The role of carotid plaque echogenicity in baroreflex sensitivity

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Objective: **The baroreflex sensitivity is impaired in patients with carotid atherosclerosis. The purpose of our study was to assess the impact of carotid plaque echogenicity on the baroreflex function in patients with significant carotid atherosclerosis, who have not undergone carotid surgery.**

Method: **Spontaneous baroreflex sensitivity (sBRS) was estimated in 45 patients with at least a severe carotid stenosis (70%-99%). sBRS calculation was performed noninvasively, with the spontaneous sequence method, based on indirectly estimated central blood pressures from radial recordings. This method failed in three patients due to poor-quality recordings, and eventually 42 patients were evaluated. After carotid duplex examination, carotid plaque echogenicity was graded from 1 to 4 according to Gray-Weale classification and the patients were divided into two groups: the echolucent group (grades 1 and 2) and the echogenic group (grades 3 and 4).**

Results: **Sixteen patients (38%) and 26 patients (62%) were included in the echolucent and echogenic group, respectively. Diabetes mellitus was observed more frequently among echolucent plaques ($\chi^2 = 8.0$; $P < .004$), while those plaques were also more commonly symptomatic compared with echogenic atheromas ($\chi^2 = 8.5$; $P < .003$). Systolic arterial pressure, diastolic arterial pressure, and heart rate were similar in the two groups. Nevertheless, the mean value of baroreflex sensitivity was found to be significantly lower in the echogenic group (2.96 ms/mm Hg) compared with the echolucent one (5.0 ms/mm Hg), ($F[1, 42] = 10.1$; $P < .003$).**

Conclusions: **These findings suggest that echogenic plaques are associated with reduced baroreflex function compared with echolucent ones. Further investigation is warranted to define whether such an sBRS impairment could be responsible for cardiovascular morbidity associated with echogenic plaques. (J Vasc Surg 2011;54:93-99.)**

Arterial baroreflex is the most important short-term regulatory mechanism of blood pressure and heart rate.[1] It originates from the carotid sinus and the aortic mechanoreceptors and operates through the autonomic nervous system to buffer abrupt transients of blood pressure.[2] The stretch applied to the mechanoreceptors modulates blood pressure by reciprocal changes in vagal and sympathetic nervous activity.[3] Spontaneous baroreflex sensitivity (sBRS) measures the sensitivity of baroreceptors. It represents an index of their activity, and it is considered to be an important determinant of autonomic cardiovascular control.[4]

Previously published studies suggest that in patients with significant carotid atherosclerosis, the histologic changes of the artery wall can alter the elastic properties of the carotid sinus and can cause a reduction in both the distensibility of the vessel wall and the sensitivity of the baroreceptors.[5,6] It is, however, unclear whether specific ultrasound carotid plaque characteristics, such as plaque echogenicity, are associated with baroreceptors' sensitivity. The present study aimed to assess the baroreflex sensitivity in patients with significant carotid atherosclerosis and to investigate potential correlations with plaque echogenicity. To our knowledge, no association between plaque echogenicity and sBRS has been previously reported.

METHODS

Forty-five patients, with at least a carotid artery stenosis of 70% to 99% as measured by digital subtraction angiography and calculated according to the North American Symptomatic Carotid Endarterectomy Trial[7] criteria were enrolled in this study. Healthy individuals as control group were not included in the study. Instead, normal sBRS values were defined according to previously published literature.[8]

Exclusion criteria were cardiac rhythm disorders, heart failure, previous carotid endarterectomy or angioplasty, carotid dissection, carotid occlusion, and hemorrhagic stroke. Medications known to interfere with autonomic dysfunction like β-blockers, calcium inhibitors, converting enzyme angiotensin inhibitors, vasodilators, statins, and neuroleptics were stopped for 24 hours before testing.[9] The study protocol was approved by our institution's ethics committee; written informed consent was obtained by all subjects.

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Competition of interest: none.

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Table I. Comparison of demographic and clinical characteristics between the two study groups

	Echolucent plaques (n = 16)	*Echogenic plaques (n = 26)*	P *value*
Demographics/clinical characteristics			
Age (years)	70.3	68.3	NS (ISTT)
Men	10 (63%)	17 (65%)	NS (χ^2)
Obesity	2 (13%)	5 (31%)	NS (FET)
Diabetes mellitus	10 (63%)	5 (19%)	(χ^2), P < .004
History of heart infarct	7 (44%)	10 (38%)	NS (χ^2)
Hypertension	11 (69%)	18 (69%)	NS (FET)
Smoking	11 (69%)	17 (65%)	NS (χ^2)
Symptomatic stenosis	11 (69%)	6 (23%)	(χ^2), P < .003
CCS >70%	6 (38%)	4 (15%)	NS (χ^2)

CCS, Contralateral carotid stenosis; *FET,* Fisher exact test; *ISTT,* independent samples *t* test; *NS,* nonsignificant.

During measurement of spontaneous baroreflex sBRS, three subjects whose electrocardiographic signal did not permit accurate analysis were excluded. Thus, a total of 42 patients (27 male; mean age, 69.1 years; range, 45-81 years) were finally evaluated. Neurologic status was assessed in all individuals by the same neurologist. Plaques were defined as symptomatic when focal symptoms of cerebral ischemia were present, ipsilateral to the carotid lesions, such as transient ischemic attack, amaurosis fugax, or stroke in the last 6 months. Of the 42 plaques that were surgically removed, 28 (67%) were asymptomatic, eight (19%) were associated with a hemispheric transient ischemic attack, three (7%) with amaurosis fugax, and three (7%) with stroke. All contralateral significant lesions (n = 10, 24%) were asymptomatic. The demographic and clinical characteristics of the patients of the two groups are shown in Table I.

Assessment of plaque echogenicity. Echogenicity of atherosclerotic plaques was assessed in all patients with duplex ultrasonography. The ultrasound examinations were executed with a commercially available Hewlett Packard ultrasound device (Sonos 1000, 7.5-MHz linear array transducer, Andover, Mass). Two trained physicians conducted the ultrasonography study and interpreted the results based on the same standardized protocol[10] with very good interobserver agreement. The echogenicity of each plaque was graded from 1 to 4 according to the Gray-Weale classification (1988).[11] Plaques of types 1 and 2 were defined as echolucent plaques (group A), and plaques of types 3 and 4 were defined as echogenic plaques (group B). Type 5 plaques according to the modified version of Gray-Weale's classification were excluded from the study, since they represent unclassified plaques in terms of echogenicity. Their heavy calcification, which results in heavy acoustic shadowing, obscures the deeper part of arterial wall and vessel lumen and thus prevents characterization of plaque material.[12] In patients with bilateral lesions, the classification was performed according to the echogenicity of the plaque causing the greater stenosis.

Assessment of baroreflex sensitivity. Carotid sinus sensitivity was assessed with sBRS using the sequence method that was first described by Parati et al.[13] This method is based on the identification of three or more consecutive beats in which progressive increases/decreases in systolic blood pressure are followed by progressive lengthening/shortening in RR interval. RR represents the interval between the peaks of two subsequent QRS complexes in an ECG. Such a technique has been reported to provide information on the baroreceptor modulation of the sinus node, while also enabling identification of factors that determine the sensitivity of this baroreceptor reflex function.[12] Besides, this method eliminates the intra- and intersubject measurement variability, compared with other methods, due to the fact that computations are automatic and standardized.[8]

Data were collected for analysis 24 hours before endarterectomy. All recordings were made in a quiet, darkened room, with ambient temperature between 20°C and 25°C. All subjects were in the supine position and were instructed not to speak during the procedure. All measurements were performed using the BaroCor System (AtCor Medical, Sydney, Australia), which can calculate sBRS during spontaneous fluctuations of systolic arterial pressure (SAP) and RR interval. Arterial pressure and electrocardiogram (ECG) were simultaneously recorded noninvasively for 20 minutes in the supine position. Continuous blood pressure measurements were made using a radial tonometer (CBM 7000; Colins Medical Instruments Corp, San Antonio, Tex), which via a validated generalized transfer function, proposed by Chen et al[14] enabled the calculation of the aortic blood pressure waveform from the radial artery waveform. SAP and diastolic arterial pressures (DAP) and ECG signals were digitized for storage and analysis with a software program (Fig 1). The computer software, BaroCor System Software (AtCor Medical), examined these digitized signals to select all sequences of three or more successive heartbeats in which there were concomitant increases or decreases in SAP and RR interval. A linear regression was applied to each selected sequence and the mean slope was calculated as the average of all slopes during each recording period (20 minutes). This mean slope (expressed in milliseconds [ms]/mm Hg) was used as an index of sBRS. The regression slope was calculated in those sequences, which had a correlation coefficient above 0.80. The minimum RR

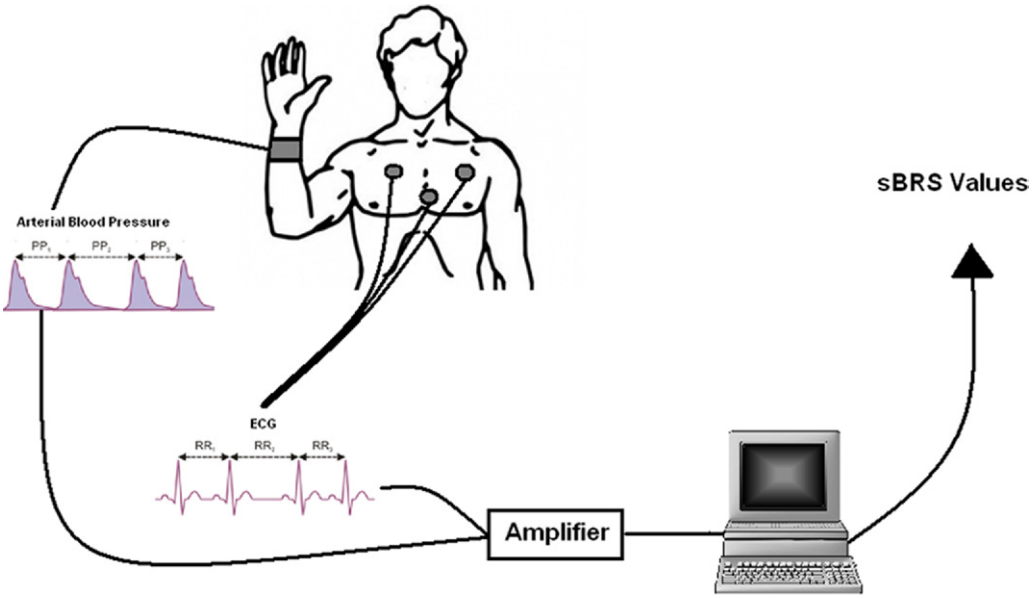

Fig 1. Schematic diagram demonstrating the noninvasive process of obtaining spontaneous baroreflex sensitivity (*sBRS*). Simultaneous recording of systolic arterial pressure via a radial tonometer and electrocardiogram (*ECG*) RR intervals and subsequent data process through a computerized standardized system. RR represents the interval between the peaks of two subsequent QRS complexes in an ECG.

Table II. Comparison of hemodynamic parameters between the two groups

	Echolucent plaques (n = 16)	*Echogenic plaques (n = 26)*	P *value*
Mean SAP (mm Hg)	134.7	131.0	$P < .5$ (NS)
Mean DAP (mm Hg)	82.3	78.9	$P < .3$ (NS)
Mean HR (s^{-1})	70.5	70.1	$P < .9$ (NS)
Mean sBRS (ms/mm Hg)	5.0	2.96	$P < .003$

DAP, Diastolic arterial pressure; *HR,* heart rate; *SAP,* systolic arterial pressure; *sBRS,* spontaneous baroreflex sensitivity.

interval change accepted was 4 ms, while the minimum change for a spontaneous fall or rise in systolic pressure accepted, was 1 mm Hg.

