Association of automated carotid IMT measurement and HbA1c in Japanese patients with coronary artery disease

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Automated Carotid IMT and its link to HbA1c in 370 Japanese Coronary Artery Disease Patients

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ABSTRACT

Aims: The purpose of this study was to evaluate whether the carotid IMT identified by using automated software is associated with HbA1c in Japanese Coronary Artery Disease Patients.

Methods: 370 consecutive patients (males 218; median age 69 years ± 11) who underwent carotid-US and first coronary angiography were prospectively analyzed. After ultrasonographic examinations were performed, the plaque score (PS) was calculated and automated IMT analysis was obtained with a dedicated algorithm. Pearson correlation analysis was performed to calculate the association between automated IMT, PS and HbA1c.

Results: The mean value of cIMT was 1.00±0.47 mm for the right carotid and 1.04±0.49 mm for the left carotid; the average bilateral value was 1.02±0.43 mm. No significant differences of cIMT were detected between men and women. We found a direct correlation between the cIMT values and the levels of HbA1c ($p=0.0007$) whereas the plaque score did not correlate with the HbA1c values ($p > 0.05$)

Conclusion: Results of our study confirm that the automated cIMT values and the levels of HbA1c in Japanese Coronary Artery Disease Patients are correlated whereas the plaque score does not show any statistically significant correlation.

Keywords: ultrasonography, intima-media thickness, carotid, HbA1c, automated measurement.

Introduction

Intima media thickness of the carotid arteries (cIMT) is a validated surrogate marker of early atherosclerosis and is associated with coronary atherosclerosis [1] and with the risk of future vascular events [2]. Because it can be measured relatively simply and noninvasively, it is well suited for use in large-scale population studies. Ultrasonic measurements correlate well with histology [3, 4] and increased IMT is associated with vascular risk factors [5] and the presence of more advanced atherosclerosis [6], which includes coronary artery disease (CAD).

In the past years, the cIMT was calculated by the sonographers that performed the examination by tracing a line between the two interfaces lumen\intima and media\adventia [7]. In the last years, thanks to the rapidly growing of the hardware and algorithms analysis [8], it became possible to automatically calculate the cIMT [9-11] avoiding one of the most important limit of the manual analysis of the IMT: the poor inter\intra-observer agreement [12, 13].

The important role of long-term hyperglycemia in the development of atherosclerosis is known and a correlation between HbA1c and cIMT was demonstrated especially in women [14] and in children [15, 16] affected by type 1 diabetes. The accurate monitoring in critical patients, such as the patients with type 2 diabetes, is crucial since persons with diabetes have 2-6 folds higher cardiovascular risk than subjects without diabetes [17-19]. Recently, male gender was also associated to a more rapid increase of the cIMT even in Type 2 diabetes [20], thus further increasing the need for accurate measurement and monitoring. In a recent review, Kurukulasuriya and Sowers showed that the reduction of the glycated hemoglobin (HbA1c) is associated with a lower incidence of myocardial infarction, but they also evidenced that the management of the cardiovascular risk factors experienced by patients with type 2 diabetes required a multidisciplinary approach with implementation of strategies to also improve the underlying cardiovascular risk factors [21]. It is, therefore, evident that accurate diagnostic and prognostic vascular tools are needed in association to the study and assessment of patients' HbA1c levels.

In this study, we aimed to evaluate whether the cIMT identified by using automated software called AtheroEdge, which can process a large set of ultrasound images automatically, was associated with HbA1c levels in a population affected by CAD.

Material and Methods

Patient population. Three-hundred-seventy consecutive Japanese patients (males 218, females 152; median age 69 ± 11 years) admitted to Toho University Ohashi Medical Center from December 2008 to January 2011 who underwent carotid-US and first coronary angiography were prospectively analyzed. Coronary angiography was performed to evaluate ischemic heart disease or cardiomyopathy and as the preoperative investigation for ischemic heart, aortic disease, or valvular disease. Our study complied with the Declaration of Helsinki, and written informed consent was obtained from all patients. Part of our population was used in a recently published study [22].

Carotid ultrasonography. Ultrasonographic examinations were performed with a scanner (Aplio XV, Aplio XG, Xario, Toshiba, Inc., Tokyo, Japan) equipped with a 7.5-MHz linear array transducer. All scans were performed by the same experienced sonographer (R Fijisaki with 10 years of experience). Subjects were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans, the probe was rotated 90° to obtain and acquire a longitudinal image of the anterior and posterior walls. The high-resolution images of the far wall were acquired according to recommendations of the American Society of Echocardiography Carotid Intima-Media Thickness Task Force.

Moreover, the high-resolution images of the internal carotid arteries (ICA) and carotid bulbs (other than the CCA) were acquired in order to calculate the plaque score (PS).

The HbA1c was calculated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value using the following formula: HbA1c (NGSP) (%) = 1.02 × HbA1c (Japan Diabetes Society) (%) + 0.25% [23].

Automated Far Wall LI/MA Delineation. The IMT measurement was completely automated. Our strategy was based on the following three basic steps:

- Step-1: automated image cropping.
- Step-2: automated carotid artery far wall recognition.
- Step-3: automated LI/MA far wall tracings.

For an automated method, we need a correct region of interest, which only consists of tissue region. Therefore, in Step-1, the goal is to automatically crop the region of interest (tissue region) in this ultrasound B-mode image. Since our images are in JPEG format, we adopt a gradient-based strategy, which removes all the image rows and columns that are black and do not contain intensity variations in ultrasound image. The detailed procedure was previously reported by Molinari *et al.* [24]. Once the grayscale region of interest image was obtained, Step-2 consists of an integrated procedure combining feature extraction and classification was used to automatically track the carotid artery [25, 26]. The hypothesis at the base of this procedure is that the far wall adventitia layer (AD_F) is the brightest feature in the image [27]. Our procedure first identifies all the “seed points”. A seed point is a local intensity maximum with intensity value higher than that of the average surrounding pixels. Seed points are located on the bright features of the image. These seed points are connected to form line segments. Line segments for the cropped image of fig. 1.A are reported in fig. 1.B.

All the line segments are then connected and the one located on the brightest interface is considered as the far adventitia layer profile. The AD_F profile for the image in fig. 1.A is depicted by fig. 1.C.

Finally, once the AD_F profile was traced, Step-3 consisted of automated LI/MA tracings. [26, 28]. We adapted three types of intensities in our approach at this point. Lumen region (cluster 1), the intima or media layer (cluster 2), or the adventitia layer (cluster 3). The pixels at the transitions of the clusters 1 and 2 form the LI boundary, whereas the pixels at the transition between the clusters 2 and 3 form the MA boundary. The final Delineation of the carotid artery of fig. 1.A is shown in fig. 2.

Statistical analysis. Correlation plots were performed to assess the relationship between the cIMT values and Plaque Score versus the percent value of HbA1c. Correlation was numerically measured by using the Pearson rho coefficient along with its 95% confidence interval. The statistical existence of correlation between the variables was measured by the correlation level of significance (correlation was considered significant if the *p* value was lower than 0.05). The normality of each continuous variable group was tested using the Kolmogorov-Smirnov *Z* test.

Results and Discussion

AtheroEdge was able to detect the cIMT in all patients and its validation was yet published in previous manuscripts of our group (blinded for peer review). In details, the mean value of cIMT evaluated at level of CCA was 1.00±0.47 mm for the right carotid and 1.04±0.49 mm for the left carotid; the average bilateral value was 1.02±0.43 mm. No significant differences were detected between men and women cIMT. The cIMT values manually measured by an expert Reader were 0.94±0.29 mm for the right and 1.03±0.41 mm for the left carotid side. Therefore, the measurement bias was equal to 0.06±0.41 mm and 0.01±0.42 for the right and left side, respectively.

Table 1 summarizes the demographics, physical and clinical characteristics of the studied subjects. In our population we had 218 subjects (prevalence of 43.5%) with evidence of coronary artery disease and the SYNTAX score (SXscore) was 8.8 ± 15.0 (Normality rejected with a p value of 0.001). The PlaqueScore (PS) was 7.0 ± 5.3 (Normality rejected with a p value of 0.001) whereas the mean Auto-IMT (obtained by averaging the left and right side) was 0.85 ± 0.25 mm (Normality rejected with a p value of 0.001).

We found a direct correlation between the cIMT values and the levels of HbA1c (rho = 0.1761; p=0.0007; Figure 3A); on the other hand, the plaque score did not correlate with the HbA1c values (rho = 0.0798; p=0.1340; Figure 3B). We also did not find a significant correlation between te cIMT and the glucose (rho = 0.060; p=0.266), LDL (rho = -0.006; p=0.943), and HDL levels (rho = -0.064; p=0.390).

Carotid IMT is considered a reliable measure of generalized atherosclerosis. Previous investigation have demonstrated that a thickened cIMT is correlated with an increased risk of stroke and myocardial infarction [29] and it is predictive of future events of coronary heart diseases in subjects with type 2 diabetes [30, 31]. In this study our purpose was to evaluate whether the cIMT, identified by using AtheroEdge automated software, is associated with HbA1c in Coronary Artery Disease Patients and we found a strong association between cIMT, measured by the means of AtheroEdge, and HbA1c in the whole study population (p = 0.0007) .

Previous investigations have demonstrated that there is an association between the diabetes and the IMT [32-34], but the association, and its strength, between IMT and the diabetes is still debated [35]. In 2010, Einarson *et al.* revised 172 papers and found a weak but statistically significant correlation between glucose levels and coronary IMT [36]. One of the limitations in the previous studies that explored the association between the atherosclerosis or the arteries' IMT and diabetes was the technology used for the IMT quantification. In particular it is well known that the IMT can suffer of multiple bias and in particular the poor inter-observer agreement [37]. Lorentz *et al.*, in a meta-analysis of 8 studies which represent 37197 subjects, highlight multiple sources of heterogeneity between the studies based on the cIMT assessment: these include the details of the ultrasound protocol, namely the precise definitions of the carotid segments investigated, the use of mean or maximal IMT, the measurement of near and far wall or only far wall IMT, and whether IMT was measured only on 1 side or on both sides [2]. The technique we used allows to standardize the measurement process and then to improve the reproducibility of the results.

Our study results are concordant with those found by Bobbert *et al*. [38], but one of the points of major originality of our manuscript is the use of a completely automated cIMT measurement using AtheroEdge. Our methodology is validated in previous publication that demonstrated an excellent reproducibility of the software. Therefore the association we found between the cIMT and HbA1c can be considered further strengthened by the methodology for the IMT quantification

We did not find any statistically significant correlation between the plaques score and the HbA1c (rho value = 0.0789); this data are concordant with the literature. In the recently published study by Herder *et al.* [39] in a population of 2741 patients, it was found that the diabetes was predictor for IMT and IMT progression, whereas the total cholesterol, smoking, and systolic blood pressure were stronger long-term predictors of carotid plaque area and carotid plaque area progression than for IMT and IMT progression.

In this study there are some limitations: the first one is that we did not consider in our analysis the diabetes duration. This fact may represent a bias because some authors consider that the diabetes duration is an important factor impacting on carotid thickening [40-42].

In conclusion, results of our study confirm that the automated cIMT values and the levels of HbA1c are correlated whereas the plaque score does not show any statistically significant correlation.

References

[1] Hodis HN, Mack WJ, Labree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 1998; 128: 262-9.

[2] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007; 115: 459-67.

[3] Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986; 74: 1399-406.

[4] Zureik M, Temmar M, Adamopoulos C, et al. Carotid plaques, but not common carotid intima-media thickness, are independently associated with aortic stiffness. J Hypertens 2002; 20: 85-93.

[5] O'leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. Stroke 1992; 23: 1752-60.

[6] Lorenz MW, Von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke 2006; 37: 87-92.

[7] Devine PJ, Carlson DW, Taylor AJ. Clinical value of carotid intima-media thickness testing. J Nucl Cardiol 2006; 13: 710-8.

[8] Molinari F, Zeng G, Suri JS. A state of the art review on intima-media thickness (IMT) measurement and wall segmentation techniques for carotid ultrasound. Computer Methods and Programs in Biomedicine 2010; 100: 201-21.

[9] Saba L, Meiburger KM, Molinari F, et al. Carotid IMT Variability (IMTV) and Its Validation in Symptomatic versus Asymptomatic Italian Population: Can This Be a Useful Index for Studying Symptomaticity? Echocardiography.

[10] Molinari F, Meiburger KM, Zeng G, et al. Automated carotid IMT measurement and its validation in low contrast ultrasound database of 885 patient indian population epidemiological study: results of AtheroEdge Software. Int Angiol 2012; 31: 42-53.

[11] Molinari F, Meiburger KM, Saba L, et al. Constrained snake vs. conventional snake for carotid ultrasound automated IMT measurements on multi-center data sets. Ultrasonics 2012; 52: 949-61.

[12] Naredo E, Moller I, Gutierrez M, et al. Multi-examiner reliability of automated radio frequency-based ultrasound measurements of common carotid intima-media thickness in rheumatoid arthritis. Rheumatology (Oxford) 2011; 50: 1860-4.

[13] Polak JF, Pencina MJ, Meisner A, et al. Associations of Carotid Artery Intima-Media Thickness (IMT) With Risk Factors and Prevalent Cardiovascular Disease: Comparison of Mean Common Carotid Artery IMT With Maximum Internal Carotid Artery IMT. J Ultrasound Med 2010; 29: 1759-68.

[14] Larsen JR, Brekke M, Bergengen L, et al. Mean HbA1c over 18 years predicts carotid intima media thickness in women with type 1 diabetes. Diabetologia 2005; 48: 776-9.

[15] Atabek ME, Kurtoglu S, Pirgon O, Baykara M. Arterial wall thickening and stiffening in children and adolescents with type 1 diabetes. Diabetes research and clinical practice 2006; 74: 33-40.

[16] Heilman K, Zilmer M, Zilmer K, et al. Arterial stiffness, carotid artery intima-media thickness and plasma myeloperoxidase level in children with type 1 diabetes. Diabetes research and clinical practice 2009; 84: 168-73.

[17] Charvat J, Chlumsky J, Szabo M, Zakovicova E, Zamrazil V. The association of masked hypertension in treated type 2 diabetic patients with carotid artery IMT. Diabetes research and clinical practice 2010; 89: 239-42.
[18] Kannel WB. Framingham study insights on diabetes and cardiovascular disease. Clin Chem 2010; 57: 338-9.
[19] Kannel WB, D'agostino RB, Wilson PW, Belanger AJ, Gagnon DR. Diabetes, fibrinogen, and risk of cardiovascular disease: the Framingham experience. Am Heart J 1990; 120: 672-6.
[20] Zhao B, Liu Y, Zhang Y, et al. Gender difference in carotid intima-media thickness in type 2 diabetic patients: a 4-year follow-up study. Cardiovasc Diabetol 2012; 11: 51.
[21] Kurukulasuriya LR, Sowers JR. Therapies for type 2 diabetes: lowering HbA1c and associated cardiovascular risk factors. Cardiovasc Diabetol 2010; 9: 45.
[22] Ikeda N, Saba L, Molinari F, et al. Automated carotid intima-media thickness and its link for prediction of SYNTAX score in Japanese coronary artery disease patients. International Angiology (in press).
[23] Kashiwagi A, Kasuga M, Araki E, et al. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. Journal of Diabetes Investigation 2012; 3: 39-40.
[24] Molinari F, Liboni W, Giustetto P, Badalamenti S, Suri JS. Automatic computer-based tracings (ACT) in longitudinal 2-D ultrasound images using different scanners. Journal of Mechanics in Medicine and Biology 2009; 9: 481-505.
[25] Molinari F, M. MK, Zeng G, et al. Carotid artery recognition system: A comparison of three automated paradigms for ultrasound images. Med Phys 2012; 39: 378.
[26] Molinari F, Zeng G, Suri JS. An integrated approach to computer- based automated tracing and its validation for 200 common carotid arterial wall ultrasound images: A new technique. J Ultras Med 2010; 29: 399-418.
[27] Molinari F, Krishnamurthi G, Acharya UR, et al. Hypothesis Validation of Far-Wall Brightness in Carotid-Artery Ultrasound for Feature-Based IMT Measurement Using a Combination of Level-Set Segmentation and Registration. IEEE Transactions on Instrumentation and Measurement 2012; 61: 1054-63.
[28] Molinari F, Zeng G, Suri JS. Intima-media thickness: setting a standard for completely automated method for ultrasound. IEEE Transaction on Ultrasonics Ferroelectrics and Frequency Control 2010; 57: 1112-24.
[29] Tsivgoulis G, Vemmos K, Papamichael C, et al. Common carotid artery intima-media thickness and the risk of stroke recurrence. Stroke 2006; 37: 1913-6.
[30] Bernard S, Serusclat A, Targe F, et al. Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. Diabetes Care 2005; 28: 1158-62.
[31] Yamasaki Y, Kodama M, Nishizawa H, et al. Carotid intima-media thickness in Japanese type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. Diabetes Care 2000; 23: 1310-5.
[32] Lee EJ, Kim HJ, Bae JM, et al. Relevance of common carotid intima-media thickness and carotid plaque as risk factors for ischemic stroke in patients with type 2 diabetes mellitus. AJNR Am J Neuroradiol 2007; 28: 916-9.
[33] Vigili De Kreutzenberg S, Tiengo A, Avogaro A. Cerebrovascular disease in diabetes mellitus: the role of carotid intima-media thickness. Nutr Metab Cardiovasc Dis 2009; 19: 667-73.

[34] Mudrikova T, Szabova E, Tkac I. Carotid intima-media thickness in relation to macrovascular disease in patients with type 2 diabetes mellitus. Wien Klin Wochenschr 2000; 112: 887-91.
[35] Gomez-Marcos MA, Recio-Rodriguez JI, Patino-Alonso MC, et al. Relationship between intima-media thickness of the common carotid artery and arterial stiffness in subjects with and without type 2 diabetes: a case-series report. Cardiovasc Diabetol 2011; 10: 3.
[36] Einarson TR, Hunchuck J, Hemels M. Relationship between blood glucose and carotid intima media thickness: A meta-analysis. Cardiovasc Diabetol 2010; 9: 37.
[37] De Groot E, Van Leuven SI, Duivenvoorden R, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. Nat Clin Pract Cardiovasc Med 2008; 5: 280-8.
[38] Bobbert T, Mai K, Fischer-Rosinsky A, Pfeiffer AF, Spranger J. A1C is associated with intima-media thickness in individuals with normal glucose tolerance. Diabetes Care 2009; 33: 203-4.
[39] Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromso Study. Stroke 2012; 43: 1818-23.
[40] Shah AS, Dolan LM, Kimball TR, et al. Influence of duration of diabetes, glycemic control, and traditional cardiovascular risk factors on early atherosclerotic vascular changes in adolescents and young adults with type 2 diabetes mellitus. J Clin Endocrinol Metab 2009; 94: 3740-5.
[41] Liu YP, Zhan WW, Zhang YF, et al. Carotid intima-media thickness and stiffness in relation to type 2 diabetes in Chinese. Endocrine 2007; 31: 289-93.
[42] Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O'leary DH, Haffner SM. Diabetes and progression of carotid atherosclerosis: the insulin resistance atherosclerosis study. Arterioscler Thromb Vasc Biol 2003; 23: 1035-41.

Figure Legends

Figure 1

A) Original and cropped B-Mode image (right carotid artery in the common tract). B) Line segments automatically traced by AtheroEdge. C) Automated tracing of the AD_F.

Figure 2

Automated AtheroEdge LI/MA tracings of the far distal wall.

Figure 3

Correlation plots between the AtheroEdge CIMT values (panel A) and Plaque Score (panel B) versus the percent value of HbA1c.

Table 1. Demographics and clinical characteristics of the patients. The rightmost column reports the p value for the normality test (Kolmogorov-Smirnov).

