Editorial Manager(tm) for Coronary Artery Disease
Manuscript Draft

Manuscript Number: CAD-D-07-00208

Title: CAROTID INTIMAL-MEDIA THICKNESS AND ENDOTHELIAL FUNCTION IN YOUNG PATIENTS WITH HISTORY OF MYOCARDIAL INFARCTION.

Article Type: Original Study (non-Clinical Trial)

Section/Category:

Keywords: carotid atherosclerosis; juvenile myocardial infarction; endothelial function; atherosclerosis.

Corresponding Author: Dr. Giuseppe Coppola, M.D., Ph.D Fellow

Corresponding Author's Institution: Chair of Cardiovascular Diseases and Division of Cardiology, University Hospital “P. Giaccone” of the University of Palermo, Italy

First Author: Giuseppe Coppola, M.D., Ph.D Fellow

Order of Authors: Giuseppe Coppola, M.D., Ph.D Fellow; Egle Corrado; Davide Piraino; Michele Carella; Ida Muratori; Pietro Camarda; Antonino Di Vincenzo; Gianfranco Ciaramitaro; Michele Farinella; Antonino Rotolo; Salvatore Evola; Enrico Hoffmann; Pasquale Assennato; Salvatore Novo

Manuscript Region of Origin: ITALY

Abstract: Aim of the study was to evaluate prevalence of carotid atherosclerosis and endothelial dysfunction in 45 young patients (38 men and 7 female) who suffered myocardial infarction (MI), age 29-45, mean age 42±3 years, to verify its possible role as a marker of coronary atherosclerosis.
METHODS: Vascular echography was performed to verify the presence of carotid atherosclerosis or/and endothelial dysfunction in 45 young patients after MI and in 45 healthy control subjects well matched for sex and age.
RESULTS: we observed a normal intima media thickness (IMT) only in 30% of patients who suffered juvenile myocardial infarction (JMI) in comparison with 66% of control group ($p<0.0001$) while 34% of patients showed an increased IMT in comparison with 24% of healthy subjects ($p<0.0001$). As compared

with control subjects, patients after JMI had lower flow-mediated reactivity of the brachial arteries ($p<0.05$). Flow-mediated dilation (FMD) was inversely associated with IMT ($p<0.001$). Severity of CAD was correlated with increased IMT and with a lower flow-mediated dilation. Finally, multiple regression analysis, demonstrated that both brachial-artery reactivity and carotid IMT were significantly and independently correlated with severity of CAD.
CONCLUSIONS: Structural (carotid atherosclerosis) and functional changes (endothelial dysfunction) were present at an early age in the arteries of persons with history of JMI.

CAROTID INTIMAL-MEDIA THICKNESS AND ENDOTHELIAL FUNCTION IN YOUNG PATIENTS WITH HISTORY OF MYOCARDIAL INFARCTION.

Coppola G, Corrado E, Piraino D, Carella M, Muratori I, Camarda P, Di Vincenzo A, Ciaramitaro G, Farinella M, Rotolo A, Evola S, Hoffmann E, Assennato P, Novo S.
Chair of Cardiovascular Diseases and Division of Cardiology, University Hospital "P. Giaccone" of the University of Palermo, Italy

For correspondence:
Giuseppe Coppola, MD, PhD Fellow
Chair of Cardiovascular Diseases and Division of Cardiology, University Hospital "P. Giaccone" of the University of Palermo, Italy

Via del Vespro 127
90129 Palermo
Tel/Fax:00390916554301
Email: g.coppola@unipa.it

Introduction

It is well know that asymptomatic coronary disease is related to an increased risk of cardiovascular disease. Thus, precocious identification and preventive treatment can, potentially, reduce the risk of this evolution. A large number of clinical and epidemiological studies used carotid IMT as precocious marker of atherosclerosis (ATS) (1,2,3). In particular, several epidemiological studies and clinical trials, used the measurement of IMT at the common carotid artery (CCA), obtained by non-invasive high-resolution B-mode ultrasonography, as an early marker of systemic ATS (4). The evaluation of the carotid artery wall with this technique is not expensive; it is highly reproducible and without risk (5, 6, 7).

A study of Salonen et al, in 1991, assessed that there is an increase of about 11% of the risk of myocardial infarction for every increase of 0,1mm of carotid IMT; such risk becomes two times greater in the presence of IMT > 1mm, four times greater in the presence of plaque and becomes six times greater in case of stenosis (8). This consideration explains the nature about a triennial B-mode ultrasonography control in case of IMT and an annual one in case of carotid plaque.

Extremely important information coming from the Rotterdam Study and the Cardiovascular Health Study (CHS), that showed the concomitant increase in the general population and especially in hypertensive patients, of carotid IMT and blood pressure (3). Also the HARVEST study documented, in patients with borderline hypertension, greater values of IMT in comparison to controls without hypertension, even after correction for age, sex, cardiac frequency, BMI, smoke, cholesterol and triglycerides (9). Among the risk factors involved in the development of carotid ATS, over arterial hypertension, age, cigarette smoking, hypertriglyceridemia, hypercholesterolemia and raised LDL-cholesterol correlate with the increase of IMT (10) a silent acceleration of it during the years (11) and a greater risk of mortality (12), as well as the emergent cardiovascular risk factors like the markers of inflammation, first of all IL-6 (13).

An increased carotid IMT is correlated to the presence of atherosclerotic lesions in other vascular districts (14); such correlation gives the possibility to consider carotid IMT as a marker of systemic ATS as well as a good index of coronary ATS for the hold association between the two districts, also in asymptomatic patients.

