THE NEW ARMENIAN MEDICAL JOURNAL
Vol.4 (2010), N 2, p. 37-44

USEFULNESS OF CAROTID ULTRASOUND IN DIFFERENTIAL DIAGNOSIS OF ISCHEMIC AND NON-ISCHEMIC CARDIOMYOPATHY

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Abstract

Introduction: *Silent course of ischemic cardiomyopathy is a big problem for cardiology, because it is usually very difficult to differentiate from non-ischemic dilated cardiomyopathy. It was proven that carotid bifurcation atherosclerosis and coronary artery disease have been shown to be strongly correlated. We prospectively examined the value of extracranial carotid atherosclerosis in distinction between ischemic and non-ischemic etiology in patients with clinically unexplained cardiomyopathy.*

Methods and results: *Within 48 months 117 patients with undetermined dilatation and diffuse impairment of the left ventricular contractility were studied. All of them underwent carotid ultrasound scan and coronary arteriography. Carotid atherosclerosis was found to be very common in ischemic and uncommon in non-ischemic cardiomyopathy. The presence of at least one abnormal carotid finding was very sensitive and quite specific for ischemic cardiomyopathy.*

Conclusion: *It is obvious that carotid ultrasound is very useful screening and decision-making method in patients with cardiomyopathy of unidentified cause. Patients with carotid atherosclerosis are likely to have severe coronary artery disease. Coronary angiography seems to be considered early during their evaluation. Quite the opposite, a negative carotid ultrasound predicts non-ischemic cardiomyopathy.*

Keywords: *ischemic cardiomyopathy, non-ischemic cardiomyopathy, carotid atherosclerosis, carotid ultrasound*

INTRODUCTION

Detection of a dilated and hypokinetic left ventricle (LV) infrequently constitutes a challenge in the daily medical practice as far as the identification of the etiology of this finding is concerned. This occurs when the underlying cause cannot be identified, despite a detailed history and a thorough clinical examination, even after cardiac ultrasound. This specific condition of the LV is attributable to two pathological entities: non-ischemic dilated cardiomyopathy (DCM), either idiopathic or secondary, i.e. a result of specific pathology but without stenoses of the coronary arteries (CA) [*Richardson P. et al., 1996*], and ischemic heart disease (IHD) that is due to severe coronary artery disease (CAD) [*Raftery E. et al.,* 1969; *Burch G. et al., 1970*]. IHD is almost always a result of a clinically obvious CAD [*Gersh B. et al., 1997*].

Nevertheless, seldom, the clinical course of the disease is artful and "silent" and thus indistinguishable from DCM [*Burch G. et al., 1970; Gersh B. et al., 1997; Rahko P., Orie J., 1988*]. Differential diagnosis between ICM and DCM is required both for therapeutic as well as for prognostic reasons [*Shugoli G. et al., 1972; Franciosa J. et al., 1983; Sugrue D. et al., 1992*]. Although prognosis of patients (pts) with ICM is poorer than prognosis of pts with DCM [*Franciosa J. et al., 1983; Sugrue D. et al., 1992*; *Likoff M. et al., 1987*], pts with hibernating myocardium may significantly benefit from myocardial reperfusion [*Kron I. et al., 1989*; *Elefteriadis J. et al., 1993*]. The "gold standard"

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examination for differential diagnosis in such cases is coronary angiography (CAG). Accurately towards the same direction, many non-invasive techniques have been used that present, however, variable sensitivity, reduced reproducibility, limited interpretation, and sometimes limited availability [*Eichhorn E. et al., 1988; Mody V. et al., 1991; Sawada S. et al. 1992; Tauberg S. et al., 1993; Sharp S. et al., 1994; Vigna C. et al., 1996*]. On the other hand, the extracranial carotid disease (ECCD) is significantly correlated with CAD and acute coronary syndrome [*Hertzer N. et al., 1985; Salonen J., Salonen R., 1991; Crouse J. et al., 1995; Kallikazaros I. et al., 1999*] and contrariwise [*Love B. et al., 1992; Sanguini V. et al., 1993; Vigneswaran W. et al., 1993*]. Moreover, the coronary and carotid arterial tree share all the factors predisposing to atherosclerosis [*Crouse J. et al., 1987; Graven T. et al., 1990*]. The ultrasound examination is reliable and easy to use in order to identify ECCD. Based on these data, we examined the value of carotid atherosclerosis prospectively in predicting CAD as an underlying cause, in cases of unexplained heart failure (HF) with dilated and diffusely hypokinetic LV.

