

Microvascular angina in diabetic patients with uninjured coronary arteries.

Research Article

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Received 14 March 2012; Accepted 26 July 2012

Abstract: Aims: The study aims at the evaluation, of patients with chest pain and uninjured coronary arteries, and the impact of diabetes mellitus on coronary microcirculation. Moreover we want to verify whether a correlation between myocardial scintigraphy results and coronary angiography or not. Methods: The study population included 316 patients (173 males,143 females) with uninjured coronary arteries. Patients with chest pain (208) were divided into two populations: diabetics (72) and non-diabetics (136).We compared 66 patients with a myocardial scintigraphy with results of angiographic indexes. On angiographic images we evaluated, on the three major epicardial, Gibson's indexes (TFC, MBG), the Yusuf's index(TMBS) and a new index: Total Timi Frame Count (TTFC). Results: Patients with positive scintigraphy had a worse TMBS than patients with negative scintigraphy ($p=0.003$) and a lower TFC of healthy vessels than diseased vessels ($p=0.0001$).We found a worse coronary microcirculation in diabetic patients with lower values of MBG and TMBS ($p=0.02$),compared with non- diabetics. New index TTFC is usually higher in diabetics than non-diabetic patients. Conclusion: The study of microcirculation by coronary angiography and myocardial scintigraphy shows a good correlation between two methods. The analysis of diabetic patients and non-diabetic with chest pain and uninjured coronary arteries has led to assess that diabetic population has a major microcirculation disease.

Keywords: Chest pain • Coronary angiography • Diabetes mellitus • Microcirculation • Myocardial scintigraphy

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1. Introduction

Coronary microangiopathy is an important pathophysiologic feature of diabetes. Insulin resistance, glycemic control, and lipid disorders are related to vascular angiopathy in diabetics. However, the specific role of these factors in coronary microangiopathy is unclear. This coronary microangiopathy is characterized by an angina with normal coronary angiography [1].

In patients undergoing coronary angiography for evaluation of chest pain strongly suggestive of coronary

artery disease (CAD), 20-30 percent is found to have normal coronary angiograms [2].

The term "Cardiologic Syndrome X" ,coined by Kemp, is now generally used to describe patients with exertional angina, completely normal coronary angiograms, and a positive ECG response to exercise testing [3]. It excludes patients with coronary artery spasm (Prinzmetal's or variant angina), left ventricular hypertrophy, systemic hypertension, and valvular heart disease [4]. The term "Microvascular Angina" (MVA), coined by Cannon and Epstein includes all such patients with coronary microcirculatory derangements but with normal

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coronary angiograms irrespective of the presence or absence of exercise-induced ST segment depression. However, often the two terms are used interchangeably [5]. MVA, at present, appears to be a heterogeneous group of disorders with varied mechanisms – still largely speculative, operating alone or in combination, in different cases. Three main pathogenetic hypotheses have been propounded so far: myocardial ischemia–caused by functional or anatomical abnormality in coronary microcirculation is the most important [6]. It may be “primary” caused by abnormal constriction of coronary microvasculature or “secondary” to anatomical restriction of vascular cross-section or reduced vasodilator capacity. Impaired endothelium mediated vasodilation and increased stimulation of coronary α -adrenergic receptors consequent to increased sympathetic activity have been suggested as possible mechanisms of this reduced vasodilator capacity [7]. The exact site of the microvascular abnormality is debatable though some investigators have incriminated the resistive arterioles while others have argued the dysfunction to be prearteriolar and caused by reduced production of endothelium-derived relaxing factor [8,9]. Maseri et al. suggested that microvascular dysfunction might be limited to pre-arterioles (which its small coronary artery resistance vessels (<500 microns), not visible during angiography), so that an inappropriate constriction or impaired pre-arteriolar dilation, in response to arteriolar metabolic dilation, could provoke an ischemia in a small myocardial area [10]. Metabolic disorder affecting the handling of energy substrates by the heart muscle is the second hypothesis suggested, in particular the role of nitric oxide is most important in the development of diabetes-related vascular disease and more studies suggest that nitric oxide metabolism and vascular responsiveness to nitric oxide are altered in diabetes mellitus diabetes type 2 [11]. The third hypothesis denies the existence of any distinct cardiac entity and attributes the symptoms to increased sensitivity to algogenic stimuli arising from a variety of organs including the heart. Although altered pain perception may certainly play an important role, the existing data as a whole is insufficient to justify the pain as normal or arising out of anxiety neurosis.

