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Vasospastic Acute Coronary Syndromes as a Manifestation of Endothelial Dysfunction and the Role of Flow Mediated Dilatation Test

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Abstract

There are many evidences and randomized clinical trials on management and treatment of acute coronary syndromes (ACS's) caused by atherotrombotic mechanisms, in opposition to those ACS's that present no evidence of having been caused by a thrombotic event and/or atherosclerotic disease. We believe that endothelial dysfunction is the pathophysiological key behind most coronary spams, both epicardial and microvascular, after the ruling out evident secondary causes. In this article we describe four different clinical scenarios of vasospastic ACS's, the potential role of flow mediated dilatation test and we generate an algorithm that will help guide clinical management.

Keywords: Coronary spasm; Vasospastic angina; No-atherotrombotic ACS; Endothelial dysfunction; Flow-mediated dilation test

Introduction

Endothelial dysfunction (ED) is a frequent entity in cardiovascular physiopathology and in clinical syndromes in the practice of cardiology. It's the underlying mechanism in diverse vascular pathologies [1,2] and, we believe, it plays a key role in those types of acute coronary syndromes that show no evidence of a thrombotic/atherotrombotic mechanism involved. Recently, it was published that coronary spasm could be documented in nearly 50% of patients with and ACS (without culprit lesion) tested by intra coronary acetylcholine (ACH) [3]. Undoubtedly, the correct identification of the spectrum of this pathology in the context of ACS will allow us to establish a better stratification of the real risk for this singular group of patients and a better/appropriate way to follow up on complementary studies. Besides, it will help underline the initial treatment and discharge plan without the need to indicate double anti-aggregation treatment for long periods of time which pose doubtful clinical benefits. In this way, we think that flow mediated dilatation test is a very useful, non-invasive and reproducible test.

Material and Methods

A series of four clinical cases from one centre, compiled retrospectively. Ultrasounds were made by experts physicians on vascular Doppler with ultrasound systems equipped with vascular software, imaging 2D, color, spectral Doppler, internal EKG monitor and linear array transducer. To assess the FMD, we use the methodology published elsewhere on the Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery [4].

First case

A 42 year-old male, with history of hypertension and type 2 diabetes, a body mass index (BMI) of 29 and 4 month history of erectile dysfunction. He was under outpatient cardiological follow up for presenting one month history of multiple episodes of rest angina. He was studied with an EKG that showed no signs of acute ischemia; an echocardiogram with good ventricular function and without wall motion abnormalities indicative of ischemia; and a carotid ultrasound that showed absence of plaque and normal intima-media thickness. Subsequently, a myocardial perfusion scan (SPECT) was indicated resulting without ischemia (Double product, 26553, 5,1 METS, 750 kg), under treatment with 100 mg aspirin once a day aspirin (OD), 2.5 mg Bisoprolol OD and 30 mg Enalapril OD. 15 days following this evaluation, he was admitted twice for rest chest pain, the EKG's showed no sign of acute ischemia, so he was performed a multislice coronary tomography (MSCT) which showed no evidence of calcium in the coronary arteries. Presuming unstable vasospastic angina, he was performed an endothelial function test with flow-mediated dilation (FMD) measured with braquial Doppler, which showed severe endothelial dysfunction with adequate media response (Figure 1). After implementing treatment with high doses of nitrates, he was discharged and didn't present new episodes within a three-month follow up.

Second case

A 56 year-old female, with history of hypertension, dyslipidemia and no cardiovascular diseases, under treatment with 50 mg atenolol OD and 20 mg simvastatin OD was admitted with an acute myocardial infarction without ST-segment elevation Killip Kimball A. The troponine T value was 0.49 ng/mL and the CPK was normal. The echocardiogram showed no alteration of the parietal motility and a coronary angiogram was performed which did not present significant obstructive lesions. Presuming endothelial dysfunction, an FMD test was performed which showed a 10% endothelial-dependent dilatation and 20% after isosorbide dinitrate, under pharmacological treatment. After three days and presenting no complications, she was discharged under 100 mg ASA OD, 6.25 mg Carvedilol OD, 2.5 mg Ramipril OD and 5 mg nitroglycerin patches. She remained asymptomatic for angina and had a new test performed within one month showing a FMD of 29%.