MATERIAL AND METHODS

Since March 2001, we identified all pts, aged >30 years old, who came to our department with signs and symptoms of HF as well as for cardiomegaly investigation. We took a detailed history and proceeded to thorough clinical examination. From the above study we immediately excluded pts with diagnosed CAD, with a history and findings of primary valvulopathy, pericardial disease, myocarditis, congenital heart disease, pregnant women and women who had given birth up to 12 months before, as well as all pts who had a history of treatment with anthracyclines or other anti-neoplastic drugs or pts who had been subject to radiation therapy of cervix. To the contrary, we chose pts with chest pain and/or Q waves in the precordial leads in the electrocardiogram (ECG) but without a clear acute myocardial infarction (AMI) history, since both findings are also encountered in DCV [*Raftery E. et al.,* 1969; *Burch G. et al., 1970; Rahko P., Orie J., 1988; Gersh B. et al., 1997*]. Since our aim was to investigate the presence of co-existing severe CAD in all pts with unexplained HF, we included pts with alcohol abuse, with all types of arrhythmia, as well as pts with systemic or endocrine diseases that are known to be predisposing or directly related to DCM. Following this initial screening, selected pts were subjected to cardiac ultrasound examination. Particular attention was given to the study of the motion of the LV wall, as well as to the degree of severity and the mechanism of any eventual mitral valve insufficiency. Pts with strong indications of CAD – such as aneurysm or hypokinetic and thin areas of the LV with coexistence of Q waves in the ECG in the respective region – were excluded from our study, while those with small motion disorders or mild regional asynergy or dyskinesia were included. Finally, pts whose history, clinical assessment, and cardiac ultrasound were not able to determine the cause of LV dysfunction were deemed appropriate study participants. We informed all these pts and proposed to undergo a hemodynamic investigation, provided of course they were clinically stable. In the last 48 months, 80 of the eligible pts accepted the procedure, signed an informed consent form and constituted the study population. One day before catheterization they underwent carotid ultrasound (CU). We also analyzed the standard major risk factors and three ECG parameters (rate, presence of Q waves in the anterior wall, left bundle branch block). In order to set the diagnosis of arterial hypertension, repeated measurements >140/90 *mm Hg* or a respective history were taken, for hypercholesterolemia – total cholesterol levels >220 *mg/dl*, for diabetes mellitus – blood glucose levels >120 *mg/dl* or use of insulin or antidiabetic tablets, for obesity - BMI >27 kg/m^2 for men and >26.5 kg/m^2 for women. Smokers were considered the active smokers (current) and those who had quit smoking in the last 6 months. Family history was considered as positive if the 1st degree relatives suffered from documented CAD before the age of sixty.

Echocardiography

We used the Hewlett-Packard Sonos 2500 system with a 2.5/2.0 *MHz* transducer for transthoracic echocardiography. The dimensions of the LV and left atrium were measured from M-mode

recordings or from two-dimensional images (2-D) images when the M-mode recording was not satisfactory. All eligible pts had end-diastolic diameter ≥4 *cm/m²* and left ventricle ejection fraction (LVEF) ≤45% (Simpson method) [*Sahn D. et al., 1978; Schiller N. et al., 1989*].

