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● *Original Contribution*

REAL-TIME SPATIAL COMPOUND IMAGING IMPROVES REPRODUCIBILITY IN THE EVALUATION OF ATHEROSCLEROTIC CAROTID PLAQUES

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Abstract—Compound imaging has the ability of reducing speckle and clutter artifacts demonstrated in *in vitro* studies compared to conventional, single-angle imaging. We investigated intra- and interobserver agreement of 38 outlines of carotid artery plaque images acquired by these techniques, by measuring the overlapping area after repeated outlines. In general, both techniques showed good agreement. When considering the images with poorest overlap, compound imaging had a significant advantage over conventional imaging regarding both intra- and interobserver agreement. The interobserver variation for the overlapping area after two outlines was 20% for conventional technique and 10% for compound. The interobserver variation of the gray scale median value (GSM) for conventional technique ranged from −32 to +20 and from −6 to +6 for compound. Likewise, the coefficient of repeatability for the GSM value was 13 for conventional imaging and three for compound imaging, and interobserver variation for the GSM value for the overlapping area was 34% and 9% for conventional and compound technique. In conclusion, compound imaging improves intra- and interobserver agreement and reduces interobserver variation in the GSM value in a clinical setting. (E-mail: stko@gentoftehosp.kbhamt.dk)

Key Words: **Ultrasound, Compound imaging, Carotid artery, Plaque, Reproducibility.**

INTRODUCTION

In the extracranial vessels, atherosclerotic plaques are estimated to be present in 25% to 50% of all stroke patients, making it one of the leading risk factors for stroke. In symptomatic patients, the benefit of surgical correction of severe internal carotid artery stenosis is well established, as demonstrated in the European Carotid Surgery Trial (1998) and the North American Symptomatic Carotid Endarterectomy Trial (Barnett et al. 1998). Recent evidence has shown that plaque echogenicity, as assessed by high-resolution ultrasound, relates directly to histologic findings and seems to be of prognostic importance (European Carotid Plaque Study Group 1995; Grønholdt et al. 1998; Matsagas et al. 2000; Polak et al.1998). A variety of plaque classification schemes that are based on the visual characteristics of the plaque have, due to their subjective nature, show a wide range of reproducibility (Arnold et al. 1999; de Bray et al. 1998; Hartmann et al. 1999; Montauban van Swijndregt et al. 1999). This has directed attention toward a more quantitative measurement of echogenicity. In one such method, computerised plaque analysis, the region-of-interest in the ultrasound B-mode image, is outlined and analysed for its gray scale content (expressed as a gray- scale median value) as a measure of plaque echogenicity (El-Barghouty et al. 1995, 1996a, 1996b). However, a major inherent disadvantage of conventional single-angle imaging is the angle-dependent backscatter. *In vitro*, multi-angle imaging studies have shown not only improvement of image quality, but also reduction of the amount of random noise known as speckle (Entrekin et al. 2000; Jespersen et al. 1998). This technique, called real-time spatial compound imaging or simply compound imaging, has recently been made possible by the substantial computational power of modern ultrasound devices.

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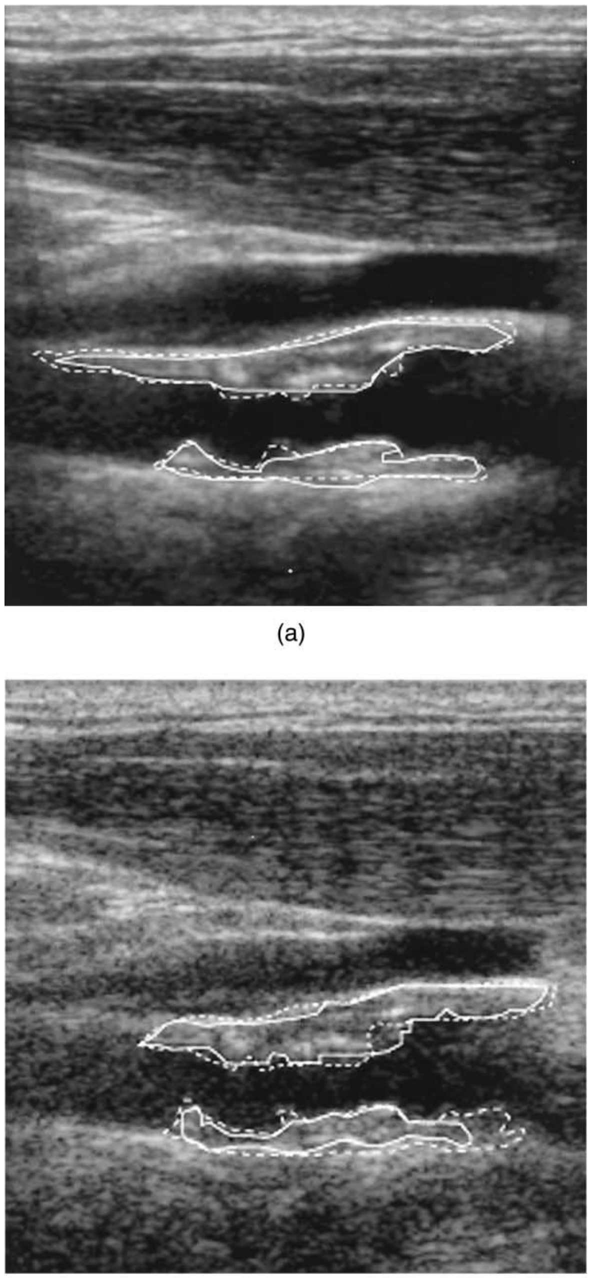

Fig. 1. (a) The first and second outline of the plaque by investigator A on the compounded image, and (b) the corresponding conventional image. The overlapping area (agreement) is greater for the compounded image.

In the present study, we tested the following hypotheses. (1) Does compound imaging improve inter- and intraobserver agreement compared with conventional technique when outlining plaques in moderate to severe carotid artery stenosis? (2) What is the interobserver variation of the gray-scale median value (GSM) of the "overlapping" area after repeated outlines for each of the two techniques?

Compound imaging

In contrast to conventional techniques, compound imaging has the ability to acquire multiple frames from different viewing angles and to combine these to form a single, multi-angle compound image. The ultrasound beam in each frame of the scan sequence is steered by a different, predetermined angle, typically within ± 20° from the perpendicular. This innovation will result in the suppression of common problems known to every ultrasonographer: these are image artifacts and angle-dependent backscatter (noise or speckle), because only signals from "true" structures are added, whereas random and artifactual echoes are being reduced.

MATERIALS AND METHODS

The internal carotid artery was assessed in 35 consecutive patients (13 females, 22 males) with 38 vessels having a stenosis in excess of 50%. All patients were admitted to the outpatient clinic with neurologic symptoms. The degree of stenosis was between 50 and 99%, measured by duplex ultrasound examination using generally accepted Doppler criteria (Londrey et al. 1991).

The ultrasound device used was the HDI 5000 (ATL Ultrasound, Bothell, WA, USA) with a 12-MHz high-resolution linear array transducer (256 element).

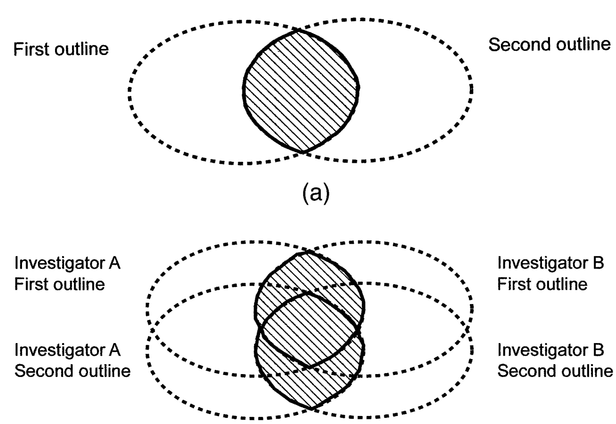

Fig. 2. (a) The intra- and interobserver agreement for each technique was evaluated by measuring the mean number of pixels in the overlapping area (hatched) of the two outlines divided by the mean number of pixels in the two outlined regions. The agreement was given in percent. (b) The interobserver variability in gray-scale median value was calculated on the basis of the overlapping area after first outline and the overlapping area after second outline between investigators. The difference in overlap was then plotted against the mean overlap in the Bland-Altman plots (Figs. 3, 4a and 4b).

We used seven angles, which covered a span from $-12.5°$ through $+12.5°$. A standard imaging procedure was adopted at the beginning of each examination, which included the following: compound imaging activated (all seven angles in use), linear gray scale map, dynamic range of 60 dB. The gain level was adjusted so that echoes just began to appear in the blood in the image. Optimum image focusing was secured by positioning the image focus at the level of the plaque. A single, experienced ultrasonographer (S.C.K.) performed all ultrasound examinations of the carotid arteries with subjects placed in the supine position. One B-mode cineloop of digital images (lasting 5 s) was captured using SonoCT compound imaging of the bifurcations of each subject.

Each cineloop acquisition, consisting of up to 300 frames, was reviewed by the ultrasonographer (S.C.K) with the use of the HDI Lab. A single good compound technique image representing the plaque was selected. Based on proprietary access to the image processing in the HDI 5000 provided by ATL, individual component frames for each steering angle were captured before compounding. These component frames could then be transferred to a PC and analysed individually, or compounded using the software HDI Lab (ATL Ultrasound, Bothell, WA, USA), which employs the same algorithms used by the HDI 5000 system. The proprietary access to image processing made it possible to find and save the exact 0°-angle image, which was a part of the seven frames, that constituted each selected compound image of the plaque. Two independent investigators (S.C.K and H.S.) reviewed all single frame images individually and blinded from each other. Each atherosclerotic plaque was outlined using the computer mouse and the software package Image-Pro Plus (Version 1.2 for Windows, Media Cybernetics). The gray-scale value of each pixel in the overlapping area was then used to generate a median gray-scale value (GSM) as an objective measure of the plaque echogenicity. In case of plaque-dependent acoustic shadowing, the outline did not include the shadow. Each investigator outlined the conventional and compound images separately, with a 1-week interval. All images were re-examined after 2 months, and the outline procedure was repeated (Fig. 1a and b).

The intra- and interobserver agreement was evaluated by measuring the mean number of pixels in the overlapping area after two outlines, divided by the mean number of pixels in the two outlined regions and expressed in percent (Fig. 2a).

The interobserver variations for the GSM values were determined on the basis of the overlapping area after first outline and the overlapping area after second outline between investigators (Fig. 2b).

Statistical analysis

The Wilcoxon signed rank sum test was used to test whether compound imaging had a higher intra- and interobserver agreement compared to the conventional technique regarding the number of pixels in the overlapping area. The interobserver repeatability of the GSM values for each technique was determined by Bland-Altman analysis for comparing two methods of clinical measurement in the absence of a gold standard (Bland and Altman 1986). The coefficient of repeatability of the GSM was calculated as the standard deviation (SD) of the differences in GSM value for the first and second overlap between investigators for each technique. For the interobserver variability, the coefficient of variance (CV) in overlapping area (both pixels and GSM) was calculated as the proportion of SD of the mean ($p < .05$ was considered significant in a two-sided test). All statistical analyses were performed with SPSS 10.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean patient age was 72 years, SD ± 7 years. The distribution of internal carotid stenoses was as follows: 25 between 50% and 69%, three between 70% and 79% and ten between 80% and 99%. In one case, investigator A was unable to identify the plaque in the conventional image, due to noise and clutter, and no outline was performed.

Intra- and interobserver agreement in carotid plaque outlining was good using the overlapping areas measured in pixels, but covered a substantial range. In four instances of conventional imaging, there was no overlap of the outlined regions. Although compound imaging showed significantly better agreement between investigators in the first outline, both investigators demonstrated almost equal ability to identify the same region after repeating the outlines regardless of the technique (Table 1).

Having arranged all conventional images according to ascending level of intra- and interobserver agreement, images could be categorised into poor and good agreement. When the 50% of these images with the poorest agreement were compared with the corresponding compound frames, compound imaging demonstrated improved concurrence (Table 2). This did not hold true when compound images were arranged in the same fashion and compared to conventional images. Considering all images, the coefficient of variation of the overlapping area after the first and second outlines between investigators was 20% for conventional imaging and 10% for compound imaging.

