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Impact of Metabolic Syndrome on Coronary Microvascular Dysfunction: A Single Center Experience

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Abstract

Coronary microvascular dysfunction (CMD) represents a widespread condition and a prevalent cause of ischemic heart disease. Total TIMI frame count (TTFC) can be a good indicator of CMD in different populations. The aim of our study was to evaluate the incidence of CMD in different populations such as METS patients compared with diabetic and hypertensive patients. The study was carried out on patients with chest pain and/or positive stress test and angiographically undamaged coronary arteries. Our CMD population was divided into three subgroups; patients with arterial hypertension, patients with type II diabetes mellitus and patients with metabolic syndrome. TIMI Frame Count (TFC) and Myocardial Blush Grade (MBG) are indices used to evaluate the degree of microcirculatory dysfunction, in particular the TIMI frame count and the Myocardial Blush degree.

Patients with Mets had worse coronary perfusion indices with a higher TFC than the hypertensive population (LAD TFC 33.1 ± 5.6 vs 28.4 ± 5.6 p = 0.018), (TFC RCA 27.2 ± 5.2 vs 23.1 ± 5.2 p = 0.014) (TFC CX 27.9 ± 5.4 vs 26.9 ± 5.4 p = 0.03). However, no differences were found in the three coronary vessels in terms of MBG which, however, was reduced in both groups (7.1 ± 0.49 versus 7.1 ± 0.6 p-value = 0.04). According to the TTFC patients with Mets had worse coronary perfusion than patients with type II diabetes (LAD TFC 33.1 ± 5.6 vs 30.6 ± 6.2 p = 0.04), (TFC RCA 27, 2 ± 5.2 vs 25 ± 5.3 p = 0.02), (TFC CX 27.9 ± 5.4 vs 27.2 ± 5.6 p = 0.05) while MBG was lower in patients with diabetes. In our study, we observed that patients with MetS had slower coronary blood flow using TFC imaging technique analysis than diabetic or hypertensive patients. These indices could help in the diagnosis and management of CMD.

Keywords: Coronary microvascular disfunction; Metabolic syndrome; Hypertensive; TIMI frame Count; Myocardial blush grade.

Introduction

Coronary microvascular dysfunction (CMD) represents a widespread condition and a prevalent cause of ischemic heart disease. It is most often associated with a deterioration in quality of life and worse patient outcomes [1]. CMD is characterized by typical anginal symptoms, evidence of myocardial ischemia on noninvasive testing, and normal to minimal coronary artery disease on coronary angiography. Furthermore, some studies argue that patients with microvascular angina and heart failure with preserved ejection fraction (HFpEF) have impaired cardiac contractile mechanics detected

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by speckle-tracking echocardiography and longitudinal myocardial strain [2-3].

A previous study using Total TIMI frame count (TTFC) have shown that coronary microcirculation is more affected in the diabetic population than patients without type II diabetes mellitus [4], stating that the TTFC can be a good indicator, in agreement with the results of other indices [5-6].

We know that CMD is also shared by other pathological conditions, such as hypertension, dyslipidemia, diabetes, and more generally with metabolic syndrome (MetS), although with different pathophysiological mechanisms.

The aim of our study was to evaluate the incidence of CMD in different populations such as METS patients compared with diabetic and hypertensive patients. In our study, we used two angiographic imaging methods to evaluate the degree of microcirculatory dysfunction, in particular the TIMI frame count and the Myocardial Blush degree. Both techniques are quick to use and relatively inexpensive, and allow for a good and reproducible degree of evaluation referred to the function of the coronary microcirculation.

Methods

Study population

The study was carried out on patients who had been referred to Cardiac Intensive Care Unit for Acute Coronary Syndrome, who had presented with acute chest pain within the past 6 hours to the Department of Emergency & Urgency of the University Hospital "Paolo Giaccone" of Palermo (Italy), in the period between November 2020 to January 2022. Inclusion criteria were: presence of chest pain and/or positive stress test and angiographically undamaged coronary arteries. Patients with the following criteria were excluded: creatinine clearance ≤ 30 ml/min, elevated transaminases 3 times the upper limit of normal and/or myocardial infarction within the last 3 weeks. Our CMD population was divided into three subgroups; patients with arterial hypertension, patients with type II diabetes mellitus and patients with metabolic syndrome.

