European Journal of Echocardiography (2011) **12**, E34
doi:10.1093/ejechocard/jer061

CASE REPORT

Transmural myocardial ischaemia complicating recovery after dobutamine-atropine stress echocardiography in patients with non-significant coronary artery disease: insights from invasive assessment of coronary physiology

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Received 3 February 2011; accepted after revision 20 April 2011; online publish-ahead-of-print 22 May 2011

In the proposed selection of cases, traditional imaging is integrated with contemporary diagnostic tools available in the cath-lab to navigate the potential mechanisms underlying a very rare complication occurring in the recovery phase of dobutamine-atropine stress echocardiography. The data, collected in a time frame of nearly 15 years, provide interesting elements to possibly evolve from speculative considerations to plausible confirmation of the candidate pathophysiological mechanism mediating the occurrence of transmural myocardial ischaemia after beta-blockers administration.

Keywords Myocardial ischaemia • Coronary spasm • Fractional flow reserve • Stress echocardiography

Case 1

A 59-year-old hypercholesterolaemic man was admitted to our department in November 1996 because of new onset angina at rest. Both resting ECG (*Figure 1A*) and echocardiogram were unremarkable. He completed a maximal exercise ECG testing with no conclusive results (mildly symptomatic with no significant ECG changes). The patient was therefore scheduled for a dobutamine-atropine stress echocardiography (DASE), dobutamine infusion with 3 min dose increments starting from 5 μg/kg and increasing to 10, 20, 30, 40 μg/kg followed by atropine 0.5 mg to reach 85% of target heart rate (HR), with no ECG or echocardiographic evidence of inducible myocardial ischaemia. Ten minutes after administration of metoprolol, 3 mg intravenously in repeated portions of 0.5 mg, the patient experienced chest pain and concomitant ST-segment elevation in the antero-lateral leads and wall motion abnormalities of the antero-septal segments (*Figure 1B*). Chest pain, ECG, and echocardiographic alterations completely reversed within 5 min after sub-lingual nitroglycerine administration (*Figure 1C*). Serial cardiac enzymes assessment was negative and coronary angiography was performed the day after. The first dye injection in the left main induced diffused spasm of the left anterior descending (LAD) and of the left circumflex (LCx) coronary artery (*Figure 1D*) with prompt regression after intracoronary nitroglycerin (*Figure 1E*). No atherosclerotic burden was present in the LCx and in the right coronary artery (RCA), whereas a non-significant, <50%, stenosis was detected in the proximal segment of the LAD (*Figure 1E*). The patient's subsequent course was uneventful, and he was discharged home on, among other medications, diltiazem to prevent recurrence of coronary spasm.

Case 2

A 54-year-old man with no cardiovascular risk factors was referred to our echo-lab in January 2008 because of recent onset exertional

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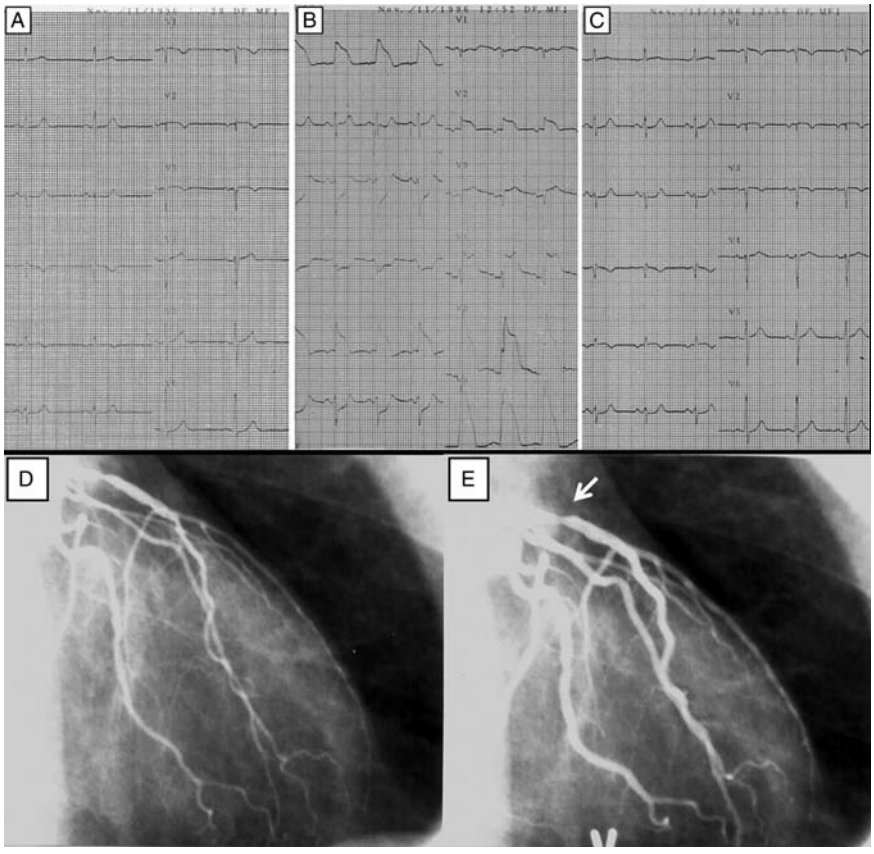

Figure 1 Twelve-lead ECG recorded at baseline (*A*), in the recovery phase of stress-echocardiography following beta-blocker administration showing ST-elevation in the antero-lateral leads (*B*), and following sub-lingual nitroglycerin with regression of ST elevation(*C*). Coronary angiograms showing diffuse spasