

RELATIONSHIP BETWEEN CAROTID ARTERY DOPPLER FLOW VELOCITY AND EXTENT OF CORONARY ARTERY DISEASE

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Contribution

YG, LTA conceived the idea and designed the study. Data collection was done by RA, HG while PV did the manuscript writing. MAC, MBB and HK did review. All authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: To determine and compare the presence and extent of coronary artery disease and its association with ICA Doppler flow parameters in patients undergoing carotid artery stenting and patients who were treated conservatively.

Methods: This cross-sectional study consisted of patients referred from our internal and neurological department, from local general practitioners, and other hospitals for carotid angiography. These patients underwent baseline carotid USG before carotid angiography and coronary angiography in the same session were evaluated retrospectively. Patients with sonographically significant lesion (diameter stenosis of $\geq 50\%$), underwent elective carotid angiography and coronary angiography in a single session were enrolled in the study at Sakarya University Training and Research Hospital from 1st June to 31st December 2016. For all analyses, a two-tailed $p \leq 0.05$ was considered statistically significant.

Results: Total of 112 patients were included. Thirty of the stented patients and 21 of the conservatively treated patients had coronary artery disease. Gensini scoring was 22 ± 8 in the stented group and 20 ± 6 in the conservative group, ($p=0.764$). The preprocedural PSV, EDV, ICA/CCA ratio were 196 ± 25 , 104 ± 33 , 3.9 ± 1.3 in the stented group and 136 ± 65 , 42 ± 6 , 1.9 ± 0.8 in the conservative group, respectively. When two groups were compared, these parameters were significantly lower in patients treated conservatively ($p < 0.001$). In addition, the percentage of patients with CAD were similar in both treatment groups (46 % and 44 %, $p > 0.05$). Atherosclerotic risk factors such as age, gender, BMI, hypertension, DM and familial history of CAD, current smoking, LDL and triglyceride levels were not significantly different between the stented and the conservative group. Significant correlation was found between two Doppler parameters (ICA PSV and ICA/CCA PSV ratio) and extension of CAD (Gensini scoring)..

Conclusion: Patients with carotid artery disease have a high incidence of concomitant coronary artery disease, which is not different between the patients treated conservatively and stenting. In addition, the extension of coronary artery disease (not the presence) were associated with these two Doppler parameters.

Key Words: Carotid artery Doppler, Coronary artery disease, Stenting, Sonography

INTRODUCTION

Although modern pharmacotherapy and revascularization have markedly enhanced the prognosis of patients with atherosclerotic vascular disease, myocardial infarction and stroke remain the leading causes of mortality and morbidity due to this disease. Concurrent coronary artery disease (CAD) and carotid artery stenosis are frequently detected in clinical practice and have important prognostic implications in patients who are considered for revascularization of one or both of these vascular beds.¹⁻⁴ In addition, the presence of CAD is associated with an increased risk of cardiovascular events in patients with Ca-AD regardless of the treatment strategy (medical therapy alone or revascularization).⁵

In spite of the widespread use of carotid intima-media thickness (IMT) as a surrogate for CAD, validation studies evaluating the correlation between carotid IMT measured by external carotid ultrasound and CAD measured by quantitative coronary angiography showed a relatively poor correlation. This latter observation confirms the correlation between carotid IMT and CAD but does not imply that carotid IMT is a predictor of the severity and extent of coronary atherosclerosis. Indeed, the prognostic impact of ultrasound characteristics of carotid plaques on cardiovascular outcomes of patients with CAD remains controversial. Hence, we advocate the screening of patients with diagnosed Ca-AD for coronary atherosclerosis.⁶

However, the relationship between ICA Doppler flow parameters and the presence or the degree of coronary artery stenosis in patients with Ca-AD are not well known.

The aim of this retrospective study was to determine and compare the presence and extent of CAD in patients with Ca-AD (undergoing CAS and treated conservatively), as well as to determine the relationship between ICA flows and the presence and extension of CAD.

METHODOLOGY

This cross sectional study consisted of patients were referred from our internal and neurological department, from local general practitioners, and other hospitals for carotid angiography. These patients underwent baseline carotid USG before carotid angiography and coronary angiography in the same session were evaluated retrospectively. Patients with sonographically significant lesion (diameter stenosis of $\geq 50\%$), underwent elective carotid angiography and coronary angiography in a single session were enrolled in the study at Sakarya University Training and Research Hospital. Modified Gensini scoring was used in the two groups in order to determine the severity of coronary atherosclerosis.