The aim of this study was to evaluate the impact of diabetes on the function of coronary microcirculation through Gibson's index (Timi Frame Count and Myocardial Blush Grade), Yusuf's index (Total Myocardial Blush Score) and a new index that we imagined, on the basis of Yusuf's experience: the Total Timi Frame Count (TTFC) as the sum of the three coronary arteries; this is a new method to study the coronary microcirculation [12]. Therefore we evaluated the role of coronary microcirculation, using nuclear imaging (myocardial scintigraphy)

and compared the obtained results with an estimation of coronary blood flow achieved by using Timi Frame Count (TFC) and tissue perfusion capability by Myocardial Blush Grade (MBG).

2. Materials and methods

The study population included patients who underwent to coronary angiographies which showed coronary arteries without any stenosis who, between January 2004 and May 2011, were admitted to Cardiology department and Cardiac Surgery department of “P. Giaccone” hospital in Palermo. Among this population we considered patients with chest pain and uninjured coronary arteries that had a myocardial scintigraphy. We then divided them into two populations: patients with positive scintigraphy and negative.

The population with uninjured coronary arteries was divided into two populations: patients who were affected by chest pain (208 patients) and patients who were not and underwent to coronary angiography as a preoperative risk assessment before heart surgery intervention (108 patients). Patients with chest pain, we split into two populations: diabetics (72) and non-diabetics (136).

In the first part, patients with chest pain and uninjured coronary arteries that had a myocardial scintigraphy were split into two populations: patients with positive scintigraphy and negative. On angiographic images of each patient, stored on suitable digital supports, Timi Frame Count (TFC) and the Myocardial Blush Grade (MBG) were calculated. TFC was obtained on the three main coronary (LAD = left anterior descending artery; CX = circumflex coronary artery; RCA = right coronary artery), using the protocol described by Gibson et al. corrected, if necessary for the excessive length of LAD, compared to other coronary vessels, by dividing its value for 1.7. The values obtained in order to make them comparable with those reported in the literature, were corrected depending on the acquisition used for speed angiography in our center.

Myocardial Blush Grade was also calculated on the three main coronary arteries (LAD, CX, RCA), strictly following the protocol described. Moreover we used a new index, proposed by Yusuf Atmaca et al., Total Myocardial Blush Score (TMBS), which consists of the sum of the myocardial blush grades of each coronary artery [13,14].

On the basis of Yusuf's experience we imagined a new index: the Total Timi Frame Count (TTFC) as the sum of the three coronary TFC. We want to see if the results of TTFC are comparable with other indices

mentioned in order to use this new index to give a more complete view of coronary microcirculation.

We expressed clinical data as mean \pm standard deviation. In order to determine the statistical significance of differences in continuous variables between subgroups we used Student t-tests. For dichotomous variables chi-square test or Fisher's exact tests when appropriate were utilized, a p-value <0.05 was considered significant.

3. Results

The study population included 316 patients (173 males, 143 females) who underwent to coronary angiographies which showed coronary arteries without any stenosis. Among this population we considered the prevalence of cardiovascular risk factors and treatments and we carried out and performed, on a subgroup, stress tests and myocardial scintigraphy. Within this population, 208 patients were affected by chest pain (65.8%) while 108 patients (34.2%) were not and underwent coronary angiography as a preoperative risk assessment before a heart surgery intervention. We split patients with chest pain into two populations: diabetics (72 patients – 34.6%) and non-diabetics (136 patients – 65.4%).

