plaque is in the fatty category by using all 4 energy levels.

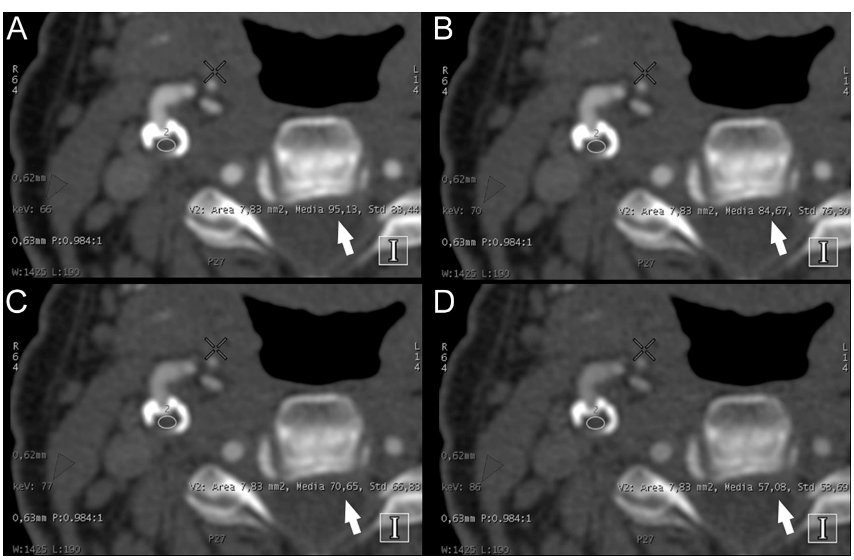

FIG 2. A 76-year-old male patient. In the 4 panels, the HU value (*white arrows*) is visible at the different monochromatic energy levels (*gray arrowheads*): 66 (*A*), 70 (*B*), 77 (*C*), and 86 keV (*D*). This plaque is in the mixed category for 66 (*A*), 70 (*B*), and 77 keV (*C*) but is in the fatty category with 86 keV (*D*) energy.

surface, intraplaque hemorrhage, ulceration in the plaque) or cases in which sonography could not provide adequate information about the degree of stenosis and plaque type. None of the patients included in the study had a medical history of reduced cardiac output or heart failure as reported in the electronic medical record. Institutional review board approval was obtained.

CT Technique

All patients underwent CT analysis of the supra-aortic vessels by using a multidetector CT scanner (Discovery HD 750, Gemstone Spectral Imaging technique; GE Healthcare, Milwaukee, Wisconsin). Angiographic phase imaging was performed by injecting 60 mL of contrast medium, iopromide (Ultravist 370; Bayer Schering Pharma, Berlin, Germany), into a cubital vein by using a power injector at a flow rate of 5 mL/s and an 18-ga intravenous catheter. A SmartPrep (GE Healthcare) technique was used to calculate the correct timing of the CT acquisition, and each patient received a 15-mL timing bolus of contrast medium to synchronize the data acquisition with the arrival of contrast material in the carotid arteries. Angiographic acquisition was performed in a caudocranial direction and included the carotid siphon.

Image Reconstruction and Plaque Analysis

Images were reconstructed on a dedicated workstation with GSI software (Advantage Windows Workstation, Version 4.4; GE Healthcare), and from the CT raw data, multiple datasets were generated at the following monochromatic energy levels: 66, 70, 77, and 86 keV (equivalent to 80, 100, 120, and 140 kV).

Two radiologists (L.S., G.M.A.) independently performed all measurements for HU analysis. A circular or elliptic region of interest ($\geq$2 mm^2) in the thickest area of the plaque was used to measure the HU value from the 66-keV data (Fig 1). We considered the 66-keV data because the lowest energy level shows the higher attenuation values. By using the option "propagate," the same region of interest (morphology and area) in the same topographic position of the plaque was placed to calculate attenuation values at 70, 77, and 86 keV, and these values were also recorded (Fig 1). This approach avoided any type of registration bias.

On the basis of the attenuation values, it was possible to identify different plaque components by using the technique proposed by de Weert et al.[4] In particular, voxels identifying lipids were those with an HU value $<$ 60 HU, voxels identifying fibrous tissue were those with an HU value between 60 and 130 HU, and voxels identifying calcium were those with an HU value $>$ 130 HU (Fig 2). Densely calcified carotid artery plaques were excluded from the analysis.

Statistical Analysis

The normality of each continuous variable group was tested by using the Kolmogorov-Smirnov *Z*-test. Continuous data were described as the mean value ± SD. The Wilcoxon test was used for the differences between the HU values in the plaques at different

Table 1: Summary table of HU values at different kiloelectron volts

Energy (keV)	Mean HU	95% CI	SD	Median	95% CI	2.5–97.5 P	Normal Distribution
66	60,39	51,598–69,182	27,854	56	44,000–65,171	21,525–129,475	.028[a]
70	55,659	47,591–63,726	25,5584	52	41,000–60,171	21,050–118,425	.028[a]
77	49,171	41,969–56,372	22,8155	49	37,000–52,285	18,000–105,950	.036[a]
86	43,049	36,483–49,615	20,8026	43	32,943–47,057	13,575–96,750	.04[a]

Note:—P indicates percentiles.
[a] Statistically significant *P* value: normality rejected.

Table 2: Wilcoxon analysis (*P* values)

Energy (keV)	66 keV	70 keV	77 keV	86 keV
66	x	.001[a]	.001[a]	.001[a]
70	.001[a]	x	.001[a]	.001[a]
77	.001[a]	.001[a]	x	.001[a]
86	.001[a]	.001[a]	.001[a]	x

Note:—x indicates not calculable.
[a] Statistically significant *P* value.

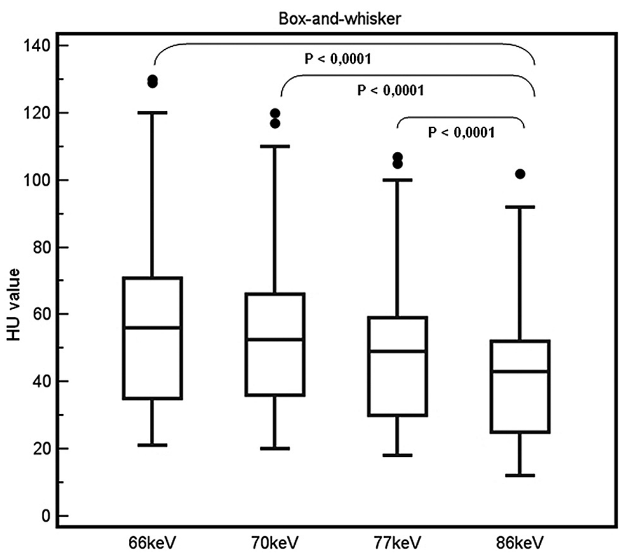

FIG 3. Box-and-whisker plot of the attenuation values according to the different kiloelectron volt levels.

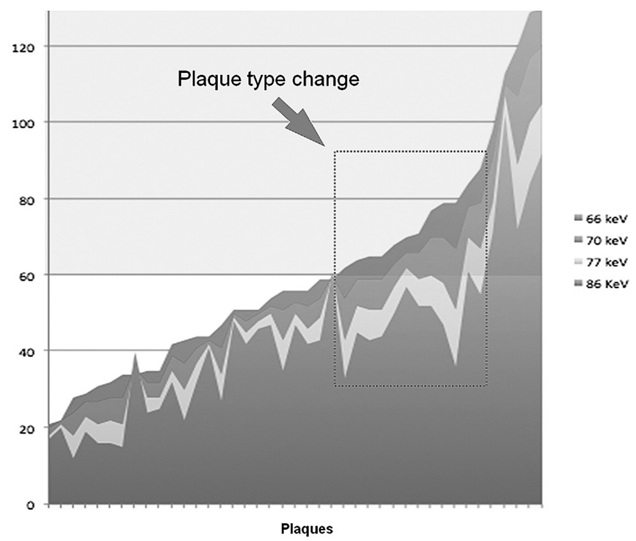

FIG 4. Graph shows the HU values of the plaque. The attenuation value of 60 HU, which is considered the threshold between mixed and fatty plaques, is visible (the HU values >60 are visible in the shaded area of the graph). The dotted rectangle indicates the plaques in which a classification shift occurred according to the energy level.

Table 3: Plaque type according to the energy (*n* = 53)

Energy (keV)	Fatty Plaques	Mixed Plaques
66	23	30
70	28	25
77	31	22
86	34	19

kiloelectron volts. The χ^2 test was used to test whether a statistically significant difference was present in the number of fatty and mixed plaques according the selected kiloelectron volt. Concordance between readers in measuring HU values was assessed with the Bland-Altman analysis. A *P* value < .05 was a statistically significance association, and all values were calculated by using a 2-tailed significance level. *R* software (www.r-project.org) was used for statistical analyses.

RESULTS

General Results

We excluded from our analysis 4 carotid arteries due to the absence of carotid artery plaque and another 7 carotid arteries because of the presence of calcified plaques. Therefore, the final number of carotid arteries that we analyzed was 53. In Table 1, the attenuation values of plaque at the different monoenergy levels are given. The Kolmogorov-Smirnov *Z*-test demonstrated an absence of normality at 66, 70, 77, and 86 keV.

