

# Managing chest pain in a diabetic patient

Maria Chiara Scali, MD, PhD

Cardiovascular Medicine Division, United Hospitals of Valdichiana, Montepulciano, 53045 Siena, Italy.

Correspondence: Maria Chiara Scali, MD, PhD, Cardiothoracic Department, Pisa University, Via Paradisa 2, 56100 Pisa, Italy  
E-mail: chiarascal1@gmail.com

## Abstract

Coronary artery disease is the leading cause of mortality in patients with diabetes. We present the case of a 61-year-old diabetic male patient with a previous history of percutaneous coronary intervention on the left circumflex coronary artery and who came to our outpatient clinic because of persistence of chest pain and limited exercise tolerance. The patient underwent stress echocardiography (stress echo), which was negative for inducible regional wall motion abnormalities but positive for left anterior descending coronary flow velocity reserve (1.7; normal values are above 2.0). The patient was intolerant to  $\beta$ -blockers and was started on ivabradine 5 mg twice daily plus trimetazidine 20 mg three times a day. After 1 month of therapy, the patient was reevaluated, and we observed a marked improvement in symptoms and a coronary flow velocity reserve of 2.1. With versatile use of stress echo, noninvasive risk stratification in diabetic patients can be obtained efficiently, at low cost, and without cumulative damage from radiation exposure, allowing a comprehensive assessment of wall motion, symptoms, electrocardiogram changes, and coronary flow velocity reserve. The latter was markedly improved by the combination of ivabradine plus trimetazidine. ■ *Heart Metab.* 2017;73:29-32

**Keywords:** B-lines; risk; stress-echo

The risk of myocardial infarction and cardiac death is two- to fourfold higher in diabetic than in nondiabetic patients; the latest European Society of Cardiology guidelines recommend the use of noninvasive testing for risk stratification of patients with known or suspected coronary artery disease, which should be performed according to clinical needs and clinical judgment and not meant as a general recommendation to be followed in all patients.<sup>1,2</sup> Stress echocardiography (stress echo) is certainly an attractive option owing to its widespread availability, low cost, and radiation-free nature, but the problem remains that the negative predictive value

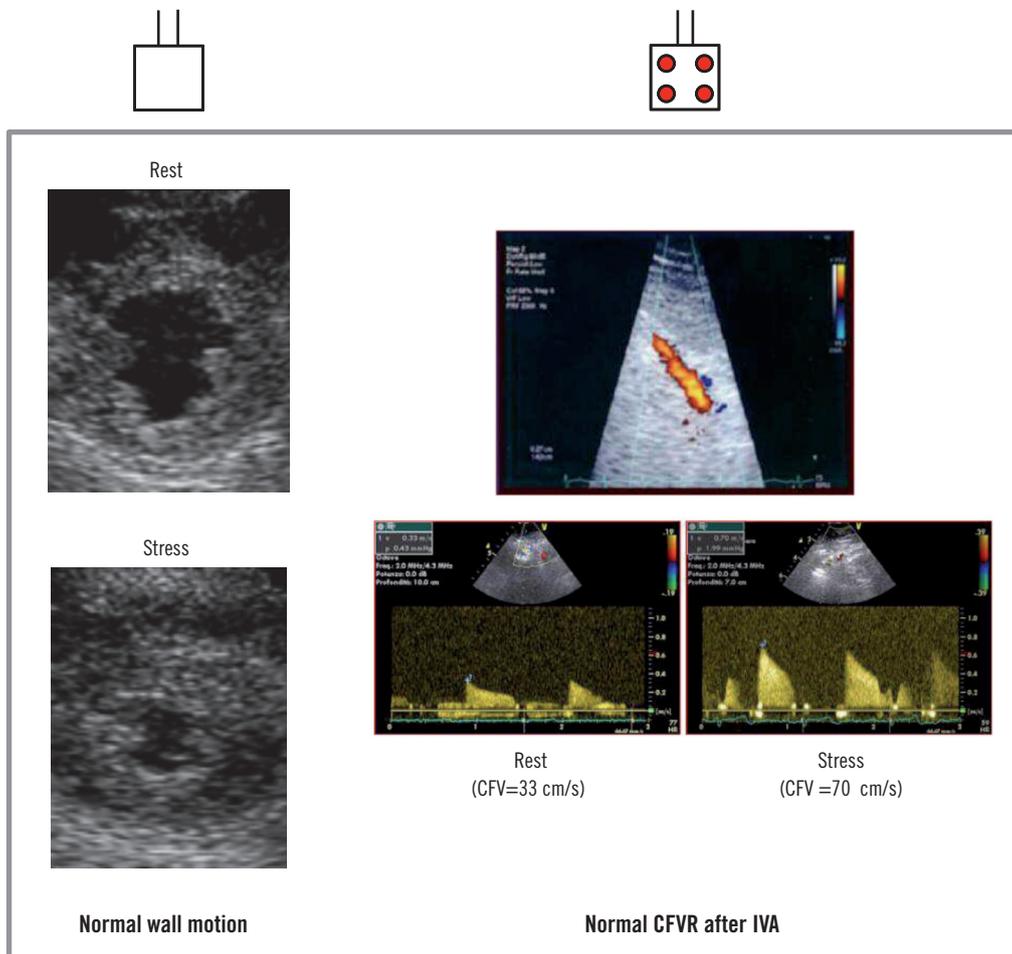
of the test is lower in diabetics than in nondiabetic patients.<sup>3</sup> Recent new evidence has emerged that a better negative predictive value can be obtained if we augment regional wall motion analysis with new parameters, such as assessment of left ventricular contractile reserve,<sup>4</sup> left anterior descending coronary flow reserve,<sup>5-7</sup> and/or B-lines during lung ultrasound.<sup>8</sup> In particular, coronary flow velocity has long-term prognostic value in diabetics, and a reduction in coronary flow velocity is associated with higher long-term mortality even in patients with normal regional wall motion.<sup>9</sup> The case presented here is of a diabetic patient with negative stress echo by wall