Our study started from the analysis of angiographic data in patients with chest pain and uninjured coronary arteries (208 patients). Within this population patients who underwent a myocardial scintigraphy were 66 (32% of patients). Within this population we created two populations: patients had positive scintigraphy (49 patients – 69.7%) and negative scintigraphy (20 patients – 29.3%). In this subgroup of patients we studied the correlation between Total Myocardial Blush Score (TMBS), predictor of impaired microcirculation, and scintigraphy and we noticed that patients with positive scintigraphy had a worse TMBS than patients with a negative one, with a high statistical significance ($p = 0.003$) (Figure 1). The second part of our study focused on the correlation between scintigraphy defect and angiography data in the venue of ischemia relieved by nuclear imaging. The analysis showed that healthy vessels had a lower TFC than diseased vessels and therefore a better microcirculation with a high statistical significance with a p value = 0.0001 (Figure 2).

Furthermore we analyzed the correlation between Total Myocardial Blush Score with Total Timi Frame Count and revealed a significant inverse proportionality between these two indexes: the higher is MBG, index of a reduced perfusion of microvesselles, the higher is usually TFC, an index of slow flow in coronary arteries. The results of scintigraphy (positive in 69.7% of patients)

Figure 1. TMBS in patients with positive and negative scintigraphy

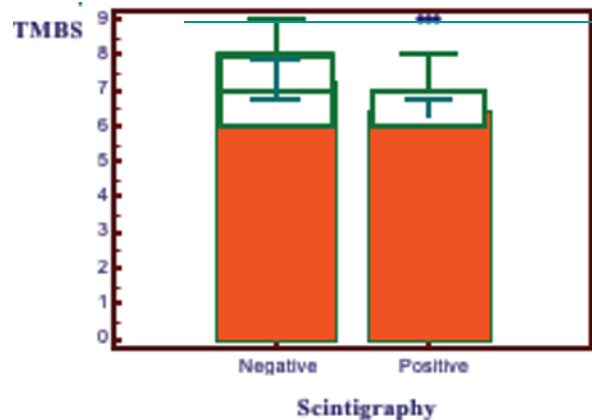
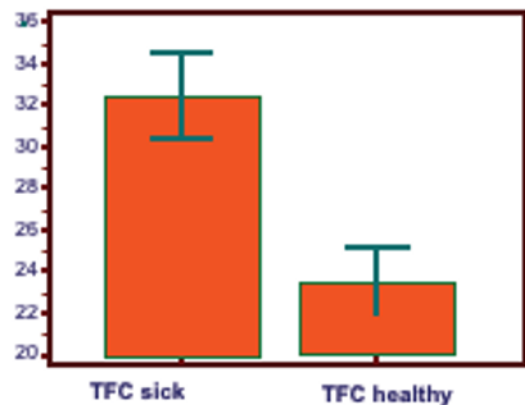


Figure 2. Comparison, in patients with positive scintigraphy, between TFC in healthy vessels and TFC in diseased vessels.



seem to endorse the hypothesis by which there is a good correlation between the study of the microcirculation performed through myocardial scintigraphy and coronary angiography: presence of perfusion defects in absence of coronary macroangiopathy is probably due to microvascular abnormalities. On the other hand our study provides a method to detect microcirculatory alterations in a very early stage of the ischemic cascade determining a redistribution of coronary blood flow.

We primarily compared two groups of patients: those who tell to have signs of heart disease, like chest pain, and those who have never suffered from chest pain. In both groups we evaluated the parameters we used for the study of microcirculation: the stress test, scintigraphy, the Timi Frame Count and the Myocardial Blush Grade and we observed some differences. By analyzing the two groups of patients with, and without, chest pain we noticed that, those who suffered of angina syndrome, had a positive scintigraphy and a positive exercise test in a larger number of cases, compared to those did not. MBG turns out to be higher in subjects without pain than in patients with pain, although this difference was not statistically significant being p-value not lower than 0.05,

Table 1. Comparison of TFC, MBG and TMBS between diabetic patients with chest pain than non-diabetic patients with chest pain.