Statistical analysis. The statistical package SPSS for Windows (Chicago, Ill), release 12, was used for data analysis. Preoperative patient characteristics (demographic data, except age) were compared using the χ^2 test or Fisher exact test, according to the sample. Age was compared between the two groups using the independent samples *t* test. The association between echogenicity of the plaque and hemodynamic parameters or sBRS, was investigated with the analysis of covariance test, since the dependent variable sBRS was normally distributed in both the echolucent and echogenic groups (skewness −0.02 and +0.3, respectively).

RESULTS

The spontaneous sequence method used to estimate sBRS, failed in three patients (7%). These patients had less than three detectable spontaneous sequences in the 20-minute SAP and ECG recordings. Sixteen patients (38%) and 26 patients (62%) were included in the echolucent and echogenic group, respectively. A history of diabetes mellitus was more common among patients with echolucent plaques (63%) compared with individuals with echogenic atheromas (19%, $\chi 2 = 8.0$, $P < .004$). Moreover, the rate of symptomatic plaques was significantly increased in the echolucent group (69% vs 23%, $\chi 2 = 8.5$, $P < .003$) (Table I).

The hemodynamic parameters recorded are presented in Table II. An analysis of covariance was used to assess whether these parameters were significantly different between echolucent and echogenic groups, after controlling for differences in the percentages of diabetes and symptomatic plaques. Systolic arterial pressure, diastolic arterial pressure, and heart rate were similar in the two groups. Nevertheless, the mean value of sBRS was found to be significantly greater statistically in the echolucent group (5.0 + 1.9 ms/mm Hg) compared with the echogenic (2.96 + 1.2 ms/mm Hg), ($F[1, 42] = 10.1$, $P < .003$) (Figs 2 and 3, Table II). Covariance analysis demonstrated that there is an association between plaque echogenicity and baroreflex sensitivity that is independent of the presence of diabetes mellitus and symptomatic nature of carotid

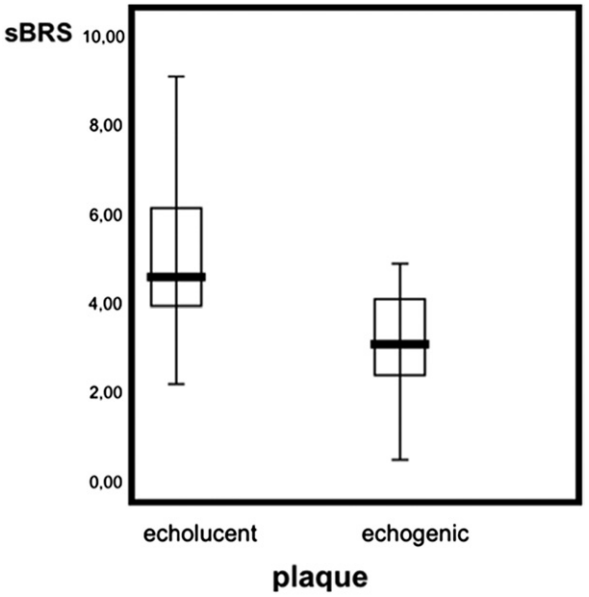

Fig 2. Box plots and whiskers showing graphically a statistically significant reduction in spontaneous baroreflex sensitivity (*sBRS*) of echogenic plaques compared with echolucent ones after controlling for differences in diabetes mellitus and symptomatic plaques.

plaque. Since contralateral carotid stenosis (CCS) demonstrated a small *P* value (.14) between the two groups and could also theoretically influence sBRS, we considered adding it as a covariate in our analysis. Interestingly, the addition of CCS in the multivariate analysis revealed an even stronger correlation between echogenicity and sBRS ($F[1, 42] = 12.0$, $P < .001$).