Neurologic examination was carried out a day before and a day after CAS by an experienced neurologist who was not involved in the CAS procedure. In addition, baseline risk factors for atherosclerosis, age, gender, hypertension, hypercholesterolemia, diabetes mellitus (DM), history of ischemic heart disease, and smoking were investigated for each patient.

The study, which complied with the Declaration of Helsinki, was approved by the local ethics committee, and all patients enrolled in the study gave written informed consent.

Atherosclerosis of both the left and right ICA was assessed by a radiologist who was blinded to the clinical data. Patients were placed in a supine position with their neck in extension and rolled contralaterally by about 45° . The carotid arteries were examined in the long- and short-axis view. ICA atherosclerosis was evaluated by the maximum percentage of diameter reduction recorded by B-mode ultrasound, and by the peak systolic velocity (PSV), end diastolic velocity (EDV), and ICA/CCA PSV ratio per Doppler. Lesion severity was defined as the greatest stenosis observed either on the right or left ICA. Ultrasound and Doppler findings were classified into two categories:⁷

- 1) Normal and noncritical: PSV < 125 cm/s with no signs or the presence of a sonographic atherosclerotic lesion (no plaque or intimal thickening is visible sonographically) correlating to diameter stenosis of $< 50\%$
- 2) Clinically significant: (PSV ≥ 125 cm/s and the presence of a sonographic atherosclerotic lesion correlating to a diameter stenosis of $\geq 50\%$).

Patients with total or near occlusion (defined as 0 PSV and no visible flow total or near occlusion) were excluded.

All procedures including carotid and coronary angiography and carotid artery stenting were performed by the femoral approach using the standard Judikin's technique. At least two projections of the carotid artery stenosis were obtained for the calculations of vessel diameter and degree of stenosis. Coronary angiography was performed in all projected patients without complications and was routinely performed before CAS. For complete visualisation of the left coronary artery system, at least five different projections were used. Clinically significant CAD was defined as the presence of a coronary lesion resulting in a lumen diameter stenosis $\geq 70\%$ in a major epicardial artery (left anterior descending artery, left circumflex artery, right coronary artery) or one of its major branches. Clinically significant left main disease was defined as a lumen diameter stenosis $\geq 50\%$. Patients were stratified according to the number of involved vessels as follows: normal coronaries or nonobstructive CAD (individuals not meeting the criteria for clinically significant CAD), 1, 2, 3 vessel disease (significant lesions in 1, 2, and 3 vessels, respectively), with or without concomitant lesions in other vessels. The carotid and coronary angiograms were reviewed by two cardiologists, who determined the severity of each lesion according to the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET).⁷

According to our research protocol, the carotid artery was stented in asymptomatic patients with $\geq 80\%$ stenosis of the extracranial carotid artery and in symptomatic patients with $\geq 70\%$ stenosis. Patients were treated conservatively because of severe circumferential calcifications, variations of the aortic arch, or the presence of noncritical lesions. All patients received aspirin 100 mg once a day. Low-molecular-weight heparin was given after stent placement and was discontinued at the time of discharge. Clopidogrel 75 mg once daily was administered 7 days before the intervention and was continued for 3 months.

The following conditions were defined as exclusion criteria: patients who did not undergo a simultaneous coronary angiography, acute coronary syndrome, urgent CAS for severe neurological symptoms, lack of compliance, and significant thyroid, renal or hepatic dysfunction.

The Gensini score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. We evaluated the reduction in the lumen diameter, and the angiographic appearance of concentric lesions and eccentric plaques (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment, namely, $\times 5$ for the left main coronary artery; $\times 2.5$ for the proximal segment of the left anterior descending coronary artery (LAD); $\times 2.5$ for the proximal segment of the circumflex artery; $\times 1.5$ for the mid-segment of the LAD; $\times 1.0$ for the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery; and $\times 0.5$ for any other arteries.

Statistical evaluation was performed using SPSS 15.0 software package for Windows (Chicago, IL, USA). Quantitative variables are given as mean \pm standard deviation, and qualitative variables

are expressed as frequency and percentage. Groups (stenting or medically and CAD or non-CAD) were compared using the Student's t test for continuous variables and χ^2 test for categorical variables. When more than two groups were compared for parameters, analysis of variance (ANOVA) was used; post hoc analysis was performed using Tukey-HSD test. Logistic regression models were fitted for CAD severity and extension, and defined by Gensini scoring as the dependent variable, with adjustment for Doppler parameters of Ca-AD, age, gender, smoking status, hypertension, DM, hyperlipidemia. For all analyses, a two-tailed $p \leq 0.05$ was considered statistically significant.

RESULTS

In this study, 138 consecutive patients were enrolled, with 26 patients excluded from the study. One hundred twelve patients with a sonographically significant lesion (diameter stenosis of $\geq 50\%$) underwent elective carotid angiography, and coronary angiography was attempted in a single session. The mean age of our patients was 66 ± 8 (range 43 to 83 years). Most of the patients were men (73/39), were smokers (51%), had hypertension (62%), about one-third of the total population (33%) had type 2 DM, and Gensini scoring was 21 ± 16 (0-148). The demographic and clinical characteristics of the entire study population are presented in table 1.

Table 1: Demographic Variables of Study Population (n = 112)

Variables	Frequency (percentage) n (%)
Male/female	73/39
Age	66 ± 8 (43-83)
Body mass index	27 ± 2
Hypertension (%)	62
Diabetes mellitus (%)	33
Current smoking (%)	51
Familial history of CAD (%)	36
Triglyceride	128 ± 28
LDL	144 ± 47
CAS	65 (58%)
ICA lesion	50 ± 22
ICA PSV	168 ± 84 (30-365)
ICA EDV	71 ± 44 (15-170)
ICA-CCA ratio	2.8 ± 1.5
CAD	51 (45%)
Gensini scoring	21 ± 16 (0-148)
One-vessel disease	18 (35.3)
Two-vessel disease	22 (43.1)
Three-vessel disease	11 (21.6)
Procedural time (min)	27 ± 16

We also analyzed angiographic carotid stenosis based on the NASCET criteria. Sixty-five patients underwent elective stenting of the ICA (36 right, 29 left) and 47 patients were treated conservatively. Of the stented patients, 30 (46%, mean age 67 ± 11) had CAD, whereas in those treated medically, 21 patients (44%, mean age 65 ± 8) had CAD. A total of 13 patients had one-vessel disease, 12 patients had two-vessel disease, and 5 patients had three-vessel disease in the stent group, whereas 5 patients had one-vessel disease, 10 patients had two-vessel disease, and 6 patients had three-vessel disease in the conservative group. The result was not statistically different between the two groups. In the two groups; modified Gensini scoring was used to determine the severity of coronary atherosclerosis. Gensini scoring was 22 ± 8 in the stented group and 20 ± 6 in the conservative group, ($p = 0.764$).

In addition; doppler measurements of ICA stenosis (PSV, EDV, ICA/CCA ratio), age, hypertension, current smoking, hyperlipidemia, and DM were compared in the two groups. The

preprocedural PSV, EDV, ICA/CCA ratio were 196 ± 25 , 104 ± 33 , 3.9 ± 1.3 in the stented group, 136 ± 65 , 42 ± 6 , 1.9 ± 0.8 in the conservative group, respectively. When two groups were compared, these parameters were significantly lower in patients treated conservatively ($p < 0.001$). Atherosclerotic risk factors such as age, gender, BMI, hypertension, DM and familial history of CAD, current smoking, LDL and triglyceride levels were not significantly different between the stented and the conservative group (Table 2).

Univariate analysis revealed that the following factors were not associated with the presence of coronary stenosis: age, gender, DM, hypertension, hyperlipidemia (LDL and triglyceride levels), and the Doppler parameters of Ca-AD (Table 3). From these factors, a multivariate stepwise logistic regression analysis selected ICA PSV (β : -0.641, t: 2.698, $p = 0.01$) and the ICA/CCA ratio (β : -1.056, t: -2.71, $p = 0.01$) as the independent predictors of the extension of coronary stenosis (Table 4,5).

Table 2: Comparison of Clinical and Doppler USG Characteristics, CAD Presence and Extension (Gensini scoring) between the CAS and Conservative Groups (n = 112)