The median GSM value of the overlapping area after the first and second outlines between investigators was 56 (range, 15–83) and 59 (range, 16–98) for con-

Table 1. Intra- and interobserver agreement of overlap between repeated outlines of all carotid plaques for conventional and compound imaging

	Agreement (%)		
	Conventional technique	Compound technique	*P* value
Investigator A, 1. vs. 2. outline	84 (70–90)	86 (79–89)	0.11
Investigator B, 1. vs. 2. outline	81 (71–85)	82 (77–86)	0.18
Investigator A vs. B, 1. outline	75 (61–84)	82 (74–85)	0.01
Investigator A vs. B, 2. outline	79 (73–83)	78 (68–84)	0.87

Values are median agreements and interquartile range. *P* values are by Wilcoxon signed rank sum test.

ventional technique. For compound-imaging technique, the median GSM values were almost identical: 55 (range, 11–89) and 56 (range, 12–90). Thus, the study covered a representative selection of plaques ranging from hypo- to hyperechoic samples. The GSM values for the intra- and interobserver study did not show significant differences between techniques (data not shown). However, the interobserver variability revealed an increasing difference between investigators with increasing echogenicity. This was evident for both techniques, as illustrated in the Bland-Altman plot (Fig. 3).

The Bland-Altman analysis revealed limits of interobserver agreement (mean $\pm$ 2 SD) ranging from -32 to $+20$ GSM (mean bias $= -6$, SEM $\pm$ 3.5) and a coefficient of repeatability of 13 for conventional imaging (Fig. 4a). Compound technique showed a range of -6 to $+6$ GSM (mean bias $= 0$, SEM $\pm$ 0.7) and a coefficient of repeatability of 3 was found (Fig. 4b). When the first and second outlines were considered for all images, the GSM values of the overlapping area between investigators yielded a coefficient of variation for conventional and compound imaging of 34% and 9%, respectively.

DISCUSSION

Today, ultrasound is regarded as the most important tool for diagnosis and quantification of carotid artery disease. In contrast to the traditional angiogram, ultrasound also provides valuable information about the atherosclerotic plaque morphology (Biasi et al. 1999; Carr et al.1996; Grønholdt et al. 1998; Sabetai et al. 2000). Conventional imaging technique displays inherent image artifacts that limit its diagnostic accuracy. *In vitro* studies of surgically removed carotid plaques have shown that compound imaging's principal advantage over the single-angle imaging technique is reduction of speckle and clutter artifacts (Jespersen et al., 2000). This will increase its applicability in evaluation of plaque morphology, especially for the detection of the echolucent plaques, which are supposed to be the most rupture-prone (Geroulakos et al. 1993, 1994; Grønholdt et al. 1998). Although results show considerable variation, several studies have suggested that, in carotid artery plaques, a relationship exists between the intensity of the reflected ultrasound signal and histologic analysis of the surgically removed specimen (European Carotid Plaque Study Group 1995; Matsagas et al. 2000; El-Barghouty et al. 1996b). Poor visualisation combined with angle dependence of the intensity of the reflected signal might contribute to the great variation seen with conventional B-mode ultrasound. Picano et al.(1985) found that backscatter intensity varied as a function of the angle, according to various subsets (fibrofatty, fibrous and calcified

Table 2. Intra- and interobserver agreement of overlap between repeated outlines of the half of the carotid plaques with the poorest agreement for conventional and compound imaging

	Agreement (%)		
	Conventional technique	Compound technique	*P* value
Investigator A, 1. vs. 2. outline	70 (53–79)	84 (79–89)	0.001
Investigator B, 1. vs. 2. outline	71 (49–78)	82 (78–86)	0.002
Investigator A vs. B, 1. outline	62 (39–72)	80 (74–84)	< 0.0001
Investigator A vs. B, 2. outline	74 (40–77)	76 (64–85)	0.04

Values are median agreements and interquartile range. *P* values are by Wilcoxon signed rank sum test.