DISCUSSION

sBRS has been proposed to be potentially useful as a global risk marker of cardiovascular diseases.[15] More specifically, it has shown that it is a valuable predictor of long-term mortality outcome after myocardial infarction,[16] and it is also a useful and independent predictor of long-term survival in heart failure patients.[17] The above indicate that sBRS has a potential clinical and prognostic value in a variety of cardiovascular disorders and thus, it could represent a new risk index that can be obtained in all patients carrying important predictive information independent of most common clinical and functional indicators.[16] Particularly, in the carotid territory, it has already been demonstrated that patients with either unilateral or bilateral carotid stenosis have impaired sBRS.[18,19]

In such a perspective, determining possible factors affecting baroreflex sensitivity (BRS) that are simply, routinely, and noninvasively obtained, such as ultrasonographic plaque characteristics, may be of potential clinical significance. In the present study, we investigated sBRS alterations in relation to the carotid plaque ultrasound echogenicity. To the best of our knowledge, there is no other study associating sBRS with carotid plaque echogenicity.

Spontaneous BRS calculation in patients with carotid occlusive disease[19] has been previously reported based on continuous blood pressure recordings in a peripheral artery, usually in a digital artery. However, the blood pressure changes that stimulate baroreceptors, either in the aorta or the carotid sinus, are located in the central region of the arterial tree, where the blood pressure waveforms are different than those in the peripheral arteries.[1] In the present study, measurement of sBRS was based on the impact of the estimated central blood pressure changes on heart rate. This estimation was obtained indirectly from radial artery recordings and is considered to be a more accurate assessment of sBRS.[20]

Our results indicate that echogenic carotid plaques are associated with a lowering of resting sBRS, after adjustment on other factors associated with sBRS reduction. Some parameters that could affect the function of baroreceptors were age, heart rate, SAP, DAP, obesity, and smoking.[21] However, all these variables were not significantly different statistically between the two groups, and thus, they were not considered responsible for differences in sBRS between the two groups.

In contrast, the incidence of symptomatic plaques and history of diabetes was significantly increased in the echolucent group compared with the echogenic one, which is in line with the results of previous studies.[22,23] One could expect that a group of patients with increased rates of symptomatic plaques and history of diabetes, such as our echolucent group, could demonstrate a reduction in sBRS according to previous literature.[24,25] In our study, however, echolucent plaques demonstrated statistically increased sBRS compared with echogenic ones, despite the fact that in the echolucent group, the incidence of symptomatic plaques and history of diabetes was increased. This reflects probably the fact that plaque echogenicity may be a stronger factor than symptomatic nature of the plaque and history of diabetes and in terms of sBRS alteration.

The reduced sBRS in the echogenic group could be explained by a possible greater stiffness in the barosensitive region of the carotid artery in these patients and the subsequent limited stretching and relaxation of the baroreceptors in response to changes in blood pressure. It is possible that patients with echogenic plaques have stiffer barosensitive regions, compared with patients with echolucent plaques, and they are not so sensitive to the rate of transmural pressure change. The association between arterial stiffness and sBRS is reported in several studies.[26,27] In Rotterdam Study,[28] arterial stiffness itself was associated with impaired cardiovagal BRS, after adjustments for various cardiovascular risk factors, like hypertension, diabetes mellitus, and carotid atherosclerosis, which are involved in the development of arterial stiffness.

Nevertheless, in this study, we did not measure the stiffness of echogenic plaques. Our primary goal was to look for a correlation between sBRS and plaque echogenicity, which is an ultrasonographic characteristic, routinely

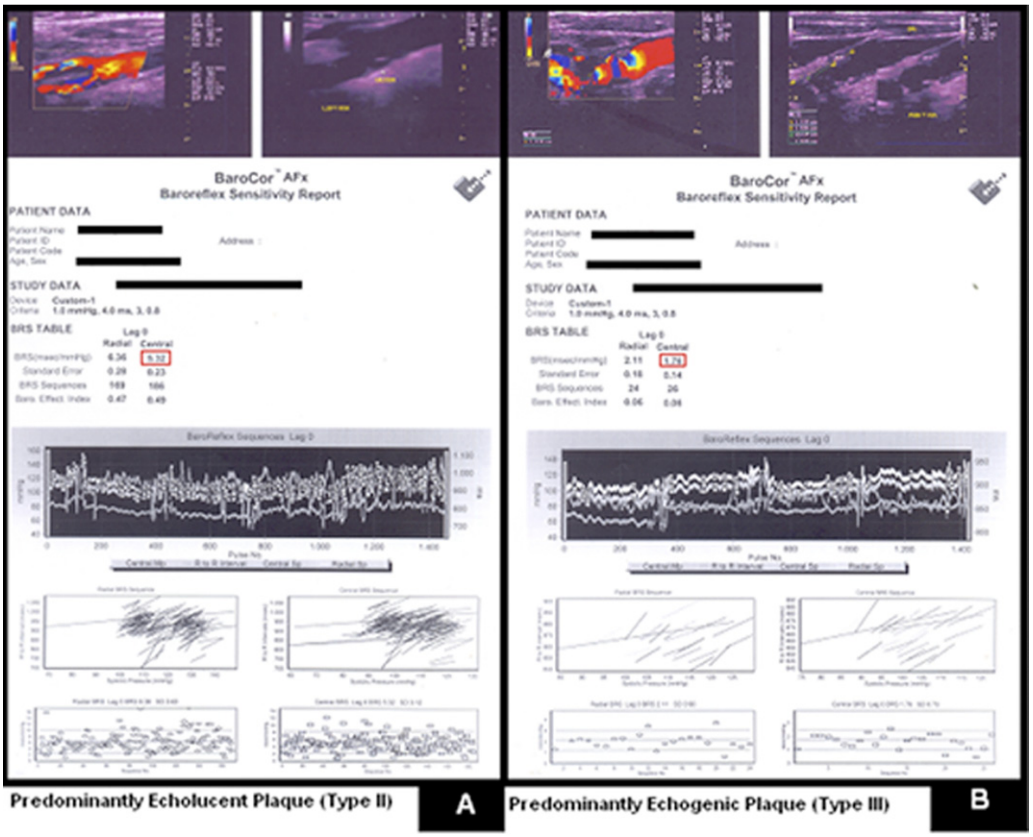

Fig 3. Carotid color duplex ultrasound matched with the respective spontaneous baroreflex sensitivity (*sBRS*) report of **(A)** a predominantly echolucent (*type 2*) and **(B)** a predominantly echogenic (*type 3*) carotid plaque. Note the different sBRS values in the red outlined boxes (5.32 vs 1.76 ms/mm Hg for echolucent and echogenic plaque, respectively).

estimated in every patient with a suspicion for carotid artery disease. Besides, it should be noted that sBRS is a composite marker of the overall integrity of the autonomic nervous system and is therefore determined by additional factors other than arterial stiffness, such as the parasympathetic and sympathetic nervous system function, paracrine factors,[29] oxygen free radicals,[30] and platelet aggregation.[31] Since, currently, there are no available studies investigating such a possible correlation between arterial stiffness and carotid plaque echogenicity, no safe conclusions can be drawn regarding this issue.

In our study, sBRS was calculated postoperatively in a part of our patient cohort and interestingly the values between patients with echolucent plaques and those individuals with echogenic plaques were found to be similar (data not shown). That similarity of sBRS values, after the removal of atheroma in both groups of patients, could support our finding that there is a relationship between plaque echogenicity and baroreflex function. The verification of these preliminary data could support such a hypothesis.

In the present study, we found different baroreceptor sensitivity in patients with different echogenicity of only the ipsilateral carotid plaque (the symptomatic one or, in cases of bilateral stenoses, the most severe one). One could claim that this finding is in contrast to the results of Nasr et al.[19] According to this study, sBRS is impaired in patients with bilateral carotid atherosclerosis, but not in patients with unilateral disease, since it seems that in unilateral stenoses, the contralateral baroreceptors can alter their functionality toward the normal values, compensating thus for the impairment in sBRS of the ipsilateral plaque. However, in our cohort beyond a small percentage of individuals (24%) with significant contralateral stenosis (>70%) (38% in the echolucent and 15% in the echogenic), a significant ratio of our patients had also a concomitant contralateral mild, stenosis (30%-50%) raising, thus, the total percentage of patients with bilateral carotid atherosclerosis up to 90%.