	PAIN+ / MD+ (72 Patients)	PAIN + / MD – (136 Patients)	p-value
MBG LAD	2,2 (+/- 0,4)	2,4 (+/- 0,5)	0,03
MBG RCA	2,2 (+/- 0,4)	2,3 (+/- 0,47)	NS
MBG CX	2,1 (+/- 0,36)	2,3 (+/- 0,4)	0,04
TMBS	6,6 (+/- 1,06)	7 (+/- 1,16)	0,02
cTFC LAD	45,7 (+/- 12,5)	41 (+/- 11,6)	NS
TFC RCA	25,6 (+/- 6,5)	25,1 (+/- 6,3)	NS
TFC CX	24 (+/- 5,4)	21 (+/- 4,7)	0,05

Figure 3. TMBS in diabetic patients and non diabetic patients

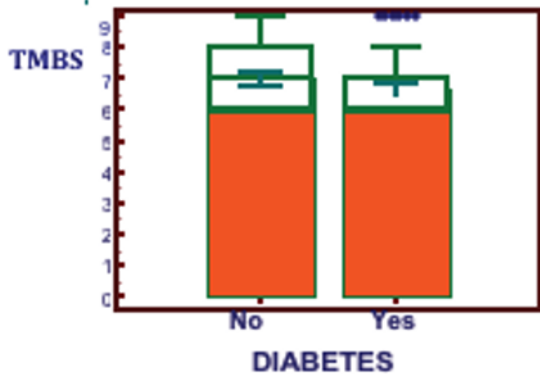
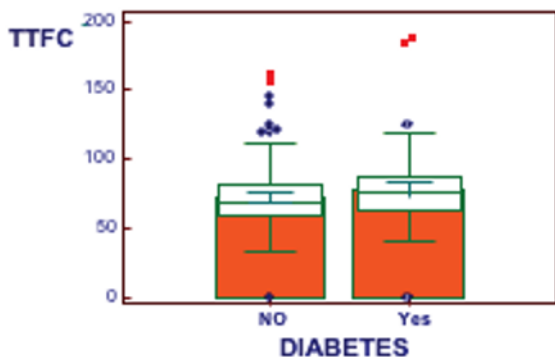


Figure 4. New index TTFC in diabetic patients and non diabetic



except for the circumflex artery. Starting from the population of patients with chest pain (208) we began to draw attention on patients with diabetes. Within the population with angina (208 patients), we created two subgroups: those who had mellitus diabetes (72 patients) and those who hadn't (136 patients).

The study of the microcirculation showed significant differences between the diabetics and non- diabetics. We considered two different indexes, as we have seen, allow us to study microcirculation: Total Myocardial Blush Grade and Timi Frame Count. As we show the compared analysis of TFC in the three coronaries between diabetic patients and non-diabetics (Table 1), showed that there is a worse perfusion in patients with diabetes

and chest pain where the three coronary vessels have a TFC greater than the population of non-diabetic.

A similar analysis can be inferred by evaluating the other index that we used in our study, MBG, in the three coronary vessels (Table 1) even here we found a worse situation involving the microcirculation in diabetic patients with lower values of MBG compared with patients without diabetes. Eventually, we compared the indexes summarizing the values of individual arteries, both in terms of TFC and MBG. Figure 3 shows as the TMBS turns out to be higher in non-diabetic subjects, compared with diabetics with high statistical significance level (p-value= 0.02). Examining TTFC this parameter has on higher in diabetics than non-diabetics (Figure 4), this show a trend towards a greater impairment of microcirculation in diabetic subjects.

4. Discussion

At the beginning, we compared myocardial scintigraphy with coronary indexes of Gibson and Yusuf to analyze whether there were similarities: patients with positive scintigraphy (49 patients 69%) had low TMBS than patients with negative scintigraphy (20 patients – 29%) with good statistical significance (p = 0.003). After this, we compared the diseased artery TFC scintigraphy and the average of the TFC in the remaining healthy vessels in a patient, and we saw the correlation between defect at scintigraphy and coronary angiography defect with good statistical significance. From our work we concluded that study of microcirculation by coronary angiography and myocardial scintigraphy shows a good correlation between two methods, allowing us to use as a first test a less invasive and reproducible method as myocardial scintigraphy that appears appropriate to detect early alterations in microcirculation. Therefore, we can use a technique such as myocardial scintigraphy which is low invasive than coronary angiography. Coronary angiography remains the gold standard for the study of the coronary tree, but sometimes this technique can cause complications such as fistulae or coronary dissection, hematoma in the puncture site and a greater exposure of the kidney to contrast especially in elderly patients who have kidney diseases. The goal is to identify the population that could be subjected once myocardial scintigraphy instead of a coronary angiography.

We analyzed a population that, according to literature, have highest risk of developing atherosclerosis: patients with diabetes mellitus type 2. Our series had 72 patients that we compared with a population of 132 patients who had chest pain with uninjured coronary arteries, but not mellitus diabetes. We studied this disease in

patients with diabetes mellitus, chest pain and uninjured coronary arteries to determine whether these patients had a greater involvement of microcirculation, compared with patients without diabetes. We combed the rate of perfusion through the Gibson coronary indexes and we saw that patients with diabetes mellitus and chest pain had a longest TFC of three major coronary arteries, than non-diabetics that indicates slow flow in diabetes coronary microcirculation.

Then we studied coronary microcirculation perfusion through Yusuf index: we found lower MBG on three coronary arteries and TMBS ($p = 0.02$) in diabetic patients with chest pain than non-diabetics, with good statistical significance. This result agrees with work of Sari *et al.* that highlighted a surprising result: the comparison of MBG between diabetic patients with coronary within significant stenosis and diabetic patients with occluded coronary arteries, showed no significant differences [15]. Such even demonstrates how a dysfunction of microcirculation in diabetic patients with uninjured coronary arteries could be a predictor of coronary heart disease. Finally, the index suggested by us, the TTFC, showed a value greater in diabetics than non-diabetics, as shown in graph. n° 4, although not reaching statistical significance, probably because our population has increased in future studies. We think that this new index may provide further information on the overall rate of perfusion of microcirculation and it can help the doctor to take up, with better security, adequate therapy to combat the impairment of microcirculation. The use of coronary angiography and indexes like TFC and Total TFC, introduced by us, may be a useful tool to evaluate coronary microvascular alterations. MBG (so also the Total Myocardial Blush Score introduced by Yusuf) has proved a reliable marker of microvascular dysfunction well correlated with TFC and scintigraphy results. These studies, therefore, can be used as a source to be predictive for future coronary artery disease. Therefore these patients should be followed with a careful follow-up to assess any worsening of coronary artery stenosis, with greater attention to those who have cardiovascular risk factors, especially hypertension, which is often present in patients and that is, along with diabetes, a major cardiovascular risk factor, therefore the need to maintain blood pressure levels lower than in non-diabetics

Figure legend

MD= Mellitus diabetes
 TFC= Timi Frame Count
 TMBS= Total Myocardial Blush Score
 TTFC= Total Timi Frame Count

is a priority, as the guidelines say [16]. There are few prospective studies on the prognosis of these patients, a long-term follow-up of these subjects should deserve more attention. As far as therapeutic strategies, many studies have shown that after prolonged treatment, as in hypertensive diabetic patients, the coronary reserve may increase [17]. Studies show that the clinical improvement of these patients is to be attributed to the role played by therapy on processes that are responsible for myocardial perfusion defects as alterations in repair mechanisms of microcirculation which was found to be damaged at both structural and physiological [18,19]. The disease state of microcirculation in diabetic patients with chest pain and normal coronaries allows us to affirm the absolute necessity to focus on this population (it is necessary to start early an appropriate treatment and it is necessary to follow a long-term follow-up) because this population have a subclinical microcirculation disease without clinical evidence, which could lead to an alteration of the quality of their lives in the future [20].

5. Take home message

From our work we deduced that the study of microcirculation thought coronary angiography and myocardial scintigraphy shows a good correlation between the two methods. This allows us to use as a first step a low-invasive and reproducible exam as myocardial scintigraphy, which appears to be appropriate in detecting early alterations in the microcirculation. In future we hope to increase number of patients.

The analysis of diabetic and non-diabetic patients, already complaining about chest pain, has led to asses that the diabetic population, compared to non-diabetic, has a greater involvement of the microcirculation.

The use of coronary angiography and indexes like TFC and Total TFC, introduced by us, may be a useful tool to evaluate coronary microvascular alterations. MBG (so also the Total Myocardial Blush Score introduced by Yusuf) has proved a reliable marker of microvascular dysfunction well correlated with TFC and scintigraphy results. These studies, therefore, can be used as a source to be predictive for future coronary artery disease.

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