Several perspective studies showed how patients with elevated values of carotid IMT have a greater probability to incur in cardio- or cerebrovascular events. The Rotterdam study (7893 patients, with age >55 years, 2,7 year-old follow-up) showed how the increase of IMT is directly, and strongly, associated to an increased risk of myocardial infarction (odds ratio 1.43, 95% ICs, 1.16 to 1.78) and stroke (odds ratio 1.14, 95% ICs, 1.25 to 1.82) (15). A similar correlation has been shown in the CHS study (4400 patients, follow-up 6 years) that showed a strong association ($p<0.001$) between IMT and cardiovascular events (3).

The data of these epidemiological and clinical studies determined the American Heart Association to affirm that "*in the evaluation of the cardiovascular risk in asymptomatic subject > 45 years old, the measurement of the IMT can give additional informations in comparison to the traditional risk factors*"(16).

Endothelial dysfunction is a systemic disorder and a variable key in the pathogenesis of ATS and its complications; a non invasive ultrasound technique to evaluate brachial artery flow–mediated dilation (FMD) has recently been much used in the study of arterial physiology. The dilation response, with increased blood flow, is mainly mediated by nitric oxide released from arterial endothelial cells.

Brachial FMD response is correlated with coronary endothelial function as tested by invasive methods(18). Major risk factors for atherosclerotic vascular disease (e.g., hypertension, diabetes, smoking, hypercholesterolemia, and obesity) have been associated with endothelial cells disfunction, and is know that coronary ATS is characterized by an early loss of endothelium-dependent vasodilation. Impaired brachial FMD is also related to the prevalence and extent of coronary ATS and predicts cardiovascular events (19).

Since endothelial dysfunction and increased IMT are interrelated, but indicative of different aspects of the atherosclerotic disease, their early detection could have strong implications in cardiovascular prevention. Some studies have already related endothelial dysfunction and carotid IMT, in patients with ATS or coronary artery disease, but little data is available in patients with early stages of ATS, such as those with asymptomatic carotid lesions.

Aim of this study was the evaluation and the prevalence of carotid ATS and endothelial dysfunction in young patients with history of myocardial infarction (age ≤ 45 years old), in comparison with healthy control group, to verify its possible role as a marker of coronary atherosclerosis.

PATIENTS AND METHODS

We studied 45 young patients (38 male and 7 female) aged 29-45, mean age 42±3years, admitted in our operative unit with a diagnosis of JMI; patients in the stable phase after MI were included in the study. Our population has been coupled to one of control, asymptomatic for cardiovascular illnesses, matched for sex and age. The project design included a medical examination, biochemical analyses, echocolor-doppler of carotid arteries and mediated vasodilatation (FMD) at the brachial artery. The adopted procedures were in agreement with the Helsinki Declaration of 1975 as revised in 1983 and were approved by the Ethic Council of the Department of Internal Medicine of the University of Palermo. All subjects gave their informed consent to participate to the study so at admission, they underwent a medical examination and also answered to a questionnaire on personal and medical items, including age, past medical history and use of medications. Among the main cardiovascular risk factors, the presence of family history of CAD (in a first-degree relative before 55 years), hypertension (systolic or diastolic blood pressure respectively ≥ 135 or ≥ 85 mmHg or pharmacological therapy with antihypertensive drugs), diabetes (fasting glucose plasma concentrations higher than 126 mg/dl or pharmacological therapy with antidiabetic drugs or insulin) and smoking habits were considered. Sitting blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. The average of two measurements obtained on one

occasion, separated by a count of the pulse rate, was used in the present analysis. Height and weight were recorded and body mass index (BMI) was expressed as Kg/m². Participants were categorized as having obesity if BMI was ≥ 30 Kg/m².

Biochemistry

A blood sample was drawn in the morning, before the medical examination, after a 12-14 hrs overnight fast. Total cholesterol, triglycerides and HDL-cholesterol were quantified by standard enzymatic-colorimetric methods and LDL-cholesterol was calculated by the Friedewald formula.

Echocolordoppler examination of carotid arteries

B-mode real-time ultrasound was performed in blind, evaluating the arterial wall thickness in the carotid arteries with a machine Esaote Caris plus and a probe of 7.5-10.0 MHz. As already reported, patients were examined in the supine position and each carotid wall or segment was examined to identify the thickest intimal-medial site.

Three segments were identified and measured in antero, posterior and lateral planes on each side: the distal 1 cm of the common carotid proximal to the bifurcation, the bifurcation itself, and the proximal 1 cm of the internal carotid artery. On each of these sites, we determined the IMT, automatically measured, and detected any possible plaque. We primarily used the maximum carotid IMT value, which was determined as the mean of the maximum IMT of near- and far-wall measurements of both the left and right side arteries for each of the 3 arterial segments. If data on 1 of the walls or 1 of the sides were missing, maximum thickness of the available wall and side was used. Carotid ultrasonography was carried out by the same sonographer to limit the risk of a large interobserver variability. The mean carotid maximal IMT in our patients was 1,8 ± 0,7 mm.

According to the most recent guidelines of the joint European Society of Hypertension/European Society of Cardiology (20), we considered normal patients those with IMT < 0.9 mm, patients with IMT between 0.9 mm and 1.5mm and patients with asymptomatic carotid plaque (ACP) those with IMT > 1.5mm.

Study Protocol

Endothelial function was evaluated according to the recent guidelines by ultrasound using a 7.5-MHz linear-array transducer (21). Patients did not ingest substances that might affect flow mediated dilatation (FMD) such as caffeine, or use tobacco for at least 6 h before the study. All vasoactive medications were withdrawn for at least four half-lives, if possible. Patients remained in the supine position for at least 10 minutes before the study and were kept in this position during the procedure. The subjects have been studied in a quiet, temperature-controlled room, in supine position.

The artery was scanned over a longitudinal section 3 to 5 cm above the elbow, the site where the clearest image can be obtained. The focus zone was set to the depth of the anterior vessel wall. Depth and gain settings were optimized to identify the lumen-vessel wall interface; the diameter of the brachial artery was measured from the anterior to the posterior interface.

We evaluated the variation of the diameter of the brachial artery at baseline, using high-resolution ultrasound, and after arterial occlusion for 5 min through cuff inflation to at least 50 mmHg above the systolic pressure. The flow-mediated vasodilator response to reactive hyperaemia was countinously recorded from 30 seconds before to 5 minutes after cuff deflation. Reactive hyperaemia (change in flow velocity) was measured when compression was released, and the new arterial diameter and flow velocity were measured one minute later. The percent change between the diameter at release of compression (D2) and the baseline diameter (D1) is the so-called endothelium dependent vasodilatation (EDV). Thus: EDV = (D2-D1)/D1.*100. Ten minutes later, when the artery returned to baseline, 0,3 mg of nitroglycerine was administered per os and four minutes later arterial dilatation was again measured. The percent change between the post-nitroglycerine diameter (D3) and the baseline value (D1) is the so called endothelium-independent vasodilatation or nitroglycerine-mediated vasodilatation (NitroMV). Thus: NitroMV = (D3-D1)/D1.*100.

Statistical analysis

Statistical analyses were performed using the Statview Program (Abacus Concepts Inc., CA, USA). Differences in the investigated parameters among study groups were assessed by the Student's t test, while differences in the prevalences were analyzed by χ^2 test. Relationships between the investigated parameters and the severity of coronary disease were assessed by the ANOVA test. Correlation between continuous variables was analyzed using Pearson's correlation coefficient. Finally, to identify the possible independently variables related with the severity of CAD, we built up a statistical model of multivariate analysis (multiple regression), including the following clinical and biochemical variables evaluated at the admission.

RESULTS

Looking for the distribution of traditional cardiovascular risk factors we found in cases, in comparison to controls, a greater prevalence of hypertension (72% vs 36%, $p<0.05$), familiarity for cardiovascular disease (52% vs 32%, $p<0.05$) and for diabetes mellitus (28% vs 16%, $p<0.01$) while we did not find differences about cigarettes smoking between the two groups. In patients who suffered JMI we observed a higher value of waist circumference (102±11 vs 93±13 respectively in cases and in controls, $p<0.05$) and of relationship W/H (20% vs 2%, $p<0.05$); we did not found a statically significative difference about lipidic pattern, while, a statically significative difference was found about fibrinogen plasma level in patients with history of JMI in comparison to controls (408±101 vs 280±88, $p<0.005$).

The echocolordoppler duplex scanning's examinations, both in cases than in controls, was done to appraise their carotid wall profile and this finding allowed us to distinguish three classes of subjects:

- patient with a regular carotid wall profile (IMT <0,9mm)
- patient with IMT (IMT between 0,9-1,5mm)

- patient with carotid plaque (IMT >1,5mm)

We found a greater prevalence of carotid ATS, as IMT as carotid plaque, in cases in comparison to controls: patients with a normal carotid wall profile resulted the 30% of our population, in comparison to the 66% of controls ($p<0.0001$), 34% showed carotid IMT, in comparison to 24% of controls, while carotid plaque were observed in the 36% of cases in comparison to 10% among healthy subjects ($p<0.0001$). Patients after JMI, in comparison to controls, showed a greater prevalence of carotid ATS, both in form of IMT than in form of carotid plaque, with a significantly difference between values of carotid IMT in both groups (1,47±0,78 vs 0,95±0,41, $p<0.0001$) (figures 1 and 2). Finally, we found a clean and clear association between the two districts (coronary and carotid) with a correspondence of 84% for patients in examination: in particular in the 66% of the patients, we found ATS in both districts and in the 18% of the cases in none of the two districts; we found a correlation between carotid IMT increasing and the involvement of coronary artery (figure 3)

These findings underline how, for 84%, carotid ATS, evaluated with a non invasive examination as echocolordoppler duplex scanning, represents a good marker of coronary ATS; carotid IMT could represent a real new cardiovascular risk factor able to furnish indications on the state of coronary ATS.

In patients after JMI we found a lower FMD in comparison to controls and a positive correlation between the vessels culprit and the presence of endothelial dysfunction (table 1 and figure 4).

A significant inverse correlation was found between brachial-artery reactivity and IMT of the common carotid artery in patients after JMI ($r= -0.663$, $P=0.0001$) but not in controls ($r= -0.223$, $P=0.161$). (Figure 5)

We have finally built a model of multiple regression analysis (table 2) to evaluate the clinical and laboratory variables significative associated with a wider and severe coronary disease; the variables significative associated were the number of daily smoked cigarettes ($r= .486$, $p<0.05$), the BMI ($r = .975$, $p <0.02$) the carotid IMT ($r = .249$, $p <0.0001$).

DISCUSSION

The carotid district has been representing for long time a cornerstone in the evaluation of the atherosclerotic disease, both for the easy availability with non invasive diagnostic techniques, like echocolordoppler for example (18), but also because carotid ATS is considered a good marker for the evaluation of ATS as a multifocal disease.

Some clinical studies underlined the hold association between cardiovascular risk factors and the appearance of carotid IMT; for example, in the study GESCO-MURST-CIFTI-4, conducted on 755 patients, it has been observed that patients with one or more traditional risk factors showed, in comparison to those deprived of them, an increase of carotid IMT (32,5% vs 14,7%), of asymptomatic carotid plaque (10,75% vs 5,37%) or both (47,2% vs 16,2%). (22)

The number of risk factors is strongly associated to the extension, the severity and the number of atherosclerotic lesions. A recent study performed by Li et al., showed a greater carotid IMT in adults with an elevated number of risk factors since children, underlining the hold relationship between the cardiovascular risk factors and the development of atherosclerotic lesions in the carotid district; this study followed 486 subjects, age between 4 and 17 years, for 23 years, to understand the importance of the presence of risk factors since childhood; in this study BMI and cholesterol LDL plasma levels showed a predictive value for the development of carotid IMT in adult age. (23)

The appearance, the extension and the progression of the atherosclerotic disease in this district is associated to an increase of the global cardiovascular risk, and it is well known an association between carotid IMT and the prevalence of coronary heart disease and stroke. (3)

The use of non-invasive high-resolution B-mode ultrasonography and the evaluation of carotid IMT for the stratification of cardiovascular risk are still, however, under discussion. According to the opinions of some authors, it could have a limited role for patient with risk factors and it could be exclusively predictive of coronary heart disease and stroke in elderly subjects (24). Davis PH and others, underlined how such relationship is also present in juvenile age, with a study conducted on

patient aged between 33 and 42, showing through an ultrasonography evaluation for the carotid arteries and computerized tomography (TC) for the coronary ones, a greater carotid IMT in patients with coronary calcifications in comparison to patients without, both in men and women (25).

Aim of our study was the evaluation of the relationship between carotid IMT and endothelial dysfunction in patient with JMI, to verify the existing relationship between carotid, endothelial function and coronary ATS.

We found, in patients with JMI in comparison to controls, a greater prevalence of carotid IMT (34% vs 24%) and carotid plaques (36% vs 10%, $p<0.0001$), according particularly with Vrtovec and others (26), that appraising the traditional and emerging cardiovascular risk factors as well as the carotid IMT, found in the examined patients, in comparison to controls, a greater IMT ($p<0.0001$) in every carotid section examined, even if in our study results more evident the difference between the two groups regarding the discovery of carotid lesions for the elevated number of patients with carotid plaques (36% vs 10%, $p<0.0001$).

According with literature's findings, we found a clean and clear association between the two districts, coronary and carotid, with a correspondence of 84% for the patients in examination: in particular in the 66% of patients, ATS has been found in both districts and in the 18% of the cases in none of the two districts. So, carotid ATS could be considered a good marker of multifocal ATS and, therefore, its presence in the carotid district is associated frequently to the presence in the coronary one and, vice versa, the absence of carotid ATS is, with good probability, associated to the presence of an uninjured coronary tree vessels. All of this confirms more and more the conception of ATS like a multifocal and multifactorial disease and confers to the peripheral involvement a not often recognized importance in the recent past.

In conclusion, the experience of this study allows us to affirm that data showed underline four fundamental points:

1) patients with JMI, in comparison to healthy subjects, present, in a greater percentage and with a greater severity, atherosclerotic lesions, both as IMT both as carotid plaques;

2) patients with JMI, in comparison to healthy subjects, present, a lower flow mediated dilation;
3) a hold correlation exists between carotid and coronary ATS, as suggested in the scientific literature. In fact, ATS is a multisystemic disease and the evaluation of carotid IMT through non-invasive methods of imaging allows us to obtain indirect informations on the sistemic condition, coronary one in particular, of ATS lesions, using, therefore, such district as an important marker, expecially in those conditions in wich could be present asymptomatic ATS lesions.
4) Carotid IMT would be considered as a real emergent risk factor and it should be preventively evaluated, in addiction with traditional and emergent risk factors, to appraise and reduce the cardiovascular risk.

The individualization of this kind of patients allow us, not only to have information on the carotid district and indirectly on coronary one, but also to be able to choose the right strategies, pharmacological or not associated to the removal of cardiovascular risk factors to reduce cerebro- and cardiovascular risk, preventing fatal and non fatal events.

References

[1] Crouse JR 3rd. Predictive value of carotid 2-dimensional ultrasound. *Am J Cardiol 2001*; **88:** 27E-30E.

[2] Grobbee DE, Bots ML. Carotid intima-media thickness as an indicator of generalized atherosclerosis. *J Intern Med 1994*; **236** : 567-573.

[3] O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK et al. on behalf of the CHS Collaborative Group. Distribution and correlates of son graphically detected carotid artery disease in the Cardiovascular Health Study. *Stroke* 1992; **23**:1752-1760.

[4] Zwiebel WJ. Duplex sonography of the cerebral arteries: efficacy, limitations and indications. *Am J Radiol 1992*; **158**: 29-36.

[5] Pignoli P, Tremoli E, Poli A, Oreste P, Paletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation 1986*; **74**: 1399-1406.

[6] Poredos P. Intima media thickness. *International Angiology 2005*; **24**: 6.

[7] Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation 1993*; **87**: 1156-1165.

[8] Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb 1991*; **11**: 1245-9.

[9] Palatini P, Mormino P, Mos L, Mazzer A, Dorigatti F, Zanata G, et al. on behalf of the HARVEST Study Group. Microalbuminuria, renal function and development of sustained hypertension: a longitudinal study in the early stage of hypertension. J Hypertens. 2005 Jan; **23**(1):175-82.

[10] Hermits Eller N, Netterstrom B. The intima media thickness and coronary risk factors. *Int Angiol 2001*; **20**: 118-25.

[11] Salonen JT, Seppanen K, Rauramaa R, Salonen R. Risk factors for carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Med 1989*; **21**: 227-9.

[12] Novo S. Influence of risk factors and aging on asymptomatic carotid lesion. In: *Adv Vasc Pathol 1997*; Excepta Medica, Amsterdam 1997: 36-46.

[13] Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults. (The Bogalusa heart study). *Am J Cardiol 2002*; **90**: 953-8.

[14] Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, Berenson GS. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA 2003*; **290**: 2943.

[15] Bots ML, Moons KG, Hollander M, Hoffman A, Koudstaal PJ, Grobbee DE, Breteler MM, Whitman JC, Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. *Circulation 1997;* **96**: 1432-1437.

