

Effects of Essential Hypertension on coronary Microcirculation: Focus on a Population of Hypertensives Affected by Microvascular Angina

Angelo Quagliana, Salvatore Evola, Oreste Fabio Triolo, Davide Piraino, Giuliana Pace, Giuseppe Riccardo Tona, Vincenzo Sucato, Giuseppe Inga, Rosaria Linda Trovato, Serena Magro, Giuseppe Andolina and Salvatore Novo*

Chair and Postgraduate School of Cardiovascular Diseases, Center for Early Diagnosis of Preclinical and multidistrict Atherosclerosis, Department of Internal Medicine and Cardiovascular Diseases, UOC of Cardiology, A.O.U.P. Paolo Giaccone, University of Palermo, Italy

Introduction

A correlation between essential hypertension and the establishment of myocardial ischemia is nowadays universally accepted [1-3]. Coronary atherosclerosis is deemed to be the most important process through which the capability of coronary district to supply a blood flow consistent with myocardial needs can be impaired, until the onset of an anginal syndrome [4,5]. Hypertension is one of the most widespread cardiovascular risk factors underlying the establishment of an atherosclerotic deterioration of arterial walls; furthermore high blood pressure levels determine a higher risk to incur in a major cardiovascular event, by destabilizing atherosclerotic plaques and boosting platelets tendency to aggregate [6]. Nevertheless, when a cardiac catheterism is performed, in order to unveil the causes of an anginal syndrome according to the positivity of exertional tests and/or myocardial perfusion scintigraphies, showing up the presence of an ischemic territory, the angiographic visualization of unharmed coronary trees is not infrequent, occurring in an overall percentage of cases settled around 30% [7]: in this context, a microvascular angina should be hypothesized. In some of these cases, however, the reason for the ischemia is still to be found within epicardial vessels (coronary spasms, myocardial bridges, endothelial dysfunction), whereas in some others none of these suitable causes can be found. In these patients, ischemia can derive from microvascular district, physiological venue of the 80% of flow resistance. A microvascular dysfunction can be assessed when its regulatory mechanisms are altered, and such abnormality leads to a decrease of coronary flow reserve, without any macroscopic impairment of macroscopic coronary vessels [8]. Nevertheless, its diagnostic definition is usually achieved by a process of exclusion, when an anginal syndrome sustained by exertional tests positivity cannot be ascribed to a narrowing of subepicardial vessels' lumen. Such situation has often been associated to the relief of essential hypertension: a considerable percentage of hypertensives, indeed, copes with the experience of chest pain, without any underlying coronary stenosis. The absence of a macrovascular impairment, in these cases, seems to deny the presence of an hypoperfused territory notwithstanding the results of the nuclear imaging tests, having been coronarographies considered, so far, unable to visualize microvascular district. In this study, we verified whether hypertensives' coronaries, seen by performing an angiographic study, are properly definable as normal, even in presence of an overt exertional angina, or if they should rather be barely defined as "macroscopically unharmed", through the clues of a microvascular alteration.

Materials and Methods

Population

The analyzed population consists of 173 patients (109 male, 64 female) who underwent heart catheterism in our institute, which showed undamaged coronary trees. Among them, 120 are affected by essential hypertension (average age 62 years, 60% male), and 47 showed a left Ventricular Hypertrophy, defined by the ultrasound measurement

of a septum thickness > 11 mm during diastole. 53 Normotensives had blood pressure levels under optimal control (< 140/90 mmHg for three consecutive supine measurements) without any medical therapy. Diabetic patients were ruled out in order to avoid diabete's influence in the establishment of a systemic microvascular dysfunction. Hypertensives and normotensives showed no substantial differences in terms of prevalence of the main cardiovascular risk factors (Table 1). Among women, none was under estrogen replacement treatment, and only a few of them (n=5) declared they had been under such therapy in the past, making a comparison between them and other women statistically irrelevant. 98 patients presented with chest pain, regressed spontaneously or by the administration of s.l. nitrates. Among them, 32 had a positive Treadmill Test, negative in 9 people and dubious in 2; in 66 a myocardial perfusion scintigraphy was performed, which highlighted perfusion defects in 69,7% of cases, being negative in the others.

Angiographic indices and scintigraphic images

Several study groups in the recent past have established protocols in order to esteem microvascular functionality in patients who undergo coronary angiography. Gibson et al. introduced Timi Frame Count as a method to study coronary blood flow according to the time spent by the contrast mean to fulfill epicardial vessels, significantly related to the resistance opposed primarily by the microvascular district. Such

| CVRF | Hypertensives | Normotensives |
|----------------------------|---------------|---------------|
| n | 120 | 53 |
| Age (yrs) | 62,16 | 59,48 |
| Male Gender (%) | 60 | 63 |
| Tabagism (%) | 29 | 35 |
| Familiarity for CVD (%) | 37 | 32 |
| Hypercholesterolemia (%) | 34 | 29 |
| Hypertriglyceridemia (%) | 9 | 11 |
| Obesity (BMI>30 kg/mq) (%) | 19 | 14 |

Table 1: Distribution of Cardiovascular risk factors (CVRF) among hypertensives and normotensives.

*Corresponding author: Prof. Salvatore Novo, Chair and Postgraduate School of Cardiovascular Diseases, Center for Early Diagnosis of Preclinical and multidistrict Atherosclerosis, Department of Internal Medicine and Cardiovascular Diseases, UOC of Cardiology, A.O.U.P. Paolo Giaccone, University of Palermo, Viale delle Alpi No 86-90144, Palermo, Italy, E-mail: salvatore.novo@unipa.it

Received December 16, 2011; Accepted January 31, 2012; Published February 05, 2012

Citation: Quagliana A, Evola S, Triolo OF, Piraino D, Pace G, et al. (2012) Effects of Essential Hypertension on coronary Microcirculation: Focus on a Population of Hypertensives Affected by Microvascular Angina. J Clin Exp Cardiol 3:176. doi:10.4172/2155-9880.1000176

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index consists of the number of frames recorded for dye to reach a standardized distal landmark of the coronary vessel considered (LAD, CX, RCA), with a correction factor obtained for the LAD by dividing its count by 1.7, according to its length [9,10]. Furthermore, Atmaca Y et al. demonstrated how microvascular functionality can be impaired in patients with Syndrome X, through the computation of a new index defined “Myocardial Blush Grade”, which evaluates the passage of the contrast mean through microvessels, visualized as a “blush” of the perfused territory, by counting the number of heart cycles required for it to fade out [11]. Moreover, they calculated a Total Myocardial Blush Score, defined as the sum of the MBG of each coronary territory, to define the overall microvascular functionality and verify its possible alterations in patients with dilatative cardiomyopathy and unharmed coronary trees [12]. Atmaca’s and Gibson’s surveys provided two diagnostic tools, demonstrating their correlation with an impaired microvascular capability to properly control coronary flow resistance. We adopted the same protocols in our hypertensive patients with normal coronary arteriograms, affected by anginal syndromes, in a bid to determine whether or not a microvascular dysfunction could underlie the onset of such symptoms, by calculating cTFC and MBG and by comparing them to the results of myocardial scintigraphies, in order to identify their eventual congruency. In details, we measured TFC for each major coronary branch and in the mean time assigned a MBG = 2 when it took more than three complete cycles for the contrast mean to be washed out of microvascular district, and a score of 3 when it took three cycles or less. As Atmaca et al. assessed, we could get an overview on the whole myocardial microcirculation by adding the MBS we relieved on the three major branches, obtaining the Total Myocardial Blush Score. Moreover, we applied for the first time the same principles to Timi Frame Count, calculating a Total Timi Frame Count as the sum of the three scores, singularly relieved. Angiographic images were separately analyzed by two independent operators, who didn’t know the clinical history of patients.