The ESC hypertension guidelines were used to divide patients into the hypertension group. In accordance with the guidelines, diabetes mellitus is diagnosed when, at least twice, blood glucose levels are higher than 126 mg/dl or higher than 200 mg/dl after oral administration (oral load) of 75 grams of glucose.

Metabolic syndrome is increasingly common and is a cluster of conditions that occur together, increasing your risk of heart disease, stroke and type 2 diabetes. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. Age, Ethnicity, women, Obesity, Diabetes, Other diseases increase your chances of having metabolic syndrome. Your risk of metabolic syndrome is higher with nonalcoholic fatty liver disease, polycystic ovary syndrome or sleep apnea.

Metabolic syndrome is defined when three or more of the following risk factors are present [7]:

- presence of a large amount of abdominal adipose tissue (values exceeding 94 cm in abdominal circumference in men and 80 cm in women are considered pathological);
- obesity (BMI>30)
- low levels of HDL cholesterol (less than 40 mg/dl in men and less than 50 mg/dl in women);
- high triglyceride values, above 250 mg/dl;
- high blood pressure (greater than 140 systolic or greater than 90 diastolic or both)
- high blood sugar levels (fasting greater than 100 mg/dl).

Patients with diabetes or hypertension alone belonged to the disease-specific group.

The study was approved by the Research Council of the "Paolo Giaccone" University Hospital. Written informed consent was obtained from all subjects.

Angiography indexes: TIMI frame count and Myocardial Blush Grade

TIMI Frame Count (TFC) and Myocardial Blush Grade (MBG) are indices used to evaluate epicardial coronary flow. All coronary angiograms were filmed at a speed of 30 frames per second. The TIMI Frame Count was tested on all three major coronary vessels: (LAD = left anterior descending artery; CX = circumflex coronary artery; RCA = right coronary artery). To standardize the protocol, we used the method described by Gibson et al. [8-9]. We also considered the Myocardial Blush Grade (MBG) according to the line proposed by Gibson et al. Myocardial blush grades were defined as follows:

- 0, no myocardial blush or contrast density;
- 1, minimal myocardial blush or contrast density;
- 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non infarct-related coronary artery;
- 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non infarctrelated coronary artery.

The persistence of myocardial blush ("staining"), suggested the leakage of the contrast medium into the extravascular space and was evaluated as 0. We evaluated the Total Myocardial Blush Score (TMBS) which was obtained by summing the degree of Myocardial Blush for each coronary area. Instead, the Total TIMI Frame Count (TTFC) was obtained from the sum of the TFCs of the three main coronary vessels [10].

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Statistical Analysis

Continuous variables were expressed with means and standard deviations or medians with interquartile range. Categorical variables were evaluated by percentages on the total population and compared using the $\chi 2$ test and Fisher's exact test. To compare two groups, the Student's T-test or, when necessary, the Mann-Whitney test was used. To compare three groups, ordinary one-way ANOVA was used. A two-tailed P-value <0.05 was considered statistically significant. Bonferroni's correction was used to correct for significance of multiple tests. All statistical analyses were performed using MedCalc, Version 15.10 (©1993–2015 MedCalc Software bvba).

Results

The total study population consisted of 445 patients (mean age 62,1 ± 3,5 years, 54 % men). Our population of 445 patients with CMD was divided into three subgroups: 157 patients with MetS (mean age 61 ± 2,5 years), 160 hypertensive patients (mean age 64 ± 1,7 years) and 128 patients with diabetes (mean age 62 ± 2,4 years). Body mass index was >30 Kg/mq in 28% of the hypertension group, >30 Kg/mq for 57,8% in the MetS group and > 30 Kg/mq for 29% of patients with diabetes. Familiar history for cardiovascular was present in the 46% of hypertension group, 56,2% in the MetS group and 48% in the patients with diabetes. There was no significant difference between patients with MetS compared with the other groups in the percentage of smokers (see Table 1).