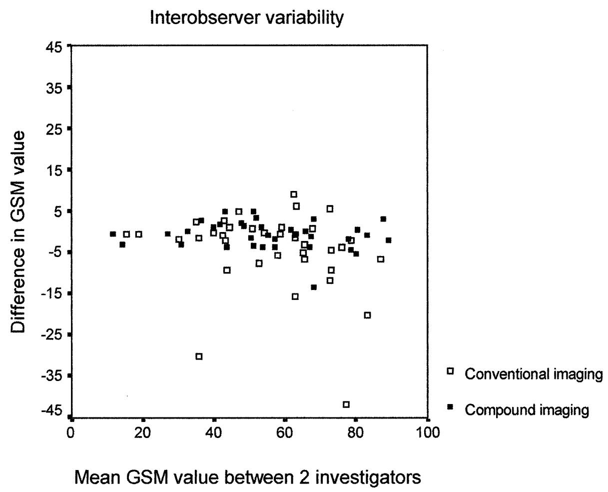

Fig. 3. Bland-Altman interobserver variability plot of the gray-scale median value (GSM) values for all observations for each technique. The mean value of two plaque outlines in GSM is seen at the abscissa. The difference between the two outlines in GSM is seen at the ordinate. Data are not normally distributed.

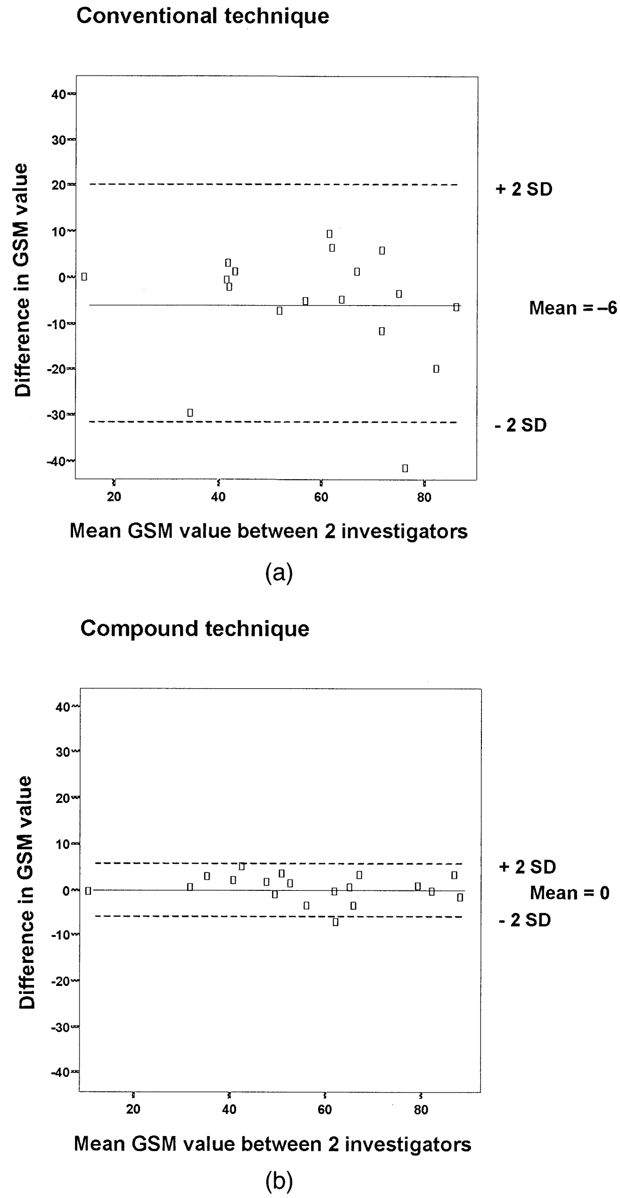

Fig. 4. Bland-Altman interobserver variability plots of the gray-scale median values (GSM). (a) Half of the conventional images showing poorest agreement, and (b) the corresponding compound images. The mean values of two plaque outlines in GSM are seen at the abscissa. The difference between the two outlines in GSM is seen at the ordinate. The dotted lines indicate ± 2 SD, which equals 95% of the observations, as data are normally distributed.

plaques). Fatty plaques, however, did not show significant angle dependence which may be considered their acoustic "fingerprint."