Statistical analysis

Angiographic data are expressed as means ± 1 SEM (Standard Error of the Mean, calculated by dividing the Standard Deviation by the square root of the sample size). In order to determine the statistical significance of differences between continuous variables we used a two-tailed t-student test. To test statistic correlations between continuous variables we made a linear regression analysis. A p-value < 0,05 was considered significant. A k value for inter-observer variability of 0,75 – for the collection of angiographic data - was achieved.

Results and Discussion

Although over the last decades several clinical studies have tried to focus on microvascular functionality in patients with chest pain and unharmed coronary trees, the role of its dysfunction in the onset of an ischemic syndrome hasn’t been totally understood, yet. The impossibility of visualizing microvessels by angiography is deemed as one of the major causes of such delay, while the common hallmarks of myocardial ischemia, such as stress-induced left ventricular contractile alterations, are often undetectable in these patients. Thus, in clinical practice the diagnosis of microvascular angina is usually assessed by exclusion, rather than by a proper demonstration of microvascular dysfunction [13].

As far as the pathophysiological mechanisms underlying the onset of a microvascular angina are concerned, the possibility for different factors of concurring in the establishment of the dysfunction is nowadays considered the most suitable by a long

way. Indeed, while some studies have described, over the last years, structural alterations of small coronary arteries [14], namely smooth muscle hypertrophy, many other study groups didn’t get to the same conclusions, and focused on a pattern of differently combined functional abnormalities, such as an altered endothelial functionality [15-17], determining an imbalance in the production of vasomotor mediators in favour of vasoconstrictors like endotheline, and a reduced response of microvessels to endothelium-independent vasodilators (e.g. adenosine) [16,17]. However, among the pathogenetic causes which lead to the onset of a coronary microvascular dysfunction, hypertension has often stood among the others as a likely player of a major role [18]. The results of the comparison of cTFC and MBG, as indices of microvascular functionality, between hypertensives and normotensives are shown in Table 2. It’s easy to notice remarkable and significant differences between the two groups, which are ascribable to the effects of hypertension on the establishment of a dysregulation of microvascular resistance and on the reduction of its ability to manage coronary flow reserve according to myocardial needs. Such observation could provide an explanation for the onset of an exertional angina in hypertensives, in spite of the absence of coronary stenosis, being coronary macroscopic indemnity, indeed, unable to clarify the genesis of such symptoms. Thus, it’s quite evident how new methods are required to push coronary angiographies’ potentialities beyond the mere visualization of epicardial vessels’ silhouette, in order to unveil

| | Hypertensives | Normotensives | Two-tailed t- test |
|-----------|---------------|---------------|--------------------|
| cTFC LDA | 27,9 ± 0,21 | 20 ± 0,12 | p<0,001 |
| cTFC CX | 25,9 ± 0,10 | 19,1 ± 0,12 | p<0,001 |
| cTFC RCA | 22,9 ± 0,11 | 17 ± 0,08 | p<0,001 |
| Total TFC | 76,4 ± 0,10 | 54,9 ± 0,14 | p<0,001 |
| MBG LDA | 2,33 ± 0,01 | 2,51 ± 0,01 | P=0,02 |
| MBG CX | 2,29 ± 0,01 | 2,61 ± 0,01 | p<0,001 |
| MBG RCA | 2,19 ± 0,01 | 2,61 ± 0,01 | p<0,001 |
| Total MBG | 6,8 ± 0,02 | 7,75 ± 0,02 | p<0,001 |

Abbreviations: cTFC=corrected Timi Frame Count, MBG= Myocardial Blush Grade, LDA= Left Descending Anterior, RCA= Right Coronary Artery, CX= Circumflex

Table 2: Timi Frame Count and Myocardial Blush Grade in hypertensives and normotensives.

