Reduction of coronary flow reserve in a patient with type 2 diabetes mellitus without epicardial coronary stenosis

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Conflicts of interest: None.

Abstract

We present a clinical case that demonstrates the usefulness of transthoracic Doppler-derived coronary flow reserve in distinguishing coronary microvascular dysfunction from epicardial coronary artery stenosis in type 2 diabetes mellitus. Our patient had signs of inducible ischemia on effort electrocardiogram and single photon emission computed tomography, but no angiographic evidence of epicardial coronary artery stenosis. On these grounds, coronary microvascular impairment was identified because the coronary flow reserve was reduced, whereas regional wall motion was completely normal, after administration of high-dose dipyridamole. These abnormalities of the coronary microcirculation were combined with concentric left ventricular hypertrophy, whereas the metabolic status (fasting blood glucose 149 mg/dL, HbA_{1c} 7.7%) was near normal.
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Keywords: Coronary flow reserve, coronary microcirculation, diabetes mellitus, transthoracic doppler echocardiography, single positron emission computed tomography

Introduction

Functional and structural alterations of the coronary microcirculation are possible in patients who have type 2 diabetes mellitus but do not present coronary artery stenosis [1–3]. Although frequently associated with myocardial perfusion defects on single photon emission computed tomography (SPECT) [4], these alterations can remain silent for several years during the time course of the disease, or contribute to the development of myocardial ischemia and angina pectoris when myocardial oxygen demand is increased [5].

The function of the coronary microcirculation may be clinically evaluated by quantitation of the coronary flow reserve (CFR), which is the ratio between hyperemic and resting coronary flow. In the absence of significant stenosis of the epicardial coronary arteries, a reduction in CFR represents a reliable marker of coronary microvascular dysfunction [6]. Today, CFR may also be determined by non invasive transthoracic echocardiography (TTE), which enables the measurement of coronary flow velocities in the mid-distal left anterior descending artery [7,8]. TTE-derived CFR shows excellent agreement with CFR estimated by intracoronary
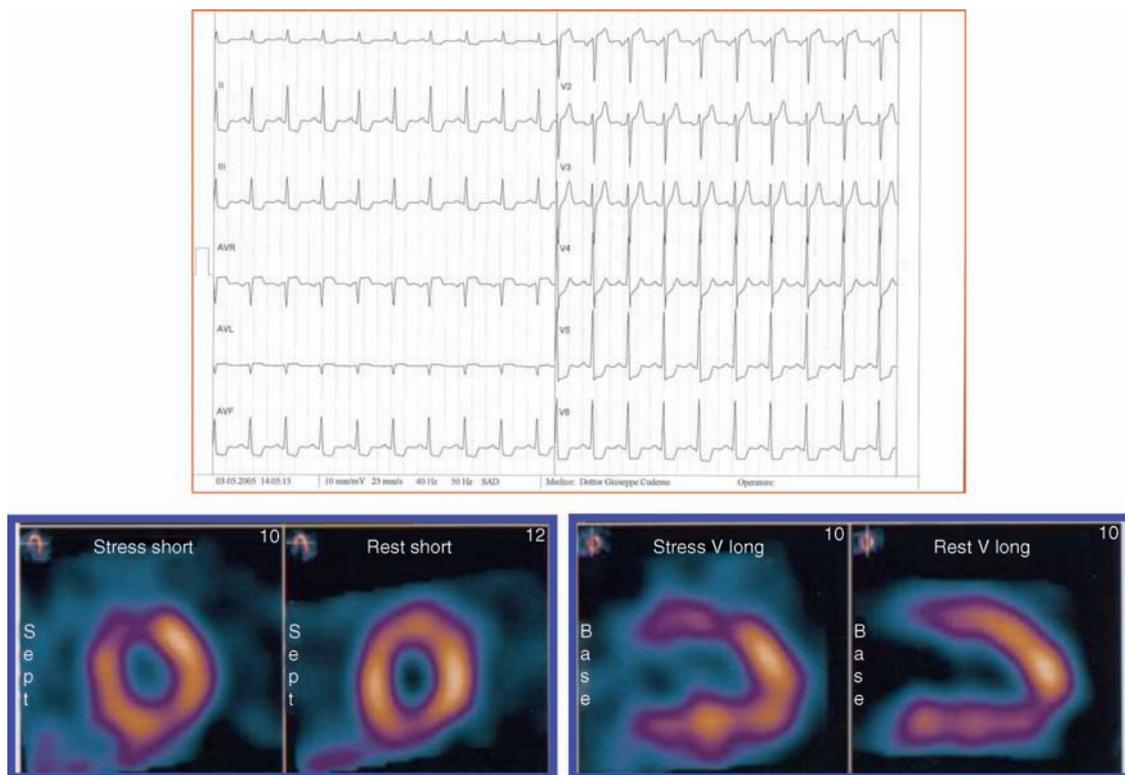
Figure 1. Effort ECG and (upper panel) corresponding myocardial SPECT (lower panel) of the DM2 patient. At maximal exercise, ECG show diffuse ST-segment depression. At the same time SPECT reveals septal myocardial perfusion defect which is reversible at rest.

Doppler flow wire [9], and is highly practicable and reproducible [7].

We present the case of a patient with asymptomatic type 2 diabetes mellitus, normal coronary angiography, and a SPECT-derived myocardial perfusion defect, in whom transthoracic Doppler-derived CFR was of additional value in achieving the correct diagnosis.

Case report

A 48-year-old woman affected by type 2 diabetes mellitus presented at the outpatient clinic of the Department of Clinical and Experimental Medicine of Federico II University Hospital. The diagnosis of diabetes mellitus was based on the American Diabetic Association guidelines [10]. Fasting blood glucose was 149 mg/dL and the glycated hemoglobin value (HbA$_{1c}$) 7.7%. The duration of the patient's type 2 diabetes mellitus was 10 years. No signs of retinopathy had been found by fundus oculi. The patient was referred to the Echocardiography Laboratory of our Department because of inducible myocardial ischemia detected on both effort electrocardiogram (ECG) and effort myocardial SPECT (*Figure 1*), and after the performance of a coronary angiography that revealed evidence of absence of significant epicardial coronary artery stenosis (*Figure 2*). At the time of the

echocardiogram, the woman was receiving antihypertensive therapy with an angiotensin-converting enzyme inhibitor and a β-blocker; her blood pressure was 140/80 mm Hg.

A standard Doppler echocardiographic examination was performed with a Vivid Seven ultrasound machine (GE, Northen, Norway), using a 2.5 MHz phased-array transducer with harmonic capability. Quantitative analysis of the left ventricle and Doppler-derived transmitral inflow, recorded and analyzed as previously reported [11], showed a typical picture of concentric left ventricular hypertrophy (LVH) (left ventricular mass index 48 g/m$^{2.7}$; relative wall thickness 0.44) and grade I diastolic dysfunction (transmitral E/A ratio 0.80; E velocity deceleration time 256 ms). Doppler assessment of the distal left anterior descending artery was performed using a 5 MHz shallow-focus phased-array transducer [12]. Coronary blood flow velocities were recorded at rest and after the administration of high-dose dipyridamole (0.84 mg/kg in a 6 min infusion). Heart rate, blood pressure, and ECG were monitored during the test. In addition, semi-simultaneous imaging of coronary flow and 2-dimensional echocardiography-derived left ventricular wall motion were performed before and after the dipyridamole infusion, according to a validated procedure [13]. Coronary diastolic peak velocities were measured at rest and

Case report
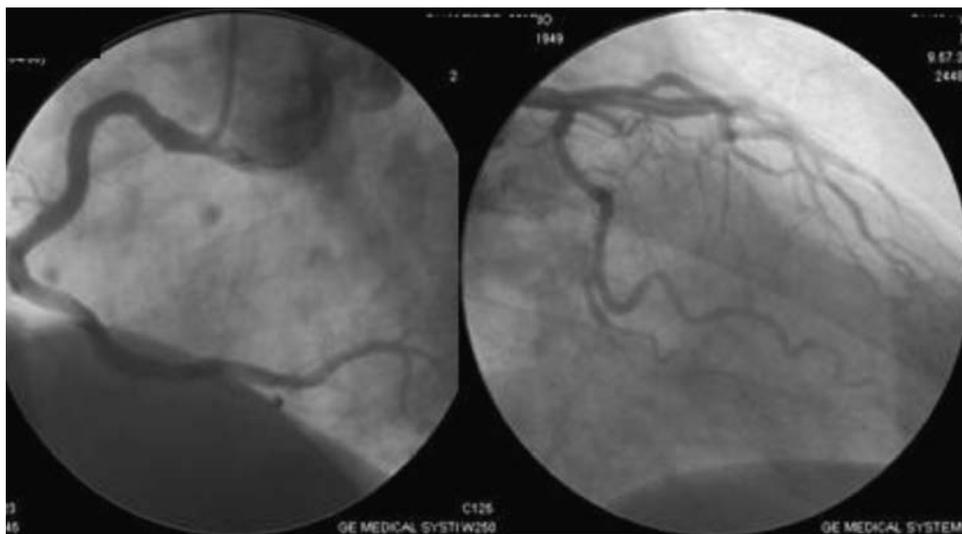*Maurizio Galderisi and Rosa Raia*

Figure 2. Coronary angiography of the DM2 patient showing absence of epicardial coronary artery stenosis.

after dipyridamole vasodilatation, and CFR was defined as the ratio of hyperemic to resting diastolic peak velocities. After the dipyridamole infusion, the patient experienced neither major adverse reactions nor symptoms of angina, and did not show significant changes on the ECG or left ventricular wall motion abnormalities. The CFR was reduced as a result of a blunted hyperemic response to stimulation of the coronary flow peak velocity by highdose dipyridamole; the velocity at rest was normal (*Figure 3*).