The aim of the present study was to investigate whether the agreement and variation of plaque outlines and the corresponding gray-scale median on B-mode images could be improved by compound imaging in a clinical situation. The main finding was that variation of interobserver agreement was lower for the compound technique. Corresponding conventional representations of images acquired by compound technique, with the poorest agreement, showed significantly better intra- and interobserver agreement as well as substantial lower interobserver variation for the GSM values. However, reproducibility studies concerning the methods for plaque identification and quantification of severe stenotic lesions, such as plaque size, are scarce. Persson et al (1992) used a computerised image-analysing system and reported intra- and interobserver differences around 16% and SD ± 12%. In the present study, absence of a standard control makes it impossible to determine whether the "true" plaque was outlined. We considered the difference in overlapping area after replicate outlines both within and between investigators to be the measure-of-choice, to compare the two techniques. The way the images were acquired in this study has a distinct advantage. Both the conventional and compound images were acquired simultaneously. This method circumvents the potential pitfall of movement (i.e., breathing or pulsation) or transducer movement, which is seen when images are acquired in two rounds, one for each technique. Thus, by removing this source of error, it was assured that agreement was calculated on the basis of the identical anatomical plane.

However, the analysis of a three-dimensional atherosclerotic plaque visualised on a 2-D B-mode image raises several problems that may contribute to biased plaque identification. First, identification of the plaque borders might be difficult, due to clutter and side lobes, grating lobes or multi-path reverberation in the vessel lumen, as well as interjacent tissue between transducer and vessel. Second, low echogenicity of the plaque makes it difficult for the investigator to judge the precise extent of the atherosclerotic process. To assist the delineation of the luminal plaque borders, several studies (Biasi et al. 1998, 1999; El-Barghouty et al. 1995, 1996b; Sabatai et al. 2000a, 2000b) have used the corresponding colour Doppler plaque images of the plaque in the outlining process. We did not make use of this procedure, because the purpose of this study was to test plaque identification solely by two B-mode techniques. Furthermore, compound imaging is not an option yet available in the colour flow facility. A source of potential bias in the present study is the possibility of "plaque recollection" by the investigator, which may have contributed to the obscuring of a difference between the techniques in the second outlining procedure. This is unlikely in the present study, because the two observers' interpretations of the images by one technique were almost equal to the other technique.

The overall variation in GSM value between investigators seemed to depend on the echogenicity of the plaque (Fig. 3). This can be expected, because an echo-rich plaque has a relatively higher intensity than blood and is, therefore, more sensitive to changes in outlining. In contrast, an echolucent plaque image with a lower gray scale content has an intensity almost equal to that of the lumen. Even then, compound imaging tends to have lower variation. This is especially evident when one focuses on the images with poorest agreement acquired by conventional technique. In a reproducibility study by Sabetai et al. (2000a), the interobserver limits of agreement showed the same pattern for variation in echogenicity. The gray-scale median of the plaque as a surrogate measure of the morphology is becoming increasingly recognised, because plaques which seem echolucent seem to carry a higher risk of stroke relative to echo-rich ones (Biasi et al. 1999; Grønholdt et al. 1998; Polak et al. 1998; Sabatai et al. 2000b; Tegos et al. 2001). Thus, a reliable GSM value based on reliable plaque identification is crucial if future patients are to be selected for surgery based on this measure. This study demonstrates that the GSM value may vary more than four times higher for images acquired by conventional technique compared to compound technique (Fig. 4a and b).

The currently accepted criteria for treating symptomatic carotid artery stenosis is exclusively based upon the degree of lumen narrowing (European Carotid Surgery Trial 1998; Barnett et al. 1998). Surgery for asymptomatic stenosis is still subject to controversy, and plaque morphology is not used routinely for selection of patients eligible for surgery, although a current multicenter trial (ACSRS) is studying the subject (Nicolaides 1995). Thus, the reliability and reproducibility of ultrasound is important to the evaluation of atherosclerotic plaque morphology for more accurate identification of which patients stand to benefit the most from surgery (Reid 1998). In conclusion, this investigation supports previous *in vitro* findings that compound imaging improves ultrasound images also in a clinical setting.

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