Variables	CAS patients (n=65)	Conservative patients (n=47)	P-value
Male/female	44/21	29/18	0.049
Age	67 ± 8	65 ± 8	0.489
Body mass index	27 ± 2	26 ± 2	0.293
Hypertension (%)	67	58	0.205
Diabetes mellitus (%)	37	28	0.537
Current smoking (%)	44	41	0.462
Familial history of CAD (%)	36	36	0.567
Triglyceride	141 ± 10	127 ± 17	0.150
LDL	128 ± 33	132 ± 42	0.702
Gensini scoring	22 ± 8	20 ± 6	0.764
ICA lesion (%)	83 ± 13	62 ± 9	< 0.001
ICA PSV	196 ± 25	136 ± 65	< 0.001
ICA EDV	104 ± 33	42 ± 6	< 0.001
ICA - CCA ratio	3.9 ± 1.3	1.9 ± 0.8	< 0.001
CAD presence (%)	30/46	21/44	0.893
One-vessel disease	13	5	0.079
Two-vessel disease	12	10	0.784
Three-vessel disease	5	6	0.087

Table 3: Comparison of Clinical and Doppler Parameters According to the Presence of CAD (n = 112)

Variables	Patients with CAD (n=51)	Patients without CAD (n=61)	P-Value
Male/female	44/21	29/18	0.049
Age	67±8	65±8	0.489
Body mass index	27±2	26±2	0.293
Hypertension (%)	67	58	0.205
Diabetes mellitus (%)	37	28	0.537
Current smoking (%)	44	41	0.462
Familial history of CAD (%)	36	36	0.567
Triglyceride	141±10	127±17	0.150
LDL	128 ±33	132 ±42	0.702
Gensini scoring	22±8	20±6	0.764
ICA lesion (%)	83±13	62±9	< 0.001
ICA PSV	196±25	136±65	< 0.001
ICA EDV	104±33	42±6	< 0.001
ICA - CCA ratio	3.9±1.3	1.9±0.8	< 0.001
CAD presence, n (%)	30/46	21/44	0.893
One-vessel disease, n	13	5	0.079
Two-vessel disease, n	12	10	0.784
Three-vessel disease, n	5	6	0.087

Table 4: Comparison of Clinical and Doppler Parameters According to the Presence of CAD (n = 112)

Variables	Patients with CAD	Patients without CAD (n=61)	P-Value
Male/female	33/18	40/21	0.171
Age	69±9	65±11	0.543
ICA lesion (%)	55±16	46±21	0.059
ICA PSV	171±42	165±36	0.258
ICA EDV	73±21	67±33	0.708
ICA-CCA ratio	2.9±1.6	2.6±1.9	0.651

**Table 5: Multivariate Logistic Regression Analysis;
Only ICA PSV and ICA/CCA Ratio were Correlated with Gensini Scoring (n = 112)**

Variables	Beta	T	P-Value
ICA PSV	1.282	2.698	0.01
ICA/CCA ratio	-1.056	-2.711	0.01

DISCUSSION

Concomitant atherosclerotic lesions of the extracranial internal carotid arteries and the coronary circulation portend an adverse prognosis in various clinical settings, including asymptomatic individuals, stroke patients, and patients undergoing coronary artery bypass surgery.⁷⁻⁸ Previous postmortem and clinical studies, often small in sample size, have reported a variable prevalence of concomitant carotid and coronary lesions in

patients with or without clinically evident cardiovascular disease.⁹⁻¹⁴ However, possible additional associations between carotid disease and the severity of CAD have not been well addressed.

In addition, recent developments in non-invasive imaging have allowed the prevalence of disease at multiple sites (usually the carotid, femoral, and coronary arteries) to be measured in large numbers of individuals during life.^{15,16} It has been shown that

Doppler sonography is the most common non-invasive imaging study performed for the diagnosis of carotid disease.¹⁷ Doppler ultrasound assessments of the carotid plaque are highly predictive of clinically significant coronary stenosis in angiography.¹⁸ Craven et al. have suggested that B-mode score is strongly and independently associated with CAD in patients aged >50 years and is at least as useful as well-known risk factors for identifying patients with CAD.¹⁹ Indeed, an increased carotid IMT has been associated with the prevalence and extent of CAD, but this relationship is weak.²⁰

To investigate this issue further, we extended our attention to the exact relationship between carotid disease and CAD. We found that fifty-one patients (45%) had clinically significant ($\geq 70\%$) coronary lesions and PSV and ICA/CCA ratio could indicate the extension (not the presence) of CAD in patients undergoing carotid and coronary angiography. This analysis confirms the findings of previous studies that have reported a direct relation between the extent of CAD and the presence of Ca-AD among patients referred for carotid and coronary angiography, though the prevalence of clinically significant CAD in these patients appears to be slightly lower than previously reported.²¹⁻²⁵

