

# The Role of Carotid Atherosclerosis in the Distinction Between Ischaemic and non-Ischaemic Cardiomyopathy

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**Introduction:** Ischaemic cardiomyopathy is occasionally a result of severe coronary artery disease with a silent course, without typical symptoms or evidence of myocardial infarction. This type of ischaemic cardiomyopathy is usually indistinguishable from non-ischaemic dilated cardiomyopathy. Carotid bifurcation atherosclerosis and coronary artery disease have been shown to be strongly correlated. We prospectively examined the value of extracranial carotid atherosclerosis in the distinction between ischaemic and non-ischaemic etiology in patients with clinically unexplained cardiomyopathy.

**Methods and results:** One hundred and seventeen patients with undetermined dilatation and diffuse impairment of the left ventricular contractility were studied within 42 months. They underwent carotid ultrasound scan and coronary arteriography. Carotid atherosclerosis was found to be very common in ischaemic and rare in non-ischaemic cardiomyopathy. The presence of at least one abnormal carotid finding (intima-media thickness >1 mm, plaques, severe carotid stenosis) was 97% sensitive and 85% specific for ischaemic cardiomyopathy.

**Conclusion:** Carotid ultrasound may be a useful screening and decision-making tool in patients with cardiomyopathy of unidentified cause. Patients with carotid atherosclerosis are likely to have severe coronary artery disease. Coronary angiography and subsequent myocardial viability studies, when indicated, should be considered early during their evaluation. On the contrary, a negative carotid ultrasound predicts non-ischaemic cardiomyopathy.

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**T**he finding of a dilated and diffusely hypokinetic left ventricle occasionally 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 left ventricle is attributable to two pathological entities: dilated cardiomyopathy, either idiopathic or secondary, i.e. a result of specific pathology but without stenoses of the coronary arteries<sup>1</sup> and ischaemic heart disease that is due to severe co-

ronary artery disease<sup>2,3</sup>. Ischaemic heart disease is often the long-term result of a clinically obvious coronary artery disease<sup>4</sup>. However, occasionally, the clinical course of the disease is insidious and “silent” and thus indistinguishable from dilated cardiomyopathy<sup>3,5</sup>. Differential diagnosis between this “silent” ischaemic and the non-ischaemic cardiomyopathy is required both for therapeutic as well as for prognostic reasons<sup>6,8</sup>. Although prognosis of patients with ischaemic cardiomyopathy is poorer than prognosis of patients with non-ischaemic cardiomyopathy<sup>7,9</sup>, patients with hibernating myocardium may significantly benefit from myocardial

reperfusion<sup>10,11</sup>. The gold standard examination for differential diagnosis in such cases is coronary arteriography. Precisely towards the same direction, many non-invasive techniques have been used, that present, however, variable sensitivity, reduced reproducibility, limited interpretation and sometimes limited availability<sup>12-17</sup>. On the other hand, the extracranial carotid disease is significantly correlated with coronary artery disease and acute coronary syndromes<sup>18-21</sup> and vice versa<sup>22-24</sup>. Additionally, the coronary and carotid arterial tree share all the factors predisposing to atherosclerosis<sup>25,26</sup>. The ultrasound examination is reliable and easy to use in order to identify carotid disease. Based on these data, we examined the value of carotid atherosclerosis prospectively in predicting coronary artery disease as an underlying cause, in cases of unexplained heart failure with dilated and diffusely hypokinetic left ventricle.

### Material and Method

Starting from June 1997, we identified all patients, aged >30 years old, who came to our department with signs and symptoms of heart failure as well as for cardiomegaly investigation. We took a detailed history and proceeded to thorough clinical examination. From the above study we immediately excluded patients with diagnosed coronary artery disease, 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 patients who had a history of treatment with anthracyclines or other anti-neoplastic drugs or patients who had been subject to radiation therapy in the cervix. To the contrary, we chose patients with chest pain and/or Q waves in the precordial leads in the electrocardiogram (ECG) but without a clear myocardial infarction history, since both findings are also encountered in dilated cardiomyopathy<sup>2-5</sup>. Since our aim was to investigate the presence of co-existing severe coronary artery disease in all patients with unexplained heart failure, we included patients with alcohol abuse, with all types of arrhythmia, as well as patients with systemic or endocrine disease that are known to be predisposing or directly related to dilated cardiomyopathy. Following this initial screening, selected patients were subjected to cardiac ultrasound examination. Special attention was given to the study of the motion of the left ventricular wall, as

well as to the degree of severity and the mechanism of any eventual mitral valve insufficiency. Patients with strong indications of coronary artery disease –such as aneurysm or hypokinetic and thin areas of the left ventricle with coexistence of Q waves in the ECG in the respective region– were excluded from the study, while those with small motion disorders or mild regional asynergy or dyskinesia were included. Finally, those patients whose history, clinical assessment and cardiac ultrasound were not able to determine the cause of left ventricle dysfunction, were deemed appropriate study participants. We informed all these patients and proposed they undergo a hemodynamic investigation, provided of course they were clinically stable. In the last 42 months, 117 of the eligible patients accepted the procedure, signed an informed consent form and constituted the study population. One day before catheterization they underwent carotid ultrasound.

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 mmHg or a respective history were taken, for hypercholesterolemia –total cholesterol levels >220mg/dl, for diabetes mellitus– blood glucose levels >120 mg/dl or use of insulin or anti-diabetic tablets, for obesity - BMI >27 kg/m<sup>2</sup> for men and >26.5 kg/m<sup>2</sup> 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 1<sup>st</sup> degree relatives suffered from documented coronary artery disease 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 left ventricle 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 patients had end-diastolic diameter  $\geq 4$  cm/m<sup>2</sup> and left ventricle ejection fraction  $\leq 45\%$  (Simpson method)<sup>27,28</sup>.

### Carotid ultrasound

The same Hewlett-Packard system with linear transducer 7.5/5.5 MHz was used, in accordance with the



**Table 1.** Demographic data of the study population.

	DCM n = 79 (67.5%)	ICM n = 38 (32.5%)	P
Age (range)	57.6 ± 11.1 (31-77)	62.1 ± 10.0 (37-80)	.038
Male Sex (%)	59 (74.7)	33 (86.8)	.133
NYHA class III or IV (%)	49 (62.0)	32 (84.2)	.015
Angina (%)	15 (19.0)	11 (28.9)	.225
Obesity (%)	35 (44.3)	12 (31.6)	.189
Diabetes mellitus (%)	13 (16.5)	17 (44.7)	.001
High cholesterol (%)	28 (35.4)	15 (39.5)	.672
Smoking (%)	34 (43.0)	25 (65.8)	.021
Hypertension (%)	20 (25.3)	20 (52.6)	.004
Heredity (%)	5 (6.3)	5 (13.2)	.216
Number of RF for CAD	1.75 ± 0.9	2.5 ± 1.2	.002

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

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 coronary arteries were found in 38 out of 117 patients (32.5%). The other 79 patients did not have angiographically significant coronary stenoses. Among patients with ischaemic cardiomyopathy, 71% (27/38) had three-vessel disease, 24% (9/38) two-vessel disease and 2/38 one-vessel disease. Eleven patients had additional significant disease of the left main coronary artery.

As shown in table 1, patients with ischaemic heart disease were smokers, hypertensive and diabetic in their majority. Furthermore, they had more severe heart failure and more coronary artery disease risk factors than those with non-ischaemic cardiomyopathy. Thirty out of thirty-eight (79%) had at least two risk factors. Among 79 non-ischaemic patients, only 6 did not have any risk factor, 31 (39%) had one risk factor, 26 (33%) two and 42 (53%) 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 ischaemic but rare in non-ischaemic patients (Table 2).

Thirty one ischaemic patients (81.6%) had IMT  $> 1.0$  mm. From the remaining patients with thickness  $< 1.0$  mm, only one had a normal carotid examination, five had plaques and one had isolated internal carotid stenosis  $\geq 50\%$ . Only 8 of the non-ischaemic patients (10.1%) had thickening of the intima-media. From them, 5 were above 65 years of age and had more than two risk factors.

Thirty-six patients with ischaemic disease (94.7%) had carotid plaques. One of the remaining patients without plaques had carotid stenosis and just one had normal carotids. On the contrary, only 9/79 non ischaemic patients (11.3%) had carotid plaques. Seven of them were above 65 years old.

Significant carotid stenosis was observed in 16 patients (42%) with ischaemic cardiomyopathy, of whom 14 had three-vessel coronary artery disease. Four patients had bilateral internal carotid stenosis. Most of the stenoses (12/16) were observed on the left side. Two patients had total occlusion of the internal carotid, five patients had 70-99% stenoses and thirteen had 50-70% stenoses. Only one female, hypertensive patient, 71 years old, with non-ischaemic cardiomyopathy had 60% stenosis of the internal carotid.

We then 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 patients with ischaemic cardiomyopathy (Table 3). Carotid plaques had a sensitivity, specificity and negative prognostic value higher than 88%. Significant

**Table 2.** Electrocardiographic, echocardiographic and carotid ultrasound data in our study patients.

	DCM (n = 79)	ICM (n = 38)	P
Atrial Fibrillation (%)	18 (22.8)	4 (10.5)	.112
Left Bundle Branch Block (%)	28 (35.4)	10 (26.3)	.324
Anterior Q waves (%) (*)	17 (23.0)	14 (36.8)	.120
LVEDD in cm (range)	6.7 ± 7.0 (59-86)	6.5 ± 5.3 (58-79)	.207
% LVEF (range)	28.4 ± 6.7 (20-45)	27.8 ± 5.8 (20-40)	.603
LA in cm (range)	4.6 ± 5.8 (36-65)	4.5 ± 4.6 (36-55)	.713
IMT in mm (range)	0.80 ± 0.17 (0.53-1.3)	1.38 ± 0.38 (0.8-1.6)	<0.001
IMT >1.0 mm (%)	8 (10.1)	31 (81.6)	<0.001
Carotid plaques (%)	9 (11.4)	36 (94.7)	<0.001
Carotid stenosis ≥ 50% (%)	1 (1.3)	16 (42.1)	<0.001
Any carotid finding (%) (**)	12 (15.2)	37 (97.4)	<0.001

DCM: Dilated Cardiomyopathy; ICM: Ischaemic Cardiomyopathy; LVEDD: Left Ventricular End-Diastolic Diameter; LVEF: Left Ventricular Ejection Fraction; LA: Left Atrial Diameter; IMT: Intima-Media Thickness.

(\*): Definition uncertain in 6 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%.

carotid stenosis had low sensitivity but at the same time it had the highest specificity (98.7%) and the highest prognostic value (94.1%). IMT gave a very satisfactory sensitivity (81.6%) and specificity (90%).

As seen in table 2, at least one pathological finding from the carotids existed in 12 non-ischaemic patients (15.2%) and in 37 out of 38 ischaemic patients (97.4%) (P<0.001). Thus, carotid ultrasound revealed coronary artery disease patients with 97.4% sensitivity and 84.8% specificity (Table 3).

In a multivariate analysis model, using as cofactors the findings from the carotids, diabetes mellitus, smoking, hypertension, heart failure functional status and the number of risk factors for coronary artery disease, carotid findings had a significant and

independent correlation with ischaemic cardiomyopathy (p=0.0002).

## Discussion

The underlying diagnosis in patients presenting with left ventricular dilation and impaired systolic function but have not been documented to suffer from a known heart disease or systemic disease, often remains clinically unclear. Patients who have never had angina or myocardial infarction may suffer from severe and extensive coronary artery disease and, on the contrary, patients with angina may not reveal angiographically documented coronary artery disease<sup>2-5</sup>. Incidence, morbidity and mortality of conge-

**Table 3.** Sensitivity, specificity, positive (PPV) and negative (NPV) predictive value of the parameters that were significantly associated with Ischaemic Cardiomyopathy.

	Sensitivity	Specificity	PPV	NPV
NYHA class >II	88.9	38.0	39.5	83.3
> 2 Risk Factors	50.0	79.7	54.3	76.8
Smoking	65.8	57.0	42.4	77.6
Arterial hypertension	52.6	74.7	50.0	76.6
Diabetes Mellitus	44.7	83.5	56.6	75.9
IMT >1 mm	81.6	89.9	79.5	91.0
Carotid plaques	94.7	88.6	80.0	97.2
Carotid stenosis ≥ 50%	42.1	98.7	94.1	78.0
Any carotid finding (%) (*)	97.4	84.8	75.5	98.5

NYHA: New York Heart Association functional class.

(\*): 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%.

stive heart failure increase in all age groups<sup>31</sup>, particularly due to the increase of incidence both of the ischaemic, as well as of the idiopathic, dilated cardiomyopathy<sup>31,32</sup>. There are indications that the percentage of ischaemic patients in recently manifested heart failure is overestimated<sup>33</sup>. Today, 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 heart failure in the future<sup>34</sup>.

The absolute distinction between ischaemic and non-ischaemic heart disease is achieved with coronary angiography that furthermore provides details on the coronary arteries 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<sup>12-15</sup>. However, overlapping and conflicting results have been recorded, particularly in low ejection fractions and significant segmental hypokinesias. Coronary ultrasound can image atheromatosis at the proximal part of the left coronary artery, thus diagnosing coronary artery disease with high probability<sup>16</sup>. This technique, however, requires special transducers and digital equipment that are not widely available. Similarly, the transesophageal ultrasound is useful in identifying coronary artery disease but it has not been tested on this population<sup>35</sup>. The same applies for the electron beam computed tomography (EBCT) that traces calcium on the coronary arteries walls<sup>36</sup>. Positron emission tomography (PET) is very useful in identifying the viability of the myocardium and in the differential diagnosis between ischaemic and non-ischaemic cardiomyopathy<sup>17</sup>. However, the interpretation of the findings is problematic in diabetic patients, while its use is particularly limited due to its high cost and consequently its limited availability.

Carotid bifurcation atheromatosis is common in coronary artery disease and vice versa<sup>18-26</sup>. 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. Extensive literature search failed to find even just one study that would correlate coronary artery disease with carotid disease in patients with unexplained cardiomyopathy. Based on all the previous

data, we prospectively tried to see whether carotid disease can identify an occult severe coronary artery disease in such a population. We found that carotid atherosclerosis was almost always present in patients with ischaemic cardiomyopathy. The identification of any pathological finding in the carotids was 97% sensitive and 85% specific in revealing ischaemic patients. On the contrary, the carotid disease was rare in non-ischaemic patients. A logical explanation of this result could be that ischaemic heart disease is usually the result of severe and advanced coronary artery disease and any concurrent carotid atherosclerosis is expected to also be advanced. It has been proven that the linear correlation between coronary artery disease and carotid disease is more evident at an advanced atherosclerosis stage<sup>18, 21, 23, 24</sup>. Indeed, the vast majority of our coronary artery disease patients had multi-vascular coronary artery disease, 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 patients with unexplained dilated and diffusely hypokinetic left ventricle, since the presence of atherosclerosis in the carotid bifurcation suggests a severe underlying coronary artery disease. As a consequence, it may be useful for patients with cardiomyopathy and carotid disease to undergo early coronary arteriography, in order to identify those patients with coronary anatomy suitable for reperfusion and proceed without any delay to tests that can determine the existence of a viable hibernating myocardium<sup>37</sup>. An additional advantage of this practice is that the results of such tests are more accurately interpreted when the coronary artery anatomy is already known. Moreover, it is desirable to determine any potential significant stenosis of the internal carotid, in order to seriously consider it when we plan for aorto-coronary by-pass. On the contrary, patients without carotid disease seem to suffer from non-ischaemic heart disease, thus further diagnostic procedures with coronary angiography 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 coronary artery disease in all patients with unexplained heart failure, we did not exclude cases of patients with diseases known to be related to dilated cardio-

myopathy, where coronary artery disease may coexist. For this reason, we included patients 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 coronary artery disease<sup>1,38,39</sup>. It is interesting that 9 of our patients were alcohol abusers and had long been characterized as suffering from alcoholic cardiomyopathy. Five of them had significant carotid atherosclerosis. In coronary angiography, all five presented significant coronary artery disease. The other 4 did not present carotid or coronary artery disease. Similar findings were observed in 3 hemodialysis patients. A separate analysis on the total of 30 diabetic patients of the study indicated results similar to the ones for the whole population of the study. Thus, carotid examination could be extremely useful in the management of patients with the above conditions.

The present study was not designed to objectively prove, either myocardial ischaemia in those patients with severe coronary stenosis, or the absence of ischaemia in those who did not present any angiographic stenoses, since our patients were not routinely examined to reveal myocardial ischaemia and viability. However, our results must not have been significantly influenced by this fact, since coronary artery stenoses were severe in the 38 cases of ischaemic heart disease. Indeed, 75 total occlusions were documented in the proximal segments of the coronary arteries, while the left anterior descending was significantly stenosed in all but two patients. As a conclusion, although hibernating myocardium was not proven in all our patients with severe coronary artery stenoses, it is almost certain that similar patients are treated, throughout the world, as suffering from ischaemic cardiomyopathy in daily clinical practice.

The study typically does not include consecutive patients, since coronary angiography was obligatory and since hemodynamically unstable patients, patients who did not survive before the investigations and unwilling patients (28 in total) were excluded. However, our patients clinically represent a consecutive series, since, in essence, daily practice proposes exactly the same procedures in patients 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, arterial hypertension, diabetes mellitus and the pre-

sence 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<sup>40</sup>. Moreover, in our study they presented clearly lower prognostic value than the carotid ultrasound data.

### **Limitations of the study**

The majority of the 12 false positive results of carotid examination (9/12) was observed in patients over 65 years of age, that is in an age group where pathological findings from the carotids are more often. Among the 117 studied patients, 34 were above 65 years old (28%) and 21/34 had non-ischaemic cardiomyopathy. The probability for the carotid examination sensitivity and specificity in predicting coronary artery disease to depend on age is very high. However, it has not been studied in this specific group of patients, and particularly in the elderly, given the relatively unknown natural course of dilated cardiomyopathy in old age. Moreover, the percentage of elderly patients in this specific study was relatively low and thus it is not expected to significantly affect our results. Finally, we performed a multivariate dependence analysis with the following cofactors: age, gender and pathological carotid findings. Only the latter were significantly and independently related with ischaemic heart disease.

We excluded 2 patients with myocarditis, 9 with antineoplastic treatment history, 1 parturient and 2 patients who underwent radiation therapy of the cervix from the study. Some of them could have had either the one or the other disease and this may have influenced our results, however, there were serious ethical reasons that prohibited their participation in this study. Additionally, the first two were very young, 5/9 patients with neoplasias had undergone cardiac ultrasound before the beginning of anti-neoplastic treatment and had normal left ventricular function, while radiation therapy of the cervix is known to cause significant fibrosis and stenoses in the carotid vessels.

The IMT was not measured in detail as is usually described in most of the studies investigating the IMT as a risk factor for vascular disease. Instead, IMT was calculated as the maximum value of the

distal segment of the carotid. It has been supported that this approach identifies IMT as an index of severity of atherosclerosis in a more realistic and practical way<sup>41</sup>. Although the limit of 1 mm for increased IMT thickness was selected arbitrarily (it is the highest median in the general population), it is exactly this value that presented the best results in the ROC curve. We chose to consider the carotid plaque as local thickening >1.3 mm since this value represents the mean value reported in literature, that is from >1.0 mm to >1.5 mm<sup>42,43</sup>. A value >1 mm would significantly influence the findings without providing, however, additional clinical benefit, while a value >1.5 mm would reduce sensitivity to the benefit of specificity. Although this study was not controlled for the accuracy of the degree of carotid stenosis that was determined by ultrasound in five ischaemic patients who were selected for aorto-coronary bypass and underwent digital carotid angiography, the results were found to be exactly the same as our own ultrasound findings.

In conclusion, the presence of carotid atherosclerosis, as it is identified by ultrasound, seems to be an accurate predictor of the existence of severe underlying coronary artery disease in patients with unexplained dilatation and diffuse dysfunction of the left ventricle.

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