Table 1		
Parameter	**Value**	***K-S test***
Male (%)	62.3%	*NC*
Age	69 ± 11	*0.018*
Diabetes mellitus	17.4%	*NC*
Hypertension	56.3%	*NC*
Albumine	4.14 ± 0.37	*0.001**
Creatinine	1.58 ± 2.09	*0.001**
Haemoglobin A1c	5.6 ± 1.0 % (37 ± 13 mmol/mol)	*0.001**
Glucose (mg/dL)	109 ± 31	*0.001**
Total cholesterol (mg/dL)	182 ± 38	*0.604*
Low density lipoprotein cholesterol (mg/dL)	105 ± 34	*0.556*
High density lipoprotein cholesterol (mg/dL)	53 ± 15	*0.029*
Triglyceride (mg/dL)	122 ± 70	*0.001**

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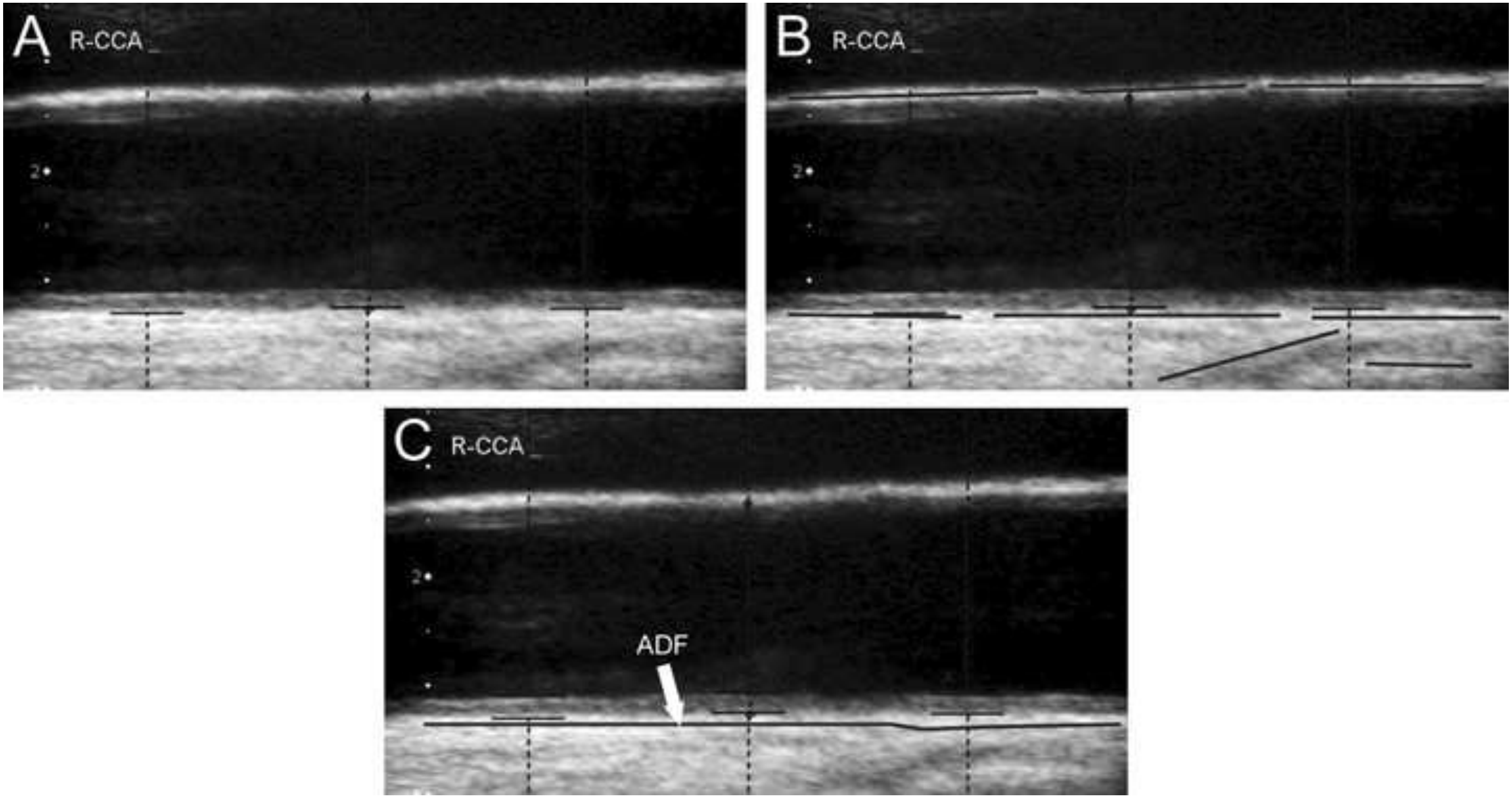