In our study, Doppler measurements of ICA stenosis (PSV, EDV, ICA/CCA ratio) were compared in the two groups. The preprocedural PSV, EDV, ICA/CCA ratio were 196 ± 25 , 104 ± 33 , 3.9 ± 1.3 , in the stented group, 136 ± 65 , 42 ± 6 , 1.9 ± 0.8 in the conservative group, respectively. These parameters were significantly lower in patients treated conservatively. The high Doppler flow parameters in the stented group was an expected result. Whether or not they were CAD, in CAS group (as shown in the angiographic results, Table 2) carotid artery lesions were more serious than the other group. Indeed, so instead of conservative treatment it was preferred stent therapy. In addition, the percentage of patients with CAD were similar in both treatment groups (46% and 44%, $p > 0.05$). Thirty of the stented patients and 21 patients who were treated conservatively had CAD. A relationship could not be determined between ICA doppler flow parameters and the presence of CAD in logistic regression analysis. However, this analysis revealed a statistically significant correlation between only two Doppler parameters (ICA PSV and ICA/CCA PSV ratio) and Gensini scoring which reveals the extension and severity of CAD. On the other hand, gender, age, BMI, hypertension, DM, smoking, familial history of CAD, triglycerides, and LDL cholesterol did not have an influence on the Gensini score ($p > 0.05$, for all). In addition, the same risk factors did not differ between the cases with and without CAD in either the stented or the conservatively treated patients

As stenting of the carotid artery is replacing surgery more and more, careful evaluation of coronary artery stenosis is essential to lower the incidence of morbidity and mortality in these patients.²⁶ On the other hand, among patients who underwent elective carotid stenting, concomitant CAD is found in 57% to 77% of cases.^{13,27-29} In 65 consecutive patients undergoing stenting for clinically significant stenosis of the carotid artery, coronary arteries were investigated angiographically. A significant stenosis in 30 patients (46%) was determined. Interestingly, 21 of 47 patients (44%) with a significant coronary stenosis were documented in the conservative group. In addition, Gensini scoring which is a severity score to each coronary

stenosis according to the degree of luminal narrowing and its geographic importance, was not different between the two groups (22 ± 8 , 20 ± 6 , $p: 0.764$, respectively).³⁰ In addition, according to the number of diseased vessel (single, two, three vessel), there were no significant differences between the two groups ($p = 0.891$).

However, a few authors reported on simultaneous stenting or conservative therapy of the carotid artery stenosis and CAD.¹³ Our study is also an important report of the retrospective determination of the presence and extent of CAD in patients undergoing CAS or conservative therapy.

Despite the known the relationship of CAD and carotid Doppler flow velocity in patients with no significant carotid stenosis ($< 50\%$)- in this study flow velocities were significantly lower in patients with CAD and correlation analysis demonstrated a negative correlation with age, the number of affected coronary arteries and especially minimal flow velocity- in patients with significant carotid stenosis ($> 50\%$), the relationship between these parameters and presence, extension of CAD is not well known.³¹ In our study, ICA lesion (%), PSV, EDV and ICA/CCA ratio were similar between patients with and without CAD. In addition logistic regression analysis revealed a significant correlation between ICA PSV, and ICA/CCA ratio and extension of CAD (Gensini scoring).

LIMITATIONS

This is a small and single-center retrospective study that carries known limitations of such a study. The lack of randomization and prospective follow-up also limits our analysis. We only studied a group of consecutive patients who were referred for elective carotid angiography because of suspected CAD. Thus, the study provides no information on the prevalence of clinically important CAD among patients with acutely symptomatic carotid artery lesions. Patients with CAS tend to be older. Thus, the percentage of patients with concomitant CAD in the present study may be higher than in the overall patient population with carotid artery stenosis. Lastly, due to the small numbers of severe CAS, the multinomial logistic regression model may be overfitted, and cross-validation is needed. Also in the literature, usually in patients with CAD, the prevalence of CAD have been investigated, thus the number of subjects in these studies is relatively high. Unlike our study, in patients with severe CAD, the presence and extension of CAD has been investigated and therefore the number of cases is relatively low.

CONCLUSION

Our study showed that the patients undergoing elective stenting of the carotid artery have a high incidence of concomitant CAD, which is not different from the patients treated medically, but all of these patients had sonographically significant atherosclerotic lesions. This means that the high Doppler velocities of atherosclerotic carotid disease is a high risk factor for extension of CAD. In addition, carotid Doppler USG is emerging as a useful complementary modality in the assessment of carotid flow velocities which are highly predictive of clinically significant coronary stenosis on angiography.

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