Carotid ultrasound

The same Hewlett-Packard system with linear transducer 7.5/5.5 *MHz* was used, in accordance with the specific procedure [*Androulakis A. et al., 1996*]. We took bilaterally anterolateral, oblique and posterolateral 2-D and color Doppler images in transverse and longitudinal sections of the common carotid, the carotid bifurcation and the proximal part of the internal carotid. The pulsed Doppler signal was obtained at an angle of 60° for each point where there was turbulent flow with color Doppler (color mosaic). The intima-media thickness (IMT) was electronically calculated via stabilized longitudinal 2-D images, synchronized with the R wave of the ECG. The final 2.5 *mm* of the posterior wall of the common carotid artery was carefully magnified to appear horizontally along the screen. IMT measurements were performed from the boundary of the distal vascular lumen to the boundary of the adventitia in each one of the three images. In the direction, the section and the position where the maximum value was obtained, five additional measurements were performed and their average was calculated; this value defined precisely the IMT. Positions with plaques were exempted from measurements. IMT values >1.0 *mm* were considered pathological, since 1 *mm* is the highest median value that has been reported in the general population [*Kanters S. et al., 1997*]. Plaques were considered the protrusions with a thickness >50% of the thickness of the surrounding wall that were found anywhere in the carotid system or local thickenings of at least 1.3 *mm*. Longitudinal or local thickenings <1.3 *mm* were not considered as plaques. We considered as significant stenoses of the carotid, those that occupied more than 50% of the vessel diameter. For the proximal internal carotid it was necessary to record blood flowvelocity >1.25 *m/sec* [*Androulakis A. et al., 1996*].

Heart catheterization

Following left catheterization, selective CAG was performed on both CA in multiple projections with the Judkins technique. Left ventriculography then followed at angle of 30-degree right oblique view. All the examinations were assessed by at least two observers who were not aware of the carotid examination findings. As significant stenosis in one or more epicardial CA was considered a >50% reduction of the diameter.

Statistical analysis

The values of the parameters studied, were expressed as a mean ± standard deviation. Comparisons between quantitative variables were done with analysis of variance (ANOVA). Correlations between qualitative variables were performed with the x^2 and the Fisher test, where necessary. Multivariate analysis of dependence was performed in order to find possible significant correlations between one dichotomous variable (DCM or IHD) and a number of independent variables. The selection of these variables was interrupted when upon the introduction of each candidate variable, there was no resulting significance at the level of $p<0.05$, while at the same time, the selected variables remained significant at the level of $p<0.10$. All tests were considered statistically significant at the level of 0.05. Analyses were performed with SPSS software (version 8.0).

RESULTS

Significant stenoses of the CA were found in 38 (32.5%) out of 80 pts. The other 42 pts did not have angiographically significant coronary stenoses. Among pts with ischemic cardiomyopathy (ICM), 79% (30/38) had three-vessel disease, 13% (5/38) two-vessel disease and 8% (3/38) one-vessel disease. Six pts had additional significant disease of the left main CA. As shown in Table 1, pts with IHD were obese, smokers, hypertensive, hypercholesterolemic and diabetic in their majority. Furthermore, they had more severe HF and more CAD risk factors than those with DCM. About 80% had at least two risk factors. Among DCM pts, only three did not have any risk factor, 40% had one risk factor, 34% had two and 55% had at least two risk factors. As far as the ECG and cardiac ultrasound parameters are concerned, no difference was observed between the two groups (Table 2). Carotid atherosclerosis was very common in ICM but rare in DCM pts (Table 2).

Table 1.

Demographic data of the study population

Factors	DCM (n=42) [52.5%]	ICM (n=38) [47.5%]	*p*
Age (range)	55.5±13.2 (32-76)	60.1±11.1 (38-80)	NS
Male Sex	20 [52.6%]	22 [52.3%]	NS
NYHA class III or IV	22 [57.9%]	20 [47.6%]	NS
Atypical chest pain	10 [23.8%]	11 [28.9%]	NS
Obesity	10 [23.8%]	22 [57.9%]	<0.01
Diabetes mellitus	4 [9.5%]	11 [28.9%]	<0.05
High cholesterol	15 [35.7%]	30 [78.9%]	<0.01
Smoking	19 [45.2%]	21 [55.3%]	NS
Hypertension	4 [9.5%]	20 [47.6%]	<0.003
Heredity	6 [14.2%]	8 [18.4%]	NS
Number of RFs for CAD	1.75 ± 1.0	3.0 ± 1.0	<0.01

NYHA: New York Heart Association functional class; DCM: Dilated Cardiomyopathy; ICM: Ischemic Cardiomyopathy; RF: Risk Factors; CAD: Coronary Artery Disease.

Table 2.

EchoCG and carotid ultrasound data in study groups

Criteria	DCM (n=42) [52.5%]	ICM (n=38) [47.5%]	*p*
Atrial Fibrillation	10 [23.8%]	11 [28.9%]	NS
Left Bundle Branch Block	11 [26.1%]	12 [31.5%]	NS
Anterior Q waves (%) (*)	15 [35.7%]	11 [28.9%]	NS
LVEDD in *cm* (range)	6.5 ± 7.0 (57-88)	6.5 ± 5.5 (56-82)	NS
% LVEF (range)	28.5 ± 7.0 (20-45)	25.5 ± 5.0 (20-40)	NS
LA in *cm* (range)	4.5 ± 5.5 (35-64)	4.5 ± 5.0 (35-56)	NS
IMT in *mm* (range)	0.80 ± 0.35 (0.53-1.3)	1.35 ± 0.38 (0.8-1.5)	<0.01
IMT >1.0 *mm*	4 [9.5%]	36 [94.7%]	<0.001
Carotid plaques (%)	6 [14.2%]	30 [78.9%]	<0.01
Carotid stenosis ≥ 50%	1 [2.3%]	20 [47.6%]	<0.001
Any carotid finding (%) (**)	7 [16.6%]	37 [97.3%]	<0.001

EchoCG : echocardiography; DCM: Dilated Cardiomyopathy; ICM: Ischemic Cardiomyopathy; LVEDD: Left Ventricular End-Diastolic Diameter; LVEF: LeftVentricular Ejection Fraction; LA: Left Atrial Diameter; IMT: Intima-Media Thickness.
(*): Definition uncertain in 4 patients.
(**): Any carotid finding means the presence of at least one of the following abnormal findings of the carotid scan: IMT>1mm, carotid plaques, carotid stenosis ≥50%

Thirty-six pts with CAD (94.7%) had IMT>1.0 *mm*. From the remaining pts with thickness <1.0 *mm*, only one had a normal carotid examination. Only 4 (4.5%) of the non-ischemic pts had thickening of the intima-media. From them, three were above 65 years of age and had more than two risk factors.

Thirty pts with ICM (78.9%) had carotid plaques. Only one of the remaining pts without plaques had carotid stenosis (CS) and just one had normal carotids. On the contrary, only 6/42 pts with DCM (14.1%) had carotid plaques. Four of them were above 65 years old.

Significant CS was observed in 20 (47%) pts with ICM, of whom 17 had three-vessel CAD. Five pts had bilateral internal CS. Most of the CS (13/20) were observed on the left side. Three pts had total occlusion of the internal carotid, 6 pts had 70-99% CS and 14 had 50-70% CS. Only one female, hypertensive patient, 71 years old, with DCM had 60% CS of the internal carotid.

Then we analyzed the diagnostic potential of all the parameters that presented statistically significant difference between the two groups. We determined their sensitivity, specificity, and positive, as well as negative, prognostic value in the identification of pts with ICM. Carotid plaques had a sensitivity, specificity, and negative prognostic value higher than 85%. Significant CS had low sensitivity, but at the same time, it had the highest specificity (95.5%) and the highest prognostic value (93.2%). IMT gave an acceptable sensitivity (81.6%) and specificity (90%).

As seen in Table 2, at least one pathological finding from the carotids existed in 7 pts with DCM (16.6%) and in 37 out of 38 pts with ICM (97.3%) ($p<0.001$). Thus, CU revealed CAD pts with 95.6% sensitivity and 82.8% specificity.

In a multivariate analysis model, using as cofactors the findings from the carotids, diabetes mellitus, smoking, hypertension, HF functional status and the number of risk factors for CAD, carotid findings had a significant and independent correlation with ICM ($p<0.005$).

DISCUSSION

The fundamental diagnosis in pts presenting with LV dilation and impaired systolic function but have not been documented to suffer from a known heart disease or systemic disease, often remains clinically unclear. Pts who have never had angina or AMI may suffer from severe and extensive CAD and, on the contrary, pts with angina may not reveal angiographically documented CAD [*Raftery E. et al.,* 1969; *Burch G. et al., 1970; Rahko P., Orie J., 1988; Gersh B. et al., 1997*]. Incidence, morbidity and mortality of congestive HF increase in all age groups [*Cleland J., 1998*], particularly due to the increase of incidence both of the ischemic, as well as idiopathic DCM [*Cleland J., 1998*; *Dec G., Fuster V., 1994*]. There are indications that the percentage of pts with ICM in recently manifested HF is overestimated [*Fox K. et al., 1998a*]. Nowadays, appreciating the fact that the immediate implementation of the appropriate treatment provides significant improvement in the quality of life, as well as prolongation of survival, may lead to the creation of clinical units for the rapid identification, diagnosis and treatment of HF in the future [*Fox K.F. et al., 1998b*].

The absolute distinction between ICM and DCM is achieved with CAG that also provides details on the CA anatomy in case of reperfusion. The invasive nature of the method has led to the effort of differential diagnosis with non-invasive techniques, mainly the radio-isotopic imaging of the myocardial perfusion and the stress echocardiography [*Eichhorn E. et al., 1988; Tauberg S. et al., 1993; Sharp S. et al., 1994; Vigna C. et al., 1996*]. Nevertheless, overlapping and conflicting results have been recorded, particularly in low LVEF and significant segmental hypokinesias. CU can image atheromatosis at the proximal part of the left CA, thus diagnosing CAD with high probability [*Sawada S. et al., 1992*]. This technique, however, requires special transducers and digital equipment that are not widely available. Similarly, the transesophageal ultrasound is useful in identifying CAD but it has not been tested on this population [*Iliceto S. et al., 1991*]. The same applies for the electron beam computed tomography (EBCT) that traces calcium on the CA walls [*Nallamothu B. et al., 2001*]. Positron emission tomography (PET) is very useful in identifying the viability of the myocardium and in the differential diagnosis between ICM and DCM [*Mody V. et al., 1991*]. However, the interpretation of the findings is problematic in diabetic pts, while its use is particularly limited due to the high cost and consequently its limited availability.

Carotid bifurcation atheromatosis is common in CAD and vice versa [*Hertzer N. et al., 1985; Crouse J. et al., 1987; Graven T. et al., 1990; Salonen J., Salonen R., 1991; Love B. et al., 1992; Sanguini V. et al., 1993; Vigneswaran W. et al., 1993; Crouse J. et al., 1995; Kallikazaros I. et al., 1999*].

Carotid atherosclerosis is easily and non-invasively identified with the use of ultrasound, which is widely available, reliable and relatively inexpensive. It can be applied in every patient, even at bedside, at any heart rate, while it does not require the patient to stop medication. Wide literature search failed to find even just one study that would correlate CAD with carotid disease in pts with unexplained cardiomyopathy.

Based on all the previous data, we prospectively tried to see whether carotid disease can identify an occult severe CAD in such a population. We found that carotid atherosclerosis was almost always present in pts with ICM. The identification of any pathological finding in the carotids was very sensitive and specific in revealing pts with CAD. On the contrary, the carotid disease was rare in pts with DCM. A reasonable explanation of this result could be that IHD is usually the result of severe and advanced CAD and any concurrent carotid atherosclerosis is expected to be advanced as well. It has been proven that the linear correlation between CAD and carotid disease is more evident at an advanced atherosclerosis stage [*Hertzer N. et al., 1985; Sanguini V. et al., 1993; Vigneswaran W. et al., 1993; Kallikazaros I. et al., 1999*]. Indeed, the huge majority of our pts with IHD had multi-vascular CAD, thus the coexistence of carotid atherosclerosis seems logical.

From the present study we can support that carotid examination may constitute a useful method for the investigation of pts with unexplained dilated and diffusely hypokinetic LV, since the presence of atherosclerosis in the carotid bifurcation suggests a severe underlying CAD. As a consequence, it may be useful for pts with cardiomyopathy and carotid disease to undergo early CAG, in order to identify those pts with coronary anatomy suitable for reperfusion and proceed without any delay to tests that can determine the existence of a viable hibernating myocardium [*Al-Mohammad A. et al., 1998*]. An additional advantage of this practice is that the results of such tests are more accurately interpreted when the CA anatomy is already known. Furthermore, it is desirable to determine any potential significant stenosis of the internal carotid, in order to seriously consider it when we plan for invasive procedures. On the contrary, pts without carotid disease seem to suffer from non-ischemic heart disease, thus further diagnostic procedures with CAG or examinations of viability should be avoided, taking into consideration both the risks as well as the cost. However, such a view should be further evaluated with specifically designed prospective studies in order to adopt it in clinical practice.

Since our perspective was to predict severe CAD in all pts with unexplained HF, we did not exclude cases of pts with diseases known to be related to DCM, where CAD may coexist. That is why we included pts with diabetes mellitus, alcohol abuse and uremia, since these conditions also predispose to atherosclerosis and they are also involved in the development of metabolic cardiomyopathy without significant CAD [*Zoneraich S., 1978*; *Richardson P. et al., 1996; Leier C., Boudoulas H., 1997*]. It is interesting that eight of our pts were alcohol abusers and had long been characterized as suffering from alcoholic cardiomyopathy. Five of them had significant carotid atherosclerosis. In CAG, all five presented significant CAD. The other four did not present carotid or CAD. Similar findings were observed in two hemodialysis pts. A separate analysis on the total of 15 diabetic pts of the study indicated results similar to those for the whole population of the study. Thus, carotid examination could be extremely useful in the management of pts with the above conditions.

The present study was not designed to objectively prove, either myocardial ischaemia in those pts with severe CAD, or the absence of ischaemia in those who did not present any angiographic stenosis, since our pts were not routinely examined to reveal myocardial ischaemia and viability. However, our results must not have been significantly influenced by this fact, since CAD was severe in the 30 (78.9%) cases of IHD. Indeed, 75% total occlusions were documented in the proximal segments of the CA, while the left anterior descending was significantly stenosed in all but two pts. As a conclusion, although hibernating myocardium was not proven in all our pts with severe CAD, it is almost certain that similar pts are treated, throughout the world, as suffering from ICM in daily clinical practice.

In a very interesting study of Aristide E. Androukalis it was clearly shown that CU is a very useful screening and decision-making tool in pts with cardiomyopathy of unidentified cause [*Androukalis A., 2002*].

The study typically does not include consecutive pts, since CAG was obligatory and since hemodynamically unstable pts, pts who did not sur-

vive before the investigations and unwilling pts (24 in total) were excluded. However, our pts clinically represent a consecutive series, since, in essence, daily practice proposes exactly the same procedures in pts similar to the ones we studied. Thus, their clinical characteristics are valuable and we further analyzed some of them on this basis. Functional status, smoking, AH, diabetes mellitus and the presence of more than two standard risk factors showed significant difference between the two groups. Significant variety and poor reproducibility have been reported in literature in the presentation of similar clinical characteristics, which may be due to differences in the selection criteria and methods. The clinical parameters, however, seem to be of moderate value in the differential diagnosis of cardiomyopathies [*Hare J. et al.*, *1992*]. Moreover, in our study they presented clearly lower prognostic value than the carotid ultrasound data.

In conclusion, the presence of carotid atherosclerosis, as it is identified by CU, seems to be an accurate predictor of the existence of severe underlying CAD in pts with unexplained dilatation and diffuse dysfunction of the LV.

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