[16] Novo S. Carotid lesion as risk factor for ischemic heart disease. *Haematologica 2001*; **86**: 12-5.

[17] Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrande D et al. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol. 1995*; **26**: 1235-1241.

[18] Takase B, Uehata A, Akima T, Nagai T, Nishioka T, Hamabe A et al. Endothelium-dependent flow mediated vasodilatation in coronary and brachial arteriesin suspected coronary disease. Am J Cardiol. 1998; **82**: 1535-1539.

[19] Corrado E, Muratori I, Tantillo R, Contorno F, Coppola G, Strano A, Novo S. Relationship between endothelial dysfunction, intima media thickness and cardiovascular risk factors in asymptomatic subjects. Int Angiol 2005; **24**: 52-8.

[20] 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial Hypertension. J Hypertens 2003; **21**: 1011-1053.

[21] Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Chrbonneau F, Creager MA et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of

the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002; **39**: 257-265.

[22] Novo S. Influence of risk factors and aging on asymptomatic carotid lesion. In: *Adv Vasc Pathol 1997*; Excepta Medica, Amsterdam 1997: 36-46.

[23] Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA 2003*; **290**: 2943.

[24] Del Sol AI, Moons KG, Hollander M, Hofman A, Koudstaal PJ, Grobbee DE et al. Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. *Stroke 2001*; **32**: 2443-5.

[25] Davis PH, Dawson JD, Mahoney LT, Lauer RM. Increased carotid intimal-medial thickness and coronary calcification are related in young and middle-aged adults. *Circulation 1999*; **100**: 838-842.

[26] Vrtovec B, Keber I, Gadzijev A, Bardorfer I, Keber D. Carotid intima-media thickness of young coronary patients. *Coron Artery Dis 1999*: **10**: 407-11.

Table

Table 1. Brachial artery diameter (BAD) and flow mediated dilatation (FMD%) in patients with Juvenile Myocardial Infarction (JMI) in comparison to controls.

	Patients with JMI	***Controls***	***p <***
BAD mm	4,3 ± 0,7	4,1 ± 0,4	ns
FMD %	14 ± 9	17 ± 3	0.05

.

Table 2. Multivariate analysis: baseline parameters independently associated with severity of coronary disease.

Variables	***r***	***P value***
Number of daily smoked cigarettes	.486	.0001
Carotid IMT (mm)	.349	.01
Body Mass Index	.275	.05

Figure
Click here to download high resolution image

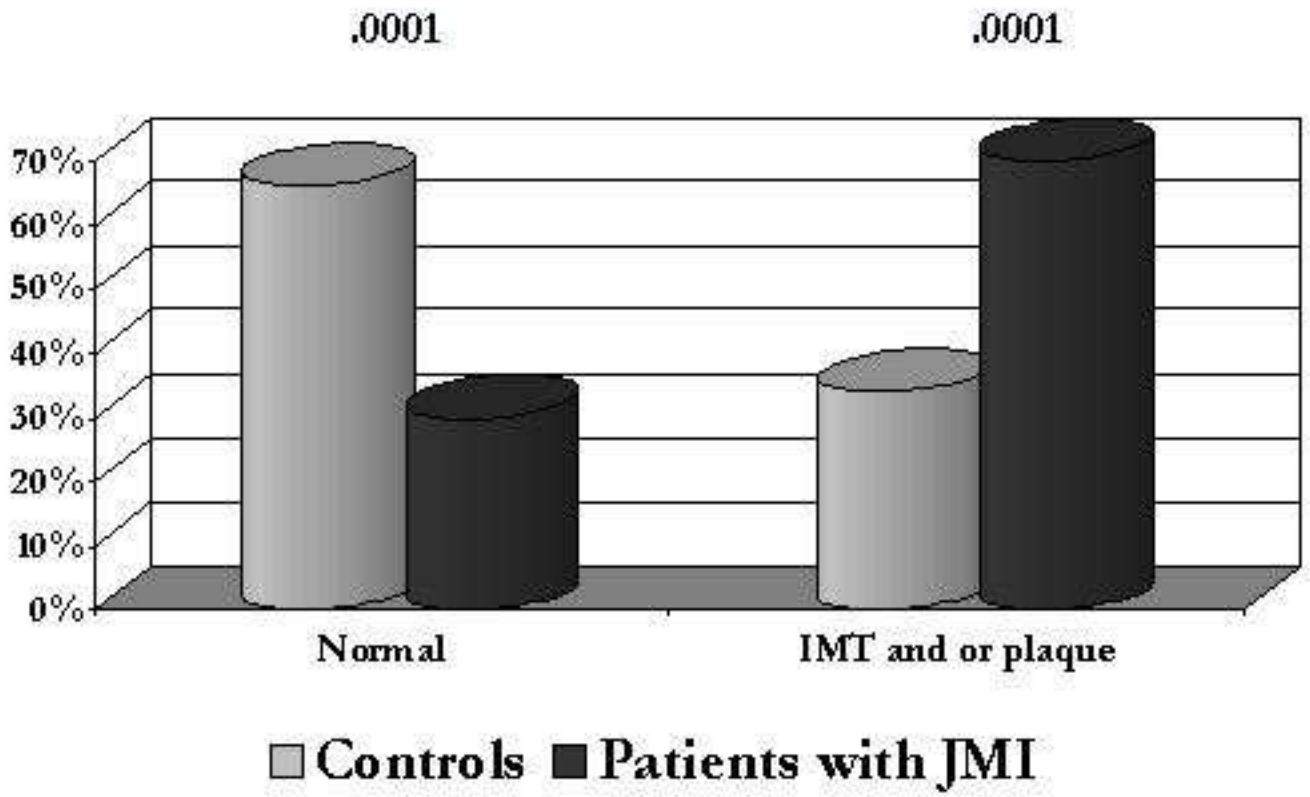

Figure I. Prevalence of carotid atherosclerosis in patients with Juvenile Myocardial Infarction (JMI) in comparison to control.