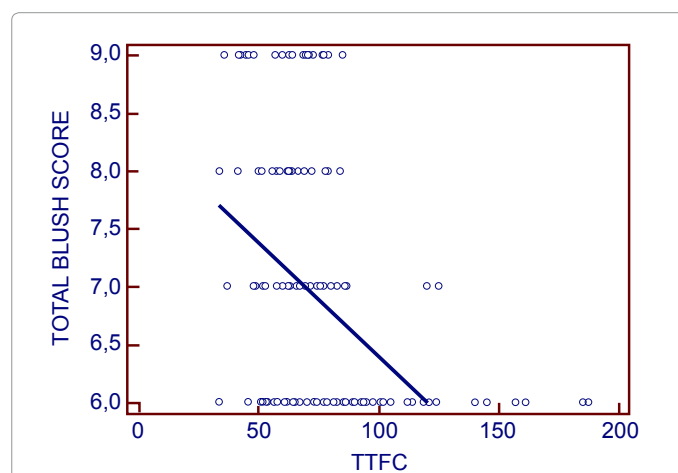
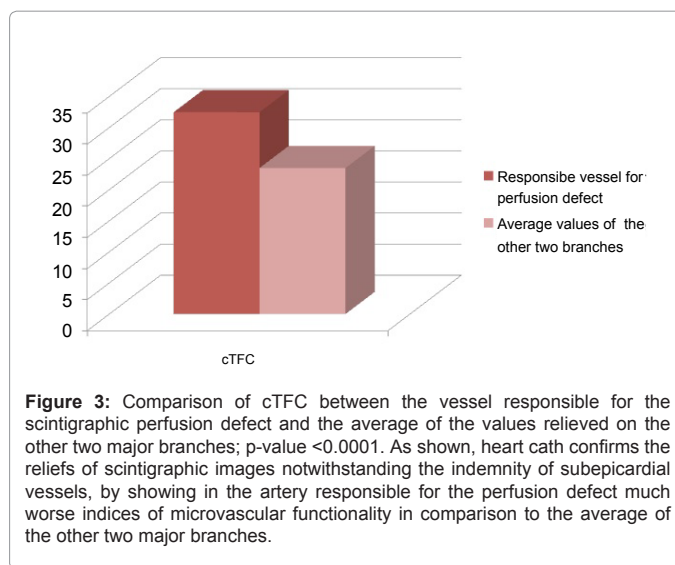
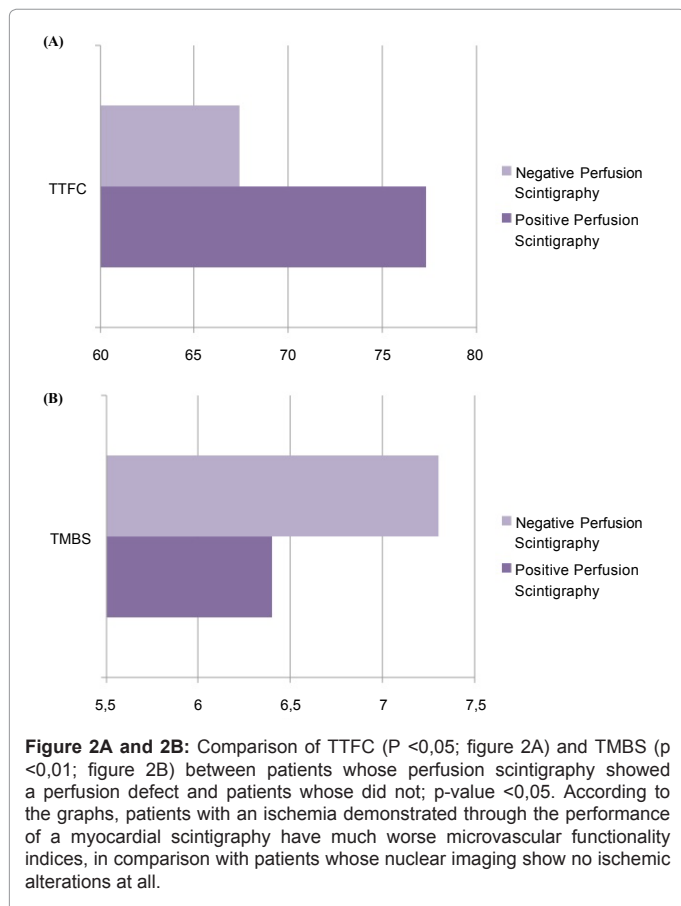