Wilcoxon Analysis

We compared the different attenuation values according to the energy used, applying the Wilcoxon test (Table 2), and these results are summarized in Fig 3.

Plaque-Shift Analysis

Because we considered 60 HU as a threshold between the fatty and mixed types, our analysis showed that the plaque at different energy levels resulted in a differential classification of a subset of plaques (Fig 4). In Table 3, the number of fatty and mixed plaques according to the monoenergy kiloelectron volt used is given; 11 plaques that were mixed at 66 keV became fatty plaques at 86 keV (20.75%) (Fig 2). The χ^2 test was used to determine whether a statistically significant difference was present in the number of fatty and mixed plaques according to selected kiloelectron volt, and Table 4 summarizes the results.

Table 4: χ^2 test to assess the variation in plaque type according to the kiloelectron volts used

Energy (keV)	66 keV	70 keV	77 keV	86 keV
66	x	0,331	0,12	.032[a]
70	0,331	x	0,557	.236
77	0,12	0,557	x	.549
86	0,032[a]	0,236	0,549	x

Note:—x indicates not calculable.
[a] Statistically significant *P* value.

Bland-Altman

The concordance between the 2 radiologists was measured with the Bland-Altman method, and the graphs are given in Fig 5. This test demonstrated a good concordance with an average measurement percentage variation of 2.6% at 66 keV (95% CI, −9.9%–15.2%)

DISCUSSION

Attenuation values of carotid artery plaque measured on CT can be used to identify thresholds that allow distinction between fatty-mixed and calcified plaques.[4] The value of such a distinction is that fatty plaques are more frequently associated with the development of ischemic strokes.[2,6] Therefore, identifying those attenuation values that reliably define a plaque as fatty has clinical relevance.

With the introduction of dual-energy technology, it is possible to obtain CT datasets that define attenuation values according to a specific level of energy used. We hypothesized that the energy level used in CT imaging may significantly modify the attenuation of the carotid artery plaques.

In the 64 carotid arteries we studied, we excluded 4 due to the absence of detectable carotid artery plaque. We also excluded 7 calcified plaques because these usually showed very high attenuation values (usually >600 HU) and SDs; and to include these plaques would have introduced a statistical analysis bias.

The use of monochromatic energy and the potential to generate multiple datasets in postprocessing allows comparison of attenuation values of the tissues at the different energies. After the data are acquired, raw data–based processing can be performed, allowing the reconstruction of images at varying monochromatic energy levels falling between the highest and lowest kilovolt levels.[10]

The Wilcoxon test showed a statistically significant difference in attenuation of the plaque (Table 2 and Fig 3) among all the energy levels with a P value $< .001$. This result is important because it demonstrates that the energy level used may significantly change the attenuation of the carotid artery plaque.

On the basis of this finding, we wanted to know whether this attenuation variation modified the inclusion of the carotid artery plaque in a specific subgroup; hence, we calculated the number of fatty and mixed plaques (by using 60 HU as a threshold according to de Weert et al[4]) on the basis of the monoenergy kiloelectron volt used (Table 3). The χ^2 test demonstrated that from 66 to 86 keV, there is a statistically significant difference in the plaque type classification, with 23 fatty plaques at 66 keV and 34 fatty plaques