Figure
Click here to download high resolution image

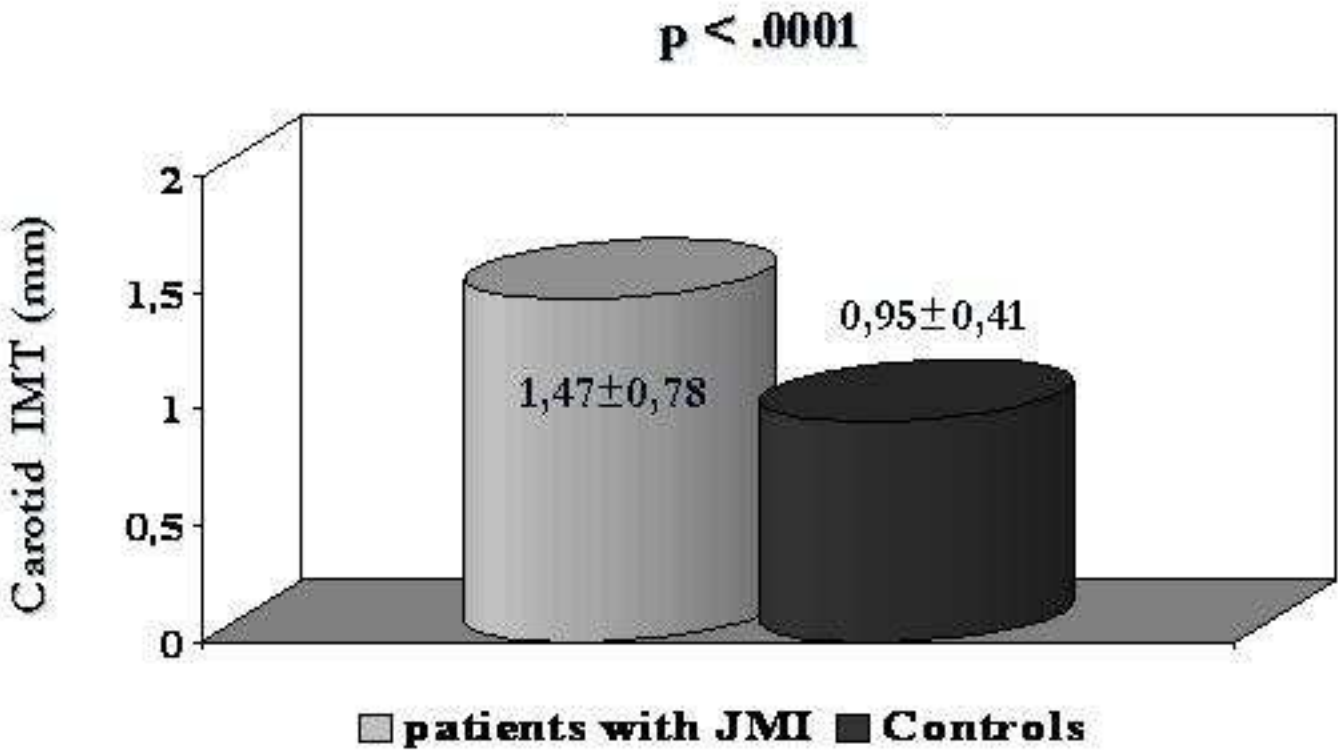

Figure II. Carotid intima media thickness in patients with Juvenile Myocardial Infarction (JMI) in comparison to controls