In order to evaluate if patients with MetS had a greater alteration of the coronary microcirculation, we compared the results obtained from the angiographic techniques (in particular TIMI Frame Count and Myocardial Blush Grade) in the three subgroups: MetS vs hypertensive, and MetS vs patients with diabetes.

In the first subgroup we analyzed the TFCs of the three vessels in patients with hypertension and comparing them with patients with MetS, we observed that the latter have a worse perfusion condition. In fact the three epicardial coronary vessels have a higher TFC than the hypertensive population (TFC LAD 33,1 ± 5,6 vs 28,4 ± 5,6 p= 0,018), (TFC RCA 27,2 ± 5,2 vs 23,1 ± 5,2 p=0,014) (TFC CX 27,9 ± 5,4 vs 26,9 ± 5,4 p= 0,03). These results indicate a slow flow of coronary microcirculation in patients with MetS (see Table 2).

However, analyzing the MBG in patients with hypertension compared to patients with metabolic syndrome, no differences were found in the three coronary vessels in terms of worsening of the coronary microcirculation (see Table 2). Comparing the indices that summarize the values of the individual arteries for both TFC and MBG, it was seen that TMBS was reduced in both groups (7,1 ± 0,49 vs 7,1 ± 0,6 p-value = 0,04). The TTFC is instead higher in patients with MetS (83,9 ± 5,8 vs 77,8 ± 6,7 p-value = 0,024). Next, we performed the same type of comparison between MetS and subgroup of diabetics, in this comparison we observed that by analyzing the TFCs of the three coronary vessels, patients with MetS have slower coronary blood flow than patients with type II diabetes mellitus (TFC LAD 33,1 ± 5,6

Table 1: Baseline population characteristics.

	Hypertension (160 patients)	MetS (157 patients)	Diabetes Mellitus 2 (128 patients)	P-value
Male	55%	54.70%	52.70%	0,8
Female	45%	45.30%	47.30%	0,8
Age (mean ± SD)	64 ± 1,7	61 ± 2,5	62 ± 2,4	<0,0001
BMI > 30	28%	57.80%	29%	<0,0001
Smoker	33%	32.80%	32%	0,9
Familiar history	46%	56.20%	48%	0,1

Table 2: Timi Frame Count (TFC) and Myocardial Blush Grade (MBG) in patients with Metabolic Syndrome (MetS) and Hypertension

	MetS Group (157 patients)	Hypertensive group (160 patients)	P-Value
TFC LAD	33.1 ± 5.6	28.4 ± 5.6	0.018
TFC RCA	27.2 ± 5.2	23.1 ± 5.2	0.014
TFC CX	27.9 ± 5.4	26.9 ± 5.4	0.03
TTFC	83.9 ± 5.8	77.8 ± 6.7	0.024
MBG LAD	2.4 ± 0.40	2.4 ± 0.47	0.9
MBG RCA	2.3 ± 0.44	2.4 ± 0.45	0.06
MBG CX	2.4 ± 0.42	2.4 ± 0.42	0.05
TMBS	7.1 ± 0.49	7.1 ± 0.6	0.04

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Table 3: Timi Frame Count and Myocardial Blush in patients with Metabolic Syndrome (MetS) and Diabetes Mellitus type 2 (DM 2)

	MetS Group (157 patients)	DM 2 group (160 patients)	P-Value
TFC LAD	33.1 +/- 5.6	30.6 +/- 6.2	0.04
TFC RCA	27.2 +/- 5.2	25 +/- 5.3	0.02
TFC CX	27.9 +/- 5.4	27.2 +/- 5.6	0.05
TTFC	83.9 +/- 5.8	82.7 +/- 8.6	0.02
MBG LAD	2.4 +/- 0.40	2.0 +/- 0.39	0.03
MBG RCA	2.3 +/- 0.44	2.4 +/- 0.41	0.01
MBG CX	2.4 +/- 0.42	2.3 +/- 0.40	0.04
TMBS	7.1 +/- 0.49	6.7 +/- 0.74	0.01

vs 30,6 ± 6,2 p= 0,04), (TFC RCA 27,2 ± 5,2 vs 25 ± 5,3 p= 0,02), (TFC CX 27, 9 ± 5,4 vs 27,2 ± 5,6 p= 0,05). On the other hand, comparing the MBG of the three coronary vessels, the flow is lower in patients with diabetes (see Table 3).