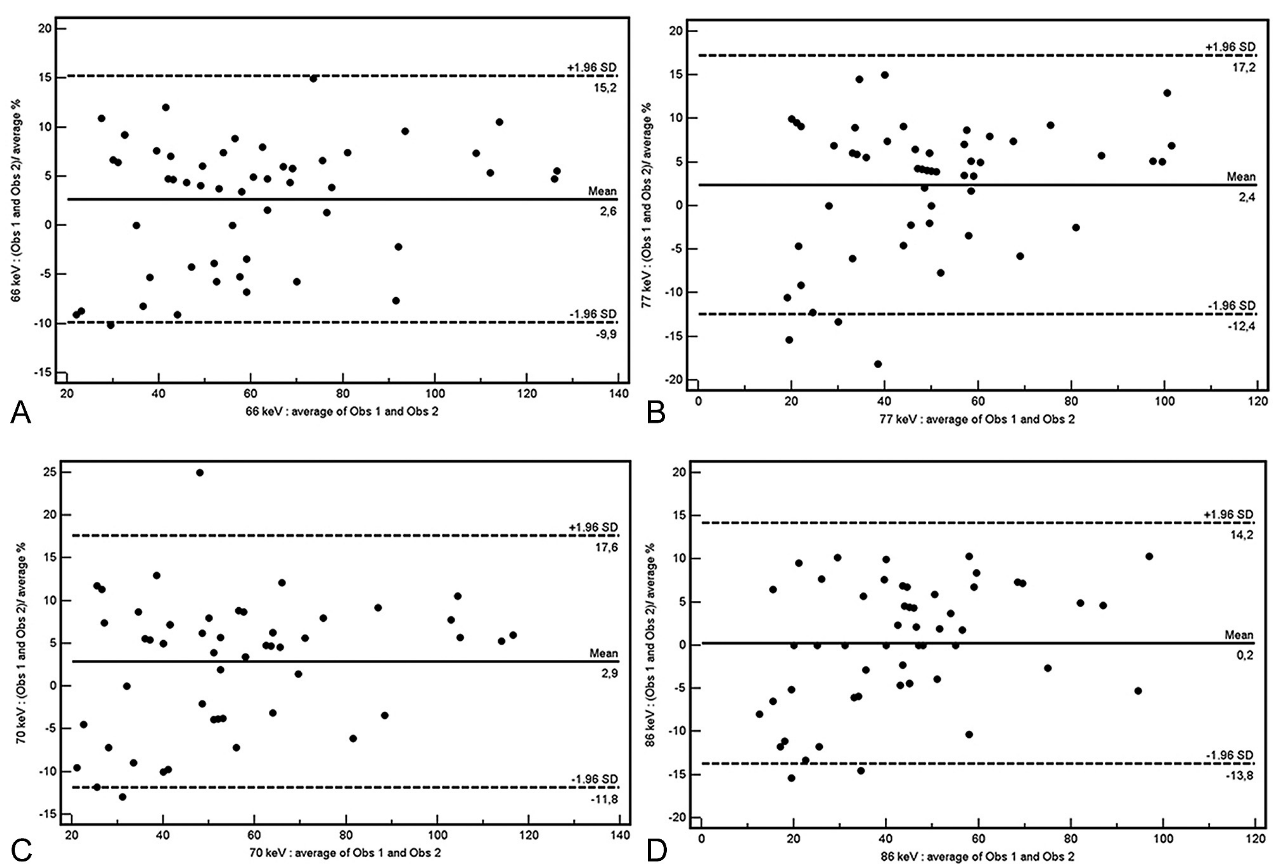

FIG 5. Bland-Altman plot analysis at 66 (*A*), 70 (*B*), 77 (*C*), and 86 keV (*D*).

at 86 keV. Regarding this significant reduction in attenuation going from 66 to 86 keV, we think that the enhancement of the carotid arteries may play a role.[11,12] Some recently published investigations have demonstrated that carotid artery plaques analyzed by CT can show contrast enhancement,[12,13] and Saba et al[13] demonstrated that the degree of intraplaque neovascularization is statistically associated with carotid plaque enhancement. Therefore, it is likely that the molecules of contrast medium get into carotid plaques because they are vascularized. The presence of the iodinated contrast medium in carotid plaques may play a significant role in the variation of the attenuation with the kiloelectron volt values. It is demonstrated that maximum attenuation is produced when the x-ray photon energy is slightly above the K-edge energy, and the K-edge for iodine is at 33 keV[14]: this means that the molecules of contrast medium in the carotid plaques maximize their attenuation (raising the HU values) when the kiloelectron volt is low.

Bland-Altman analysis demonstrated a good concordance with an average measurement percentage variation between readers of 2.6% at 66 keV (95% CI, −9.9%–15.2%). At 86 keV, the average variation was only 0.2% (95% CI, −13.8%–14.2%). In only a few cases was there a significant difference (>10%). Regarding this point, 2 of the most recurrent artifacts connected with the endoluminal injection of contrast material are the so-called edge blur and the halo.[15,16] Edge blur indicates the transition or sharpness of the outer luminal margin as a percentage of the luminal diameter, whereas halo artifacts refer to periluminal increased attenuation. These 2 artifacts can likely account for the small differences between the 2 readers.

In this study, there are some limitations: first, the small number of carotid artery plaques included ($n = 53$). Therefore, our study results need to be confirmed with a larger number of carotid artery plaques. A second limitation is the size of the plaque versus the size of the region of interest: We used a circular or elliptic region of interest ≥ 2 mm^2 in the thickest area of the plaque to measure the HU value, but we did not consider the entire plaque and this omission may determine a bias. The potential for misregistration was not a limitation of our study because the multiple datasets at different monochromatic energy levels (66, 70, 77, and 86 keV) maintain exactly the same geometric properties and the only element that varies is the attenuation of the voxel of the matrix.

CONCLUSIONS

Our study suggests that HU values of carotid artery plaque can significantly change according to the selected kiloelectron volt; therefore the HU-based plaque type (fatty and mixed) should be classified according to the energy level applied. With the use of multienergy imaging, the exact definition of the energy level is possible with a consequent improved and reliable classification of the carotid artery plaque type according to the level of energy applied.

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