Third case

69 year old woman with history of hypertension and dyslipemia, former smoker and no cardiovascular events. She had a negative exercise

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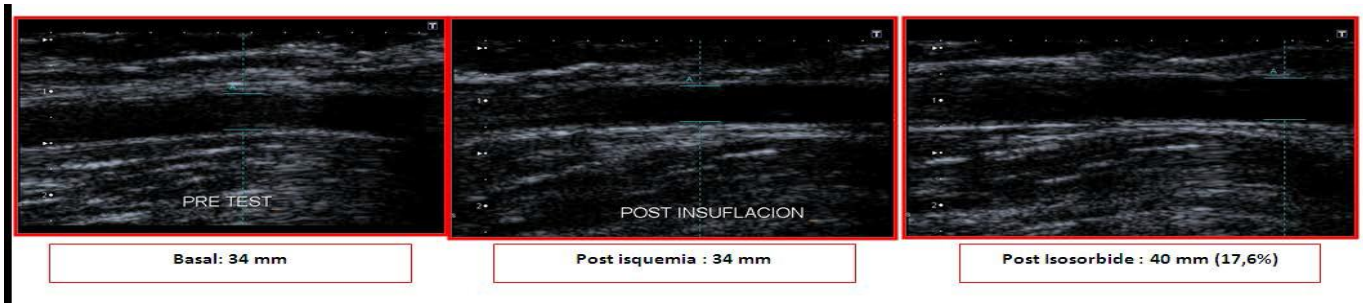

Figure 1: Endothelial function measured with braquial Doppler ultrasound. Left: Basal diameter of the humeral artery 34 mm. Center: Due to lack of endothelial nitric oxide (NO) the braquial artery doesn't change its diameter after the ischemic phase generated by a five-minute compression of the pneumatic cuff. Right: 17,6 % direct vessel dilatation when administering exogenous NO (5 mg ISDN, sublingual), showing adequate media function and severe endothelial failure.

myocardial SPECT in 2009 and a carotid ultrasound presenting small plaques the same year. She was recently admitted for hypertension and epistaxis with an EKG without ischemic signs and positive troponin of 1.34 ng/ml. After 24 hrs she was discharged without further evaluation, and readmitted to our institution within a few days with suspicion of atherotrombotic acute coronary syndrome during out-patient follow up. Although she went asymptomatic, she presented with anterior T wave inversion with elevated LDH, and we required a coronary angiogram that showed normal coronary arteries. The echocardiogram was normal and finally, she was discharged with possible diagnosis of vasospastic ACS. We completed the evaluation twenty days later with an endothelial function test with flow-mediated dilation (measured with braquial Doppler), that evidenced 0% of dilatation, despite the full treatment with Aspirin, Diltiazem, Enalapril and Atorvastatin.

Fourth case

A 52 year-old male with history of hypertension and dislipemia, former smoker, obese (BMI 29); no previous cardiovascular history until January 2009 when he presented with recent functional class III-IV angina. The ECG showed T ± waves in V1-V3 and DI and a VL with troponin value of 0.09 ng/ml. Treatment were prescribed and he was referred to our Institute, where we initially made a presumptive diagnosis of atherothrombotic unstable angina. He was admitted and reported last pain episode within 24 hours of hospital admittance. Cardiac enzymes were negative and the EKG presented no changes. Interpreted as moderate-to-high-risk unstable angina, he was prescribed treatment with Aspirin, Clopidogrel, Heparin, Carvedilol, Enalapril and Atorvastatin, and within 24 hours a coronary angiogram (CA) was performed with the following report: anterior descending artery (ADA) presenting with mild proximal lesion with contrast retention (Figure 2) and no other significant lesions found (dominant right coronary artery). Reinterpreted as unstable angina of vasospastic origin, we added Diltiazem 120 mg/d to the treatment. Next day at 1:30 AM, the patient again presented rest angina, with anterior and inferior-posterior ST-segment elevation, which rapidly receded with 5 mg sublingual IDN. We added 60 mg/d of isosorbide mononitrate to the treatment and he was discharged within 48 hours, asymptomatic. 15 days later he was readmitted presenting precordial pain, the EKG did not show signs of ischemia, but 24 hours later he presented with a new episode of angina with anterior-lateral and inferior-posterior ST-segment elevation (See EKG 1), which receded with IDN. The CA performed did not show changes from the last one and the pharmacological treatment was adjusted. He was studied as an outpatient for collagen diseases, with negative results. His cardiologist re-added Carvedilol to the treatment for angina recurrence and FC II dyspnea; he later required hospital admittance for rest pain within 7 days of last discharge. Carvedilol was suspended and we added a calcium channel blocker, adding Verapamil 240 mg/d to the Diltiazem. After 72 hours asymptomatic, we performed a stimulation/rest perfusion test and a hyperventilation and cold-pressure test. Both were negative for angina and without ST segment changes, although the Figures showed in both cases apical-inferior, mid-inferior and lateral apical ischemia (Double product 20700, 600 Kg) (Figure 2). After this study, on the 5th day of admittance, the patient presented a new episode of chest pain with antero-septal ST segment elevation which receded with IDN and the following morning at the same time, he presented with angina with lateral and inferior ST segment elevation which receded with IDN. We performed a MSCT to rule out dissection suspicion aroused by the Figure of contrast retention in the proximal third of the ADA showed in both previously performed CCGs (Figure 2). Validating our vasospasm diagnosis, we started the patient on nitroglycerin patches, using a scheme of 10 mg every 12 hour, intended to provide adequate night coverage. Clopidogrel was suspended and we continued treatment with Aspirin, 270 mg Diltiazem OD, 240 mg Verapamil OD, 10 mg Enalapril OD and 80 mg Atorvastatin OD.

Continuing his follow-up as an asymptomatic outpatient, we decided to perform laser Doppler to measure endothelial function. We observed a pronounced alteration of the endothelial-dependent phase, without muscular compromise. Given the patient's susceptibility to repeating early symptoms of angina caused either by cold exposure or NTG patch withdrawal, we added 100 mg/d Cilostazol every 12 hours to the treatment.

The endothelial function test was repeated within 7 days showing remarkable improvement of the curve that shows the endothelial function. The patient stated feeling better and within one-year follow-up, wasn't admitted again for unstable angina.

Discussion

In most cases ACS's are atherotrombotic events. Most medical bibliography, clinical trials and clinical practice guidelines focus their effort almost exclusively in studying, describing and discussing this physiopathology. Furthermore, in the last few years, it increased with the arrival of new oral anticoagulants and anti-platelet drugs, posing real therapeutic dilemmas in individual medical practice. All this, has outshone the importance of other physiopathological mechanisms involved in ACS's, such as endothelial dysfunction mediated by a non-atherotrombotic event. The ED hypothesis explains well, as a spectrum of the same disease, the vasomotion pathology of vasospastic syndromes in both the epicardial and microvascular coronary bed. The ACOVA study shows, in patients with stable angina who underwent ACH testing, that 45% of documented spasm were epicardial and 55%

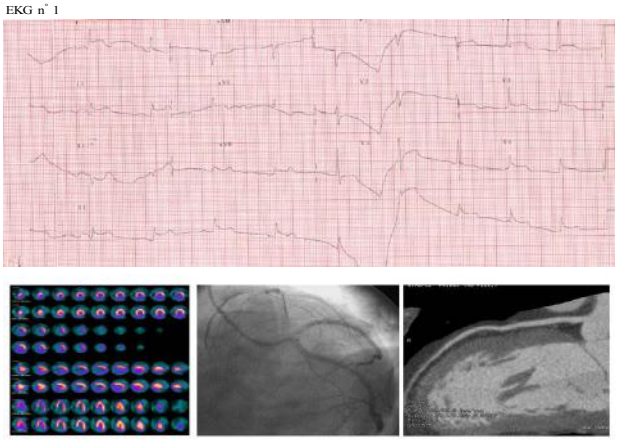

Figure 2: Left: Myocardic perfusion with apical-inferior, mid-inferior and lateral apical ischemia. Center: Spider with contrast retention in proximal third of the ADA and no other significant lesions. Right: MSCT showing normal ADA.

microvascular. Data from this trial suggests that epicardial spasm often began in the microvascular coronary bed [5].

Recently, different methods to measure endothelial function were published and began being included in patient evaluation in particular clinical contexts [6], although still haven't been implemented to full potential [7-10]. We consider humeral arterial Doppler to be the best non-invasive method in daily practice to evaluate endothelial function. To be more accurate, this is an arterial function test [11,12] consisting of two phases. The first one evaluates endothelial response through "flow-mediated dilation". Forearm ischemia is generated by inflating a blood pressure cuff 50 mmHg above systolic arterial pressure for five minutes. When the cuff is released, there is a marked blood flow to the forearm increasing endothelial shear stress, which stimulates nitric oxide sintetase that causes vasodilatation. The amount of vasodilatation is directly proportional to the NO released by the endothelium. The percentage of diameter change and arterial flow between pre and post vasodilatation is measured by 2D ultrasonography - Doppler and sets a parameter of endothelial function. The second phase evaluates muscle layer response with 5 mg ISD (isosorbide dinitrate). This exogenous contribution of NO skips the physiological mechanism of the endothelium and directly tests the muscle layer. In this phase, we again evaluate the percentage of diameter change and arterial flow as previously described (Table 1).

Several factors affect the magnitude of reactive hyperemia and FMD results. A particular issue is baseline arterial diameter which is influenced by sex, age and patients presenting spinal cord injury. Also, technical considerations as cuff position, occlusion [13] duration and addition of ischemic exercise (handgrip) [14]. The magnitude of a given FMD response reflects the functionality and the magnitude of the stimulus; in vessels with different diameters the same flow may represent different shear stress. Pyke et al. performed a FMD test on 8 healthy subjects demonstrating an inverse relationship between baseline arterial diameter and peak share rate and change in diameter; and a direct relationship between peak flow and baseline diameter [15]. They also proposed the use of ratio normalization (e.g., FMD/shear), matter that is currently unresolved and, at this time, no recommendation to use such normalization can be provided [16].

Several studies have shown the correlation between the brachial endothelial function test and the alteration of the coronary endothelial function [17,18]. In the same way, it is well documented that endothelial function does not only serve as a diagnostic marker but as a relevant prognosis tool as well. ED has been associated with an increased risk for new or recurrent cardiovascular events in several clinical settings. Brachial artery FMD was measured in a case-cohort sample in MESA trial (The Multi-Ethnic Study of Atherosclerosis), a population free of clinical cardiovascular disease, finding a significant and inverse association with incident cardiovascular events in multivariable model and independent of mayor cardiovascular risk factors. Compared with the Framingham risk score (FRS) alone, the addition of FMD to the FRS net correctly reclassifies 52% of subjects with no incident CVD event, but net incorrectly reclassifies 23% of subjects with an incident CVD event, and finally overall net correct reclassification of 29% (p 0.001) [19]. Inaba et al. conducted a meta-analysis of observational studies concluding that impairment of brachial FMD is significantly associated with future cardiovascular events [20]. Neunteufl et al. followed 73 patients who underwent cardiac catheterization for chest pain and evaluation of brachial artery FMD by ultrasound over a mean of 5 years. Cardiovascular events occurred more often in patients with impaired FMD compared with patients with preserved FMD [21]. Only a few studies explored the prognostic significance of FMD on ACS [22,23]. Careri et al. studied the prognostic value of FMD in 60 patients admitted with an atherotrombotic NSTE ACS and matched with patients admitted to elective coronary angiography for a history of stable angina. FMD values were significantly lower in patients with ACS on admission and improved at 3 months with no differences. During follow up (32 months media), 23% had an event and was significantly associated with FMD values in the lowest tercile (<4.1%) on multivariable Cox regression analysis, essentially readmission for ACS or angina [24]. Recently, Kitta et al. have demonstrated the negative impact of endothelial dysfunction in the follow-up of coronary patients versus a control group, with values and therapeutic goals according to actual treatment guidelines [25].

ED possesses a spectrum of seriousness and plays a role in various pathologies. In the context of acute coronary syndromes without evidence of an atherotrombotic mechanism involved, endothelial function should be reviewed in detail to understand the physiopathology of the event. Hoffman and collaborators have recently published that most precordial pains admitted to the emergency room and diagnosed as probable ACSs without electrocardiographic ischemic signs or serological markers, presented a multislice CT without significant illness [26]. A question that comes up is: are we correctly evaluating precordial pain in the emergency room? Or is it that we are not taking into account in our routine evaluation the importance of the spectrum of patients with non-atherotrombotic functional coronary pain? It is likely that a significant amount of patients presenting in the emergency room with angina are expressions of different levels of myocardial ischemia caused by endothelial dysfunction [27]. This dysfunction might be pointing out either to the early stages of an atherosclerotic disease or to a simple coronary manifestation of intense physiological stress [28]. The documentation of the physiopathological mechanism through brachial Doppler ultrasound and ruling out of probable thrombotic causes, allows us to adjust the treatment to the actual vascular problem avoiding treatments that are not suited for the mechanism that produced the ACS. We know the stratification

Response / Phases	Endothelial phase	Medium phase
Normal	Positive	Positive
Endothelial dysfunction	Negative	Positive
Muscle vasospasm	Negative	Negative

Table 1: Chart n° 1

of risk for coronary and hemorrhagic events in the context of the physiopathology of an atherothrombotic ACS as well as its course of treatment but, without a doubt, we ignore what the best strategy for ACS caused by non-atherotrombotic endothelial dysfunction is. There are no randomized trials for the pharmacological treatments of this group of patients.

In the first case description it's clear that the patient has an endothelial dysfunction, probably as an early sign of atherosclerosis, which manifested at first as an erectile dysfunction and subsequently as chest pain [29,30]. The studies performed to measure the atherosclerotic burden and the emergency room evaluations to document atherothrombotic were normal. These patients are likely to be dismissed as coronary patients, and referred to frustrating psychiatric counselling.

The second and third case description shows the diagnostic importance and evolutional prognosis of the correct identification of this group of patients and how the FMD test allows evaluation of the treatment response. Accordingly, we think it is very valuable to evaluate the endothelial function with the best pharmacological treatment, and a prognosis measurement of the anti-ischemic therapeutic efficiency can be explored, as it is done with beta-blockers before evocative myocardial ischemia tests. On the other hand, it is not considered safe to withhold pharmacological treatment for evaluation purposes, as it is not done before performing a functional test on atherosclerotic coronary patients. Furthermore, the magnitude of the variation of the vessel-dilation percentage in patients presenting acute or subacute conditions also offers interesting information.

Finally the fourth case description, clearly more complex and severe, shows us transient sub-epicardial injuries in different consecutive coronary territories. This patient presented various symptoms of ED, from angiographic contrast retention in the anterior descending artery to episodes of anterior ST segment elevation and subsequent infero-postero-lateral ST segment elevation with circadian rhythm. Furthermore, we would like to point out that the hyperventilation and cold-pressure tests are technically difficult to perform adequately and provide quite an indirect way of exploring the vascular mechanism. Pautaso et al. observed that almost 10% of the patients who underwent these tests couldn't complete the evaluation due to cold intolerance or vagal reactions [31].

The arterial Doppler ultrasound test has the advantage of being a safe, reproducible, non-invasive diagnostic method, which allows us to stratify patients in the event of non-invasive angiographic tests such as multislice CT. However, the intracoronary acetylcholine test is considered to be the gold standard for diagnosis of vasospasms in patients studied by coronary angiograms [32]. Even though publications have demonstrated its safety, this test cannot be reproduced to evaluate patient follow-up.

It is important to remark that acetylcholine receptor mediated dilatation and FMD do not provide the same information about endothelial function. FMD is more physiologically relevant since shear stress and not acetylcholine is the major stimulus for NO release in vivo and acetylcholine infusion in incompletely blocked by L-NMMA infusion, indicating that it is only partially NO mediated [33].

Therefore, we propose a diagnosis and treatment algorithm that generates future hypothesis for those patients presenting with an ACS without evidence of atherosclerotic atherotrombotic disease, after ruling out obvious secondary mechanisms (Figure 3). Depending on which part of the FMD test fails, endothelial or muscle phase, there are different kinds of drugs available. For endothelial phase treatment, we have nitroglycerin that improves NO availability (activating guanilato-ciclase) and on the other hand, ACE inhibitors [34] (especially Quinapril), ARBs (valsartan, candesartan) and statins acting by mechanisms not fully clarified yet [35].

In patients with altered media function with preserved endothelium (in our experience, not as usual as was described in past medical literature), the first line of treatment should be based on different types of calcium channel blockers that showed clinical efficacy, such as nifepidine, verapamil, diltiazem or benidipine [36,37] Also Sildenafil, with an innovative mechanism, allows the endothelium to "stay in command" of the homeostasis process inhibiting the metabolization of NO second messenger (cGMP) and the new Rho-kinase inhibitor, Fasudil, is also potentially useful [38]. Finally, other drugs act in both phases: Nicorandil and Cilostazol [39]. Nicorandil stimulates the e-NOS, as endothelial cells do, and opens ATP-sensitive potassium channels leading to artery vasodilatation [40]. Cilostazol favors endothelial NO production and it directly stimulates smooth muscle cell relaxation through the cAMP cascade. Recently, the first risk score for vasospastic angina was published showing the harmful role of β-blockers at increasing 2.3 hazard ratios of cardiovascular events. The mechanism proposed consists in the inhibition of the vasodilator effect of β adrenergic receptor, setting free α adrenoceptors, therefore generating coronary constriction [41].

We are convinced that the strength of our work is the connection established between how to explore the pathophysiology of ED and the consequent potential optimization of medical treatment of coronary vasospastic disease. The ability to understand more precisely from the physiological point of view, with a simple and reproducible method such as FMD, which arterial layer generates the vascular spasm allowing the cardiologist in his daily practice to, diagnose, guide and monitor established treatment more accurately and undoubtedly, improves the response, as a minimum the symptoms of our patients.

We were moved by the idea to generate future hypothesis for those patients presenting with an ACS without evidence of atherosclerotic/¬atherotrombotic disease and the common idea in clinical practice that if there is not present obstructive atherosclerostic disease, there is not a relevant problem to get further investigation. The medical literature is full of papers of FMD as a prognostic tool of atherotrombotic ACS. We

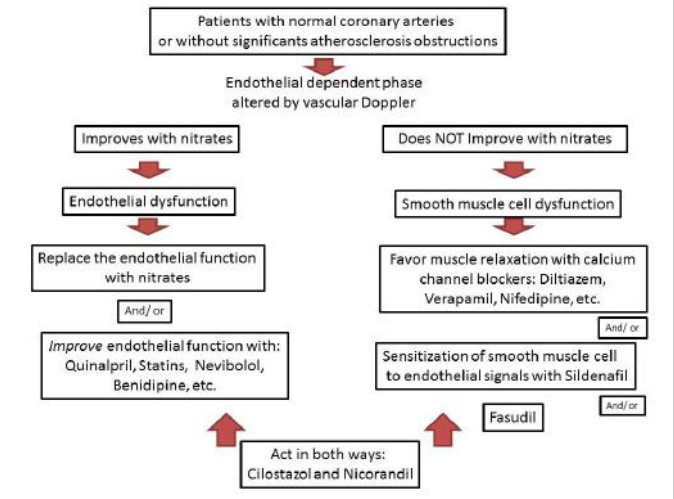

Figure 3: Diagnosis and treatment algorithm for those patients presenting with an ACS without evidence of atherosclerotic¬/atherotrombotic disease.

think FMD central role stays in this kind of ACS, vasospactic coronary syndromes. Larger studies should be performed on this conceptual base in search of prognostic improvements,

Limitations

This is a retrospective analysis of different cases of vasospastic acute coronary syndromes in one Argentine cardiovascular center. The steps of each evaluation were determined by the treating cardiologist.

Conclusion

These case studies illustrate part of the spectrum of patients presenting with coronary vasospasm syndrome and how a simple evaluation, consisting of an endothelial function test, allows us to perform a more accurate diagnosis of the underlying vascular disorder and reach an optimal treatment.

It's still not certain whether this can modify the prognosis of the illness, but we've observed remission of the symptoms during patient admittance and follow-up. Further large-scale, controlled trials should be performed to continue validating this hypothesis.

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