Figure 1: Linear regression analysis: inverse proportionality between TTFC (Total Timi Frame Count) and TMBS (Total Myocardial Blush Score). In hypertensive patients, a worsening of microvascular functionality is demonstrated by the simultaneous alterations of the two parameters, analyzing the modalities through which the contrast mean fulfills coronary vessels during the injection (TTFC) and is washed out from microvessels, afterwards (TMBS).

the presence of a myocardial ischemia even when it is not ascribable to the encroachment of coronary lumen by an atherosclerotic plaque. We compared TTFC to TMBS in a bid to assess their eventual consistency. What we found through a linear regression analysis, shown in Figure 1, is an inverse proportionality by which the increase of the former, highlighting a slow flow of the contrast mean into the epicardial vessels, goes hand in hand with the reduction of TMBS, which underlines its slow removal from the microvascular territory perfused by the same coronaries. Such correspondence allows us to assess the congruity of the two indices and their agreement in relieving the clues of an altered microvascular functionality, although such data do not permit the identification a proper threshold, whose overcoming would determine the onset of an ischemia and the raise of its related symptoms.

A detailed analysis of patients affected by Left Ventricular Hypertrophy didn't highlight any significant difference between hypertrophic and non hypertrophic hearts, in terms of microvascular functionality. Such data do not provide an explanation for the higher incidence of anginal syndromes with normal coronary angiograms in patients with LVH [19,20]. Nevertheless, in hypertrophic hearts the growth of myocardial tissues is not followed by a contemporary expansion of the vascular network, establishing a disproportion between blood supply and perfused territories' mass [21]. Moreover, there are experimental evidences of an attenuated activity of vasodilating and bradycardia-inducing reflexes in hypertrophic patients, normally activated in response to the rise of intracameral pressure, occurring during an ischemic episode [22], suitable explanations for the higher incidence of ischemic syndromes in hypertensives affected by LVH.



As far as myocardial perfusion scintigraphy is concerned, among hypertensives with a positive nuclear imaging, showing a partially reversible hypoperfused area, far worse angiographic indices were relieved (TTFC = $77,27 \pm 0,9$ vs. $67,38 \pm 1,25$, $p < 0,05$, Figure 2A; TMBS = $6,4 \pm 0,03$ vs. $7,3 \pm 0,06$, $p < 0,01$, Figure 2B). Furthermore, in a comparison between the vessel responsible for the perfusion of the scintigraphic defect and an average of the other two vessels, the former's indices were usually significantly worse (namely considering data about cTFC, $32,48 + 0,68$ vs. $23,5 + 0,52$, $p < 0,0001$, Figure 3). Such evidence may be read as a substantial agreement between the two angiographic indices and scintigraphic results, by which patients with a positive nuclear imaging for perfusion defects usually show altered microvascular conditions, despite the indemnity of subepicardial vessels. Much as nuclear sequences are, in such cases, often labelled as "false positives", the opportunity of a microvascular dysfunction, invisible in arteriograms as they are usually meant, should be kept in consideration, in order not to omit the diagnosis of a real ischemia established in spite of the indemnity of macroscopic coronaries [23]. If coronarography is certainly the gold standard technique for the assessment of an atherosclerotic impairment of epicardial vessels, perfusion scintigraphy, by identifying an ischemic area from a metabolic point of view and regardless the causes underlying the onset of the ischemia itself, may fit more the need to define the microvascular genesis of a microvascular anginal syndrome, being coronary silhouette, in such cases, not impaired at all. Nevertheless, being not perfusion scintigraphy routinely included in the diagnostic process of ischemic patients, angiographic sequences can still provide useful informations about coronary blood flow, through the worthwhile computation of the examined indices, able to raise the suspicion of an involvement of microvascular district in the perfusion lacks.

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