TTFC was higher in patients with MetS (83,9 ± 5,8 vs 82,7 ± 8,6 p = 0,02). While TMBS was lower in patients with diabetes than in MetS patients (7,1 ± 0,49 vs 6,7 ± 0,74 p = 0,01).

Discussion

According to the ATP III definition, MetS is a clinical entity characterized by at least three clinical conditions including: hypertriglyceridemia, hypertension, impaired fasting glucose, low HDL cholesterol levels, and central obesity [11-12]. It is now established that adipose tissue, especially in central obesity, plays a key role in the generation of the chronic pro-inflammatory state [13].

Pathological changes present in adipose tissue induce the secretion of proinflammatory adipokines, including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a) along with plasminogen activator inhibitor-1, which we know to be an important prothrombotic factor (PAI-1) [14-15]. These adipokines are able to promote oxidative stress in endothelial cells resulting in direct dysfunction with reduced NO availability or increasing ET-1 synthesis [16-17]. As a result of endothelial dysfunction, this could cause dysregulation of vascular tone [18-21].

Coronary microcirculation plays an important role in regulating coronary blood flow and cardiac metabolism. Indeed, CMD may involve an inability of the coronary arteries to increase coronary blood flow (vasodilatory abnormality) and/or a reduction in coronary blood flow (coronary microvascular spasm). The latest evidence seems to support a change in microvascular structure and density in subjects with MetS, as in the case of the “Ossabaw swine" with MetS, in which a reduced vascular response to adenosine was found, as well as reduced microvascular density [22 -23].

To date, the mechanism of microcirculatory dysfunction has not been fully clarified, various hypotheses have been proposed and supported by various evidences [24].

Due to the important role played by the CMD and above all due to the close correlation with the increased susceptibility of these patients to subsequently develop an atherosclerotic cardiovascular disease, as well as myocardial hypertrophy and heart failure before any type of angiographic evidence, it is necessary to act in the very early stages of development of the dysfunction, in order to improve the diagnostic-therapeutic approach and better define the prognosis of the aforementioned patients [25].

Furthermore, the considerable importance relating to the socio-economic impact, in terms of health strategies, must be added.

In our study we observed in the patient population with angiographically undamaged coronary arteries, suffering from anginal symptoms, the MetS subgroup had slower coronary blood flow on TFC analysis, compared with hypertensive or type II diabetic patients alone. This result demonstrates that flow reduction can be observed in the early stages of development of CMD and that it is more prevalent in the MetS group than in the diabetic or hypertensive groups.

The low-grade chronic inflammation present in MetS patients secondary to paracrine adipose tissue production most likely plays a pivotal role in this particular process [26].

Limitations

The main limitation of this study is the too small sample size. Many patients were not included because they did not meet the inclusion criteria, mainly due to the lack of important data to conduct our study.

Conclusion

In our study, we observed that MetS patients had slower coronary blood flow using TFC imaging technique analysis than diabetic or hypertensive patients, these differences were found to be statistically significant. A clinical evaluation of these parameters using TFC as in this study, could provide further information on CMD in order to develop the best treatment for these patients and improve their clinical conditions. However, further studies with larger samples are needed to validate the assessment of these parameters in clinical practice.

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Author Contributions:

Project administration, validation: V.S.; Supervision and conceptualization: A.R.G. Methodology, data curation, formal analysis: S.E., S.N. G.V. Writing—original draft preparation: G.M., L.D Writing—review and editing, V.S., C.M., G.V. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest:

The authors declare no conflict of interest.

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