One could criticize that, in the interpretation of results, we did not take into account the presence of aortic atheroma. It is known that sBRS is a composite marker of the overall integrity of the autonomic nervous system,[32] and it is determined by the mechanical properties of both the carotid and aortic wall. The results in the literature about the relative importance of carotid versus aortic baroreceptors are contrasting.[33] However, in a study of patients with

atherosclerosis in carotid arteries,[19] there was no correlation between aortic atheroma and sBRS; this supports the idea of predominance of the carotid component of baroreflex over its aortic component. In the present study, the strong association between plaque echogenicity and sBRS suggests that the role of aortic baroreceptors compared with carotid baroreceptors may be subordinate. Certainly, additional studies are needed to further clarify this issue.

Another limitation of this study is that B-mode ultrasound has a tendency towards an easier assessment of echogenic plaques. Nevertheless, the two sonographers, who performed the examinations, were quite experienced (14 and 22 years of experience), and they followed a standardized protocol that lowers interobserver variability.[34] Thus, we obtained a very good agreement on their classification of carotid plaque echogenicity, better than other studies using the Gray-Weale classification.[35] However, computerized evaluation of plaque echogenicity (grayscale median method) probably may represent a more objective and quantitative method than visual analysis alone.[36]

Although the present study was not designed to estimate the clinical significance of impaired sBRS in patients with echogenic carotid plaques, our results have potential clinical implications, given the fact that reduced sBRS is an important and independent index of cardiovascular risk.[37,38] Impaired BRS is strongly associated with the development of life-threatening arrhythmias and increased sympathetic activity resulting in increased coronary vasoconstriction, increased platelet aggregation, and impaired ventricular remodeling.[39,40] Therefore, it could be speculated that echogenic plaques with impaired BRS may represent a strong risk factor for cardiac morbidity and mortality in patients with carotid artery stenosis. Certainly, our study does not support that echolucent plaques are overall less dangerous than echogenic ones, however, it suggests that patients with echolucent plaques seem to have a specific advantage as far as sBRS impairment is concerned, compared with patients with echogenic plaques. The fact that echolucent plaques are associated with greater risk for cardiovascular events, despite their lower sBRS impairment, may simply reflect that additional variables other than sBRS play a stronger role in determining the final clinical significance of each plaque type. This, however, does not abolish the possible role of sBRS in assessing a patient with carotid artery disease. Thus, it seems that echolucent plaques may be more "dangerous" in terms of cerebrovascular morbidity and mortality, but echogenic plaques with impaired BRS may also represent a strong risk factor for cardiac morbidity and mortality. Consequently, echogenic plaques when detected may contribute to the recognition of a patient population that is probably in high risk for cardiac events (eg, arrhythmias), due to the impaired function of baroreflex, despite the advantage in terms of lower probability for cerebrovascular events, compared with patients with echolucent plaques. Besides, prophylactic treatment with specific drugs (eg, anti-arrhythmic agents or angiotensin-converting enzyme inhibitors to increase BRS activity) could be also tested in patients detected with echogenic plaques with low BRS.

In conclusion, the present study showed that echogenic plaques are associated with a significant reduction of sBRS compared with echolucent ones. Despite the fact that echolucent plaques are associated with more cardiovascular events, compared with echogenic ones, the latter carry also a significant cardiovascular risk; baroreflex dysfunction could potentially explain part of the cardiovascular morbidity and mortality in this group of patients. Further studies are necessary to confirm these findings and investigate potential clinical implications of such observations.

AUTHOR CONTRIBUTIONS

Conception and design: NT, IS, SG, CB
Analysis and interpretation: NT, EEB, SG, CK, EAB
Data collection: NT, IS
Writing the article: NT, AK, EEB
Critical revision of the article: NT, AK, IS, EEB, SG, CK, CB, EAB
Final approval of the article: NT, AK, IS, EEB, SG, CK, CB, EAB
Statistical analysis: NT, AK, EEB, SG
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NT and AK contributed equally to this work.

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