motion criteria but reduced coronary flow reserve that improved after initiation of therapy with ivabradine and trimetazidine.

### Case report

We present the case of a 61-year-old diabetic male patient with persistent chest pain and dyspnea after a percutaneous coronary revascularization (3 years earlier) with drug-eluting stent implantation on the proximal left circumflex coronary artery. The patient was referred to the outpatient clinic because of the persistence of symptoms. While under standard anti-ischemic therapy, the patient underwent stress echo (with dipyridamole) testing; the results were negative for wall motion abnormalities, but the chest pain was

reproduced and was associated with a 2-mm ST-segment depression on the anterior leads. After that, the coronary flow velocity reserve on the mid-distal left anterior descending coronary artery (calculated as stress/rest ratio of peak diastolic velocity) was assessed, yielding a value of 1.7 (normal values >2.0). Pharmacologic treatment was modified with the introduction of ivabradine (5 mg twice daily) plus trimetazidine (20 mg thrice daily), and the patient was reevaluated after 1 month. Quality of life was substantially ameliorated with the disappearance of chest pain. The stress echo test was repeated, confirming the absence of regional wall motion abnormalities, now without symptom or ST-segment changes and showing an increase in the coronary flow velocity reserve from 1.7 to 2.1 (Figure 1).



**Fig. 1** The conceptual approach to dual imaging with vasodilator stress echo (with dipyridamole). The left upper panel shows the schematic representation of a normal epicardial coronary artery perfusing a normally contracting myocardium (square box). In the left lower panel, the standard two-dimensional (2D) stress echo (the end-systolic frames of the 2D short axis view) shows normal wall motion, consistent with the absence of critical coronary stenosis after revascularization. In the right upper panel, the damaged microcirculation (red circles) is schematically shown. The patient, on ivabradine, had a coronary flow velocity reserve within normal limits (2.1) during high-dose dipyridamole testing (right lower panels). The right middle panel shows the color Doppler image of coronary flow in the mid-distal left anterior descending artery; the left, the pulsed Doppler tracing at rest; the right, after dipyridamole. The ratio of stress/rest peak diastolic flow velocity is the index of coronary flow velocity reserve. It was 1.7 in a test performed 1 month before, off ivabradine.

**Abbreviation:** CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; cm/s, centimeters per second; IVA, ivabradine.

## Discussion

Diabetic patients often pose challenging diagnostic problems. In ischemic diabetic patients, chest pain may be absent or atypical when present. Provocative tests may be required to associate symptoms with objective signs of myocardial ischemia, such as regional wall dysfunction and/or ischemic electrocardiogram changes.

The case we present here was difficult to assess by a standard approach because of the atypicality of symptoms and the absence of transient akynesis during stress. So, we resolved to take advantage of the most recent developments in stress echo imaging, where the classical imaging based on regional wall motion analysis has been augmented by assessment of coronary flow velocity reserve. Regional wall motion abnormalities are influenced by the epicardial coronary artery stenosis, whereas the coronary artery flow velocity reserve is affected by the coronary microcirculation.

Coronary microvascular dysfunction may be effectively targeted by cardiometabolic and hemodynamic agents. Ivabradine has been shown to increase the coronary flow reserve in angina patients—with and without diabetes—in the poststenotic territory, as well as in areas remote from the epicardial coronary stenosis.<sup>10</sup> Reported increases in flow velocity reserve vary from 2.6 to 3.5 (+30%), probably through a combination of effects, including the increase in diastolic perfusion time, improved isovolumic ventricular relaxation, a reduction in end-diastolic pressure responsible for extravascular resistances, and improved flow through collaterals.<sup>11</sup> This approach is not only pathophysiologically appealing, but also expands the potential of risk stratification because in ischemic patients (and especially in diabetics), many cardiac events can occur independently of the coronary plaque targeted by the stress-induced approach and are linked to microcirculatory disease.

We usually focus solely on coronary stenosis, but the pathophysiological inconsistencies and clinical collateral damage driven by this simplistic approach are well-known.<sup>12</sup> Dual-imaging stress echo allows many different variables to be brought into focus.<sup>9</sup> The cardiovascular hard-event rate of a diabetic patient with negative stress echo by conventional wall motion criteria is 2%, but with the addition of a normal

response of coronary flow reserve, the hard-event annual rate drops off to less than 0.5%. It remains to be clarified with prospective randomized studies whether an improvement in coronary flow velocity reserve achieved with drugs such as ivabradine—and/or trimetazidine, also effective through a different cardiometabolic effect in patients still symptomatic on standard therapy—modifies the long-term prognosis in diabetic patients. In particular, the role of trimetazidine in diabetics has a strong pathophysiological rationale, as diabetes also affects the microcirculation, which cannot be treated by revascularization and is the preferential target of trimetazidine treatment. Such treatment may compensate for the deteriorated glucose uptake and utilization in myocardial cells caused by altered insulin levels.<sup>13</sup> ■

## REFERENCES

1. Ryden L, Standl E, Bartnik M, et al; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. *Eur Heart J*. 2013;28:88-136.
2. Bax JJ, Young LH, Frye RL, et al. Screening for coronary artery disease in patients with diabetes. *Diabetes Care*. 2007;30:2729-2736.
3. Cortigiani L, Bigi R, Sicari R, et al. Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease. *J Am Coll Cardiol*. 2006;47:605-610.
4. Cortigiani L, Bombardini T, Corbisiero A, et al. The additive prognostic value of end-systolic pressure-volume relationship in diabetic patients with negative dobutamine stress echocardiography by wall motion criteria. *Heart*. 2009;95:1429-1435.
5. Cortigiani L, Rigo F, Gherardi S, et al. Additional prognostic value of coronary flow reserve in diabetic and nondiabetic patients with negative dipyridamole stress echocardiography by wall motion criteria. *J Am Coll Cardiol*. 2007;50:1354-1361.
6. Lowenstein JA, Caniggia C, Rousse G, et al. Coronary flow reserve during pharmacologic stress echocardiography with normal contractility adds important prognostic value in diabetic and nondiabetic patients. *J Am Soc Echocardiogr*. 2014;27:1113-1119.
7. Kawata T, Damon M, Hasegawa R, et al. Prognostic value of coronary flow reserve assessed by transthoracic Doppler echocardiography on long-term outcome in asymptomatic patients with type 2 diabetes without overt coronary artery disease. *Cardiovasc Diabetol*. 2013;12:121.
8. Scali MC, Cortigiani L, Simionuc A, Gregori D, Marzilli M, Picano E. Exercise-induced B-lines identify worse functional and prognostic stage in heart failure patients with depressed left ventricular function. *Eur J Heart Fail*. 2017 Feb 15. Epub ahead of print. doi:10.1002/ehf.776.
9. Cortigiani L, Gherardi S, Faggioni M, et al. Dual-imaging stress echocardiography for prognostic assessment of high-risk asymptomatic patients with diabetes mellitus. *J Am Soc Echocardiogr*. 2017;30:149-158.
10. Skaliadis EI, Hamilos MI, Chlouverakis G, Zacharis EA, Vardas PE. Ivabradine improves coronary flow reserve in patients with stable coronary artery disease. *Atherosclerosis*.

- 2011;215(1):160-165.
11. Tagliamonte E, Cirillo T, Rigo F, et al. Ivabradine and bisoprolol on Doppler-derived coronary flow velocity reserve in patients with stable coronary artery disease: beyond the heart rate. *Adv Ther.* 2015;32(8):757-767.
  12. Marzilli M, Merz CN, Boden WE, et al. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! *J Am Coll Cardiol.* 2012;60:951-956.
  13. Dezsi CA. Trimetazidine in practice: review of the clinical and experimental evidences. *Am J Ther.* 2016;23:e871-e879.