Figure
Click here to download high resolution image

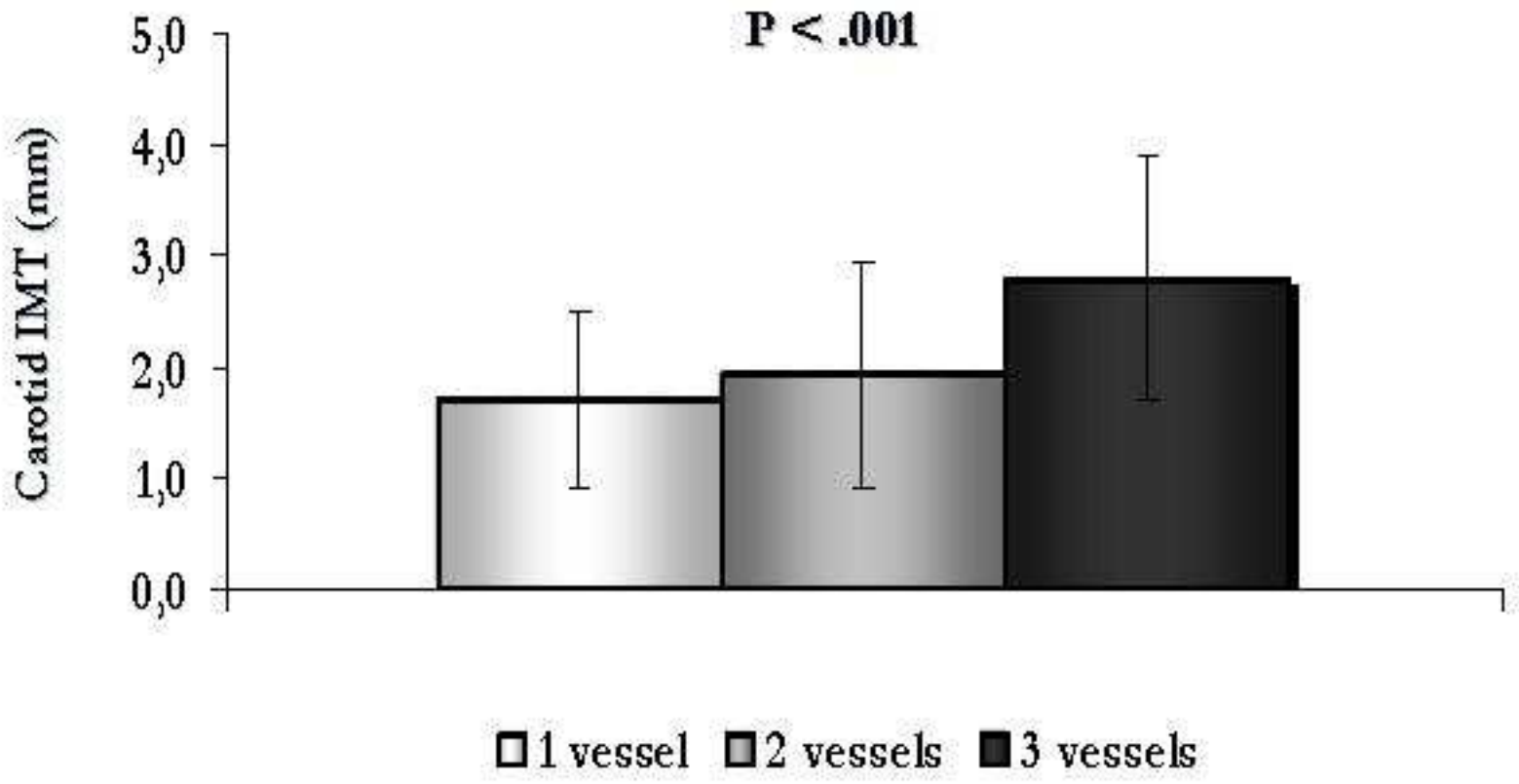

Figure III. Carotid intima media thickness in patients with JMI

Figure
Click here to download high resolution image

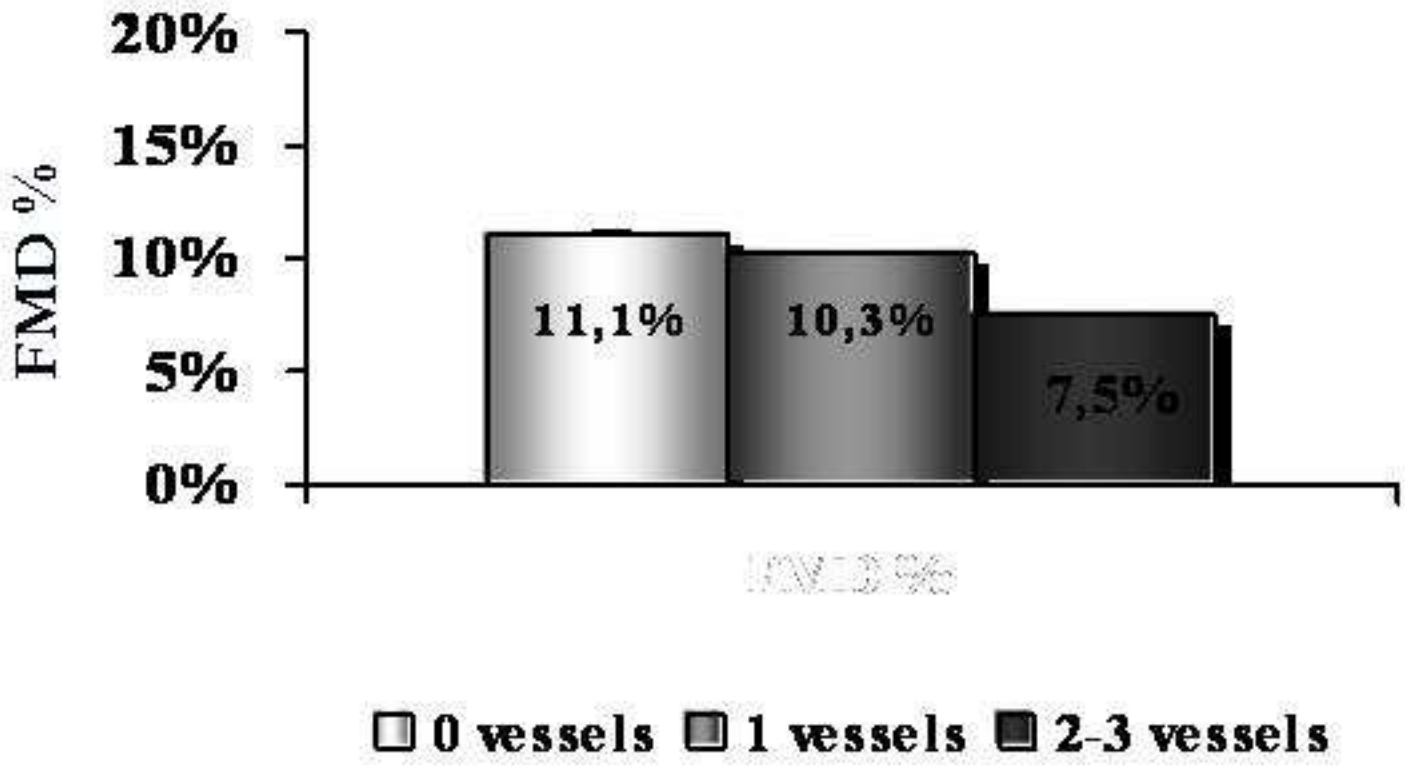

Figure IV. Association Between Coronary Atherosclerosis Disease Severity and Flow Mediated Dilatation (FMD%).