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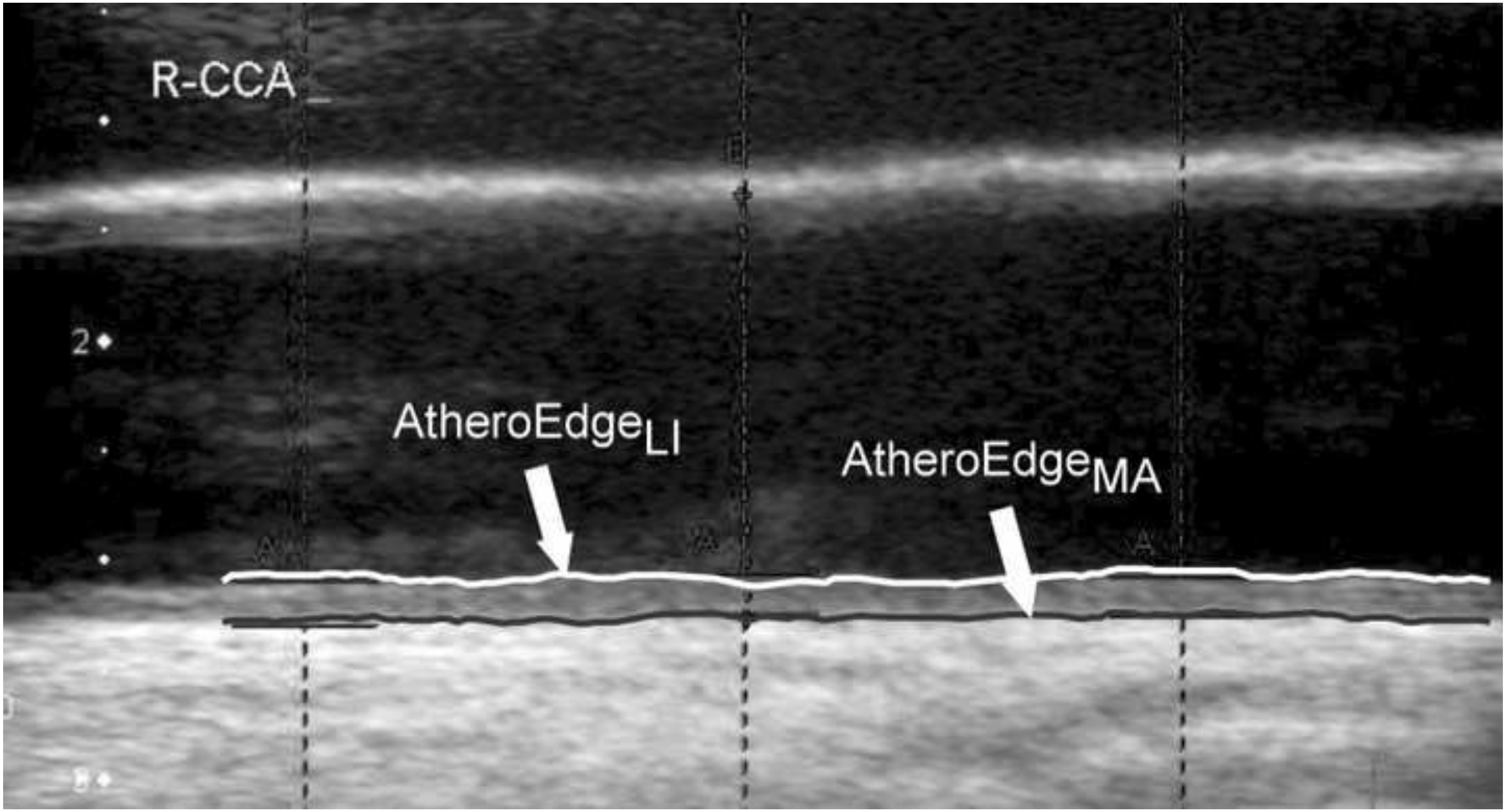

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