Discussion

The case presented here demonstrates the usefulness of transthoracic Doppler-derived CFR in distinguishing coronary microvascular dysfunction from epicardial coronary artery stenosis in type 2 diabetes mellitus. Our patient, in fact, had signs of inducible ischemia on effort ECG and SPECT, but no angiographic evidence of epicardial coronary artery steno-

sis. On these grounds, coronary microvascular impairment was identified because the CFR was reduced, whereas regional wall motion was completely normal, after high-dose dipyridamole.

Diabetes mellitus induces functional and structural abnormalities of the coronary microvascular environment, which can play a part in the development of diabetic cardiomyopathy [14,15]. Coronary microvascular function may be evaluated non invasively by the assessment of TTE-derived CFR. Reduction in CFR corresponds to coronary microvessel damage when stenosis of the epicardial coronary arteries is excluded [6]. An impairment of CFR has been documented in both type 1 and type 2 diabetes mellitus. Several factors such as hyperglycemia, insulin resistance, endothelial dysfunction, and increased cardiac sympathetic activity [16–19] can be involved in this impairment. However, the impact of concomitant cardiovascular risk factors, particularly of increased blood pressure, should also be taken into account [15].
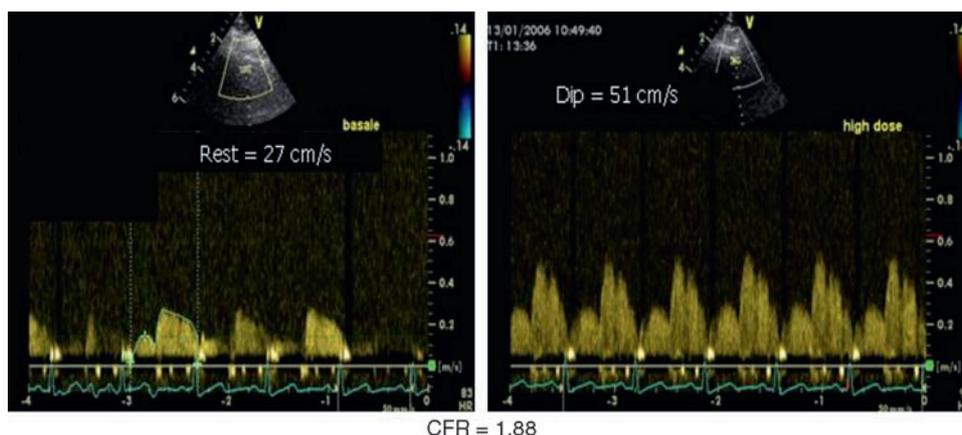

Figure 3. CFR is reduced because of the blunted response of coronary flow velocity to dipyridamole induced hyperemic stimulation.

Left ventricular hypertrophy is an independent hallmark of cardiovascular risk in the general population [20]. It develops frequently in diabetic patients, independent of the effect of concomitant risk factors [21], but can also be induced by the often coexisting increased blood pressure [20]. Worthy of note, the presence of LVH is associated with left ventricular diastolic dysfunction [22]. In agreement with previously reported observations [15,23], the CFR in our patient with type 2 diabetes mellitus was reduced, mainly as a result of a blunted hyperemic response to dipyridamole. The reduction in CFR was combined with structural changes to the left ventricle, mainly concentric LVH and left ventricular diastolic dysfunction, whereas the metabolic picture (fasting blood glucose concentration, HbA_{1c} values) was near normal. This evidence is in agreement with the findings of previous studies indicating that impairment of the coronary microvessels in patients with type 2 diabetes mellitus and hypertension could be, at least in part, mediated by changes in left ventricular structure associated with LVH. Extravascular compressive forces and concomitant hypertrophy of the coronary microvascular walls might be mechanisms underlying the abnormalities of CFR observed in the diabetic and hypertensive heart [15].

Conclusion

The clinical case presented highlights the role of transthoracic Doppler-derived CFR in the diagnosis of isolated coronary microvascular dysfunction in type 2 diabetes mellitus, and illustrates that abnormalities of the coronary microvessels are associated more with myocardial structural changes than with metabolic status. ■

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