Figure
Click here to download high resolution image

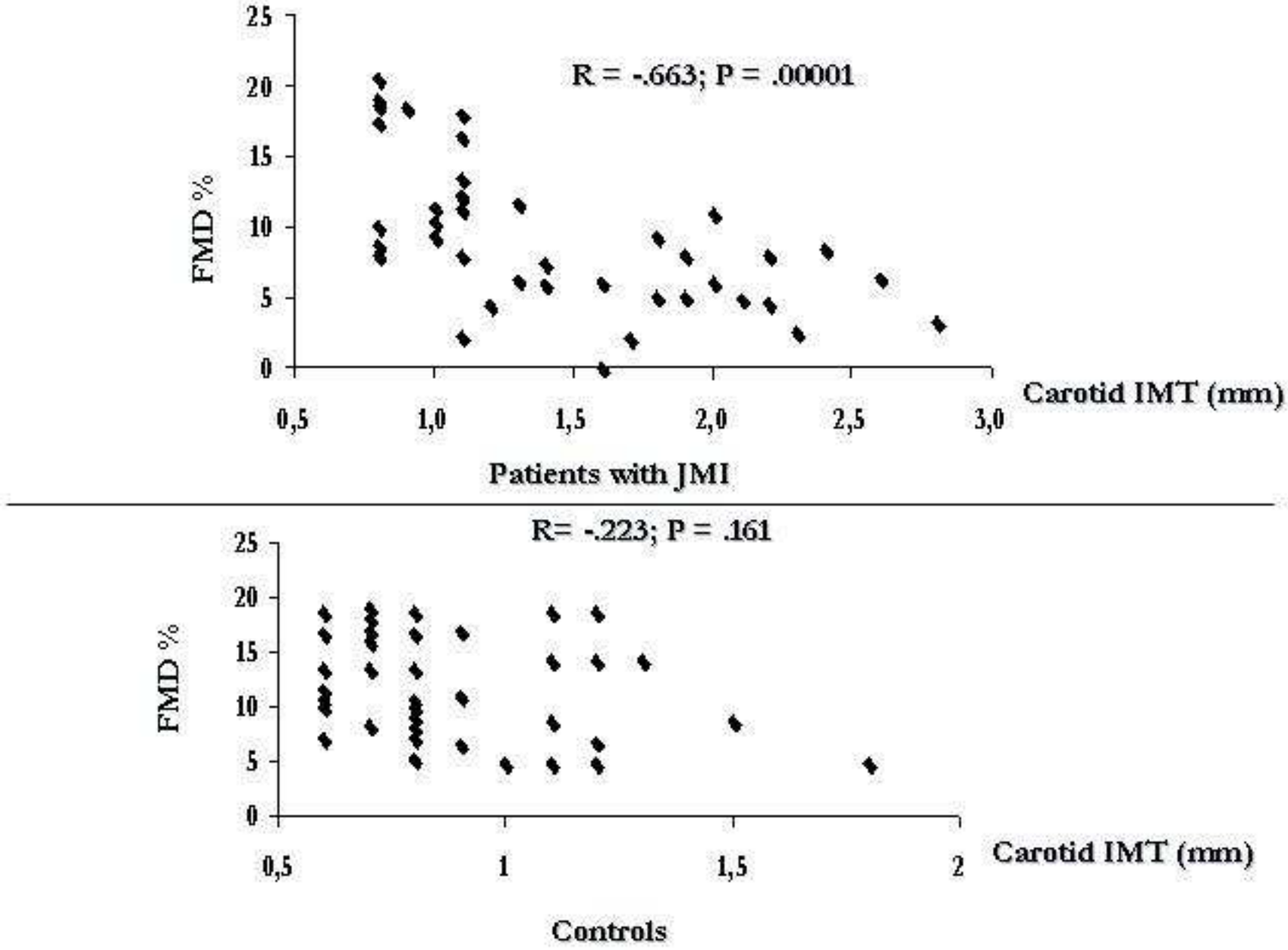

Figure V: Correlation between flow mediated dilatation (FMD%) and carotid IMT in subjects with Juvenile myocardial infarction (JMI) and controls.

Palermo 28/11/2007

To:
Professor Burton E. Sobel MD
Editor-In-Chief
Coronary Artery Disease

From:
Prof. Salvatore Novo, MD
Head Chair of Cardiovascular Diseases
Department of Internal Medicine, Cardiovascular and Nephro-Urological Diseases
Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone"
Via del Vespro 141 – 90127 – Palermo – Italy
Tel. +39-091-655.43.01; Fax +39-091-655.43.01
E-mail: novosav@unipa.it

Dr. Giuseppe Coppola, PhD Fellow
Head Chair of Cardiovascular Diseases
Department of Internal Medicine, Cardiovascular and Nephro-Urological Diseases
Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone"
Via del Vespro 141 – 90127 – Palermo – Italy
Tel. +39-091-655.43.01; Fax +39-091-655.43.01
E-mail: g.coppola@unipa.it

Dear Editor,

I am glad to submit our manuscript entitled "*CAROTID INTIMAL-MEDIA THICKNESS AND ENDOTHELIAL FUNCTION IN YOUNG PATIENTS WITH HISTORY OF MYOCARDIAL INFARCTION*" for possible publication in *"Coronary Artery Disease"*.
All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.
We will send at your journal office the standard cover letter form we have download from journal website in which you will find all authors' signs.

Thanks for considering our manuscript.
Best regards,

Prof. Salvatore NOVO

Dr. Giuseppe COPPOLA

Dr. Egle CORRADO

Dr. Davide PIRAINO

Dr. Michele CARELLA

Dr. Ida MURATORI

Dr. Antonino DI VINCENZO

Dr. Gianfranco Ciaramitaro

Dr. Michele FARINELLA

Dr. Antonino ROTOLO

Dr. Salvatore EVOLA

Prof. Enrico HOFFMANN

Prof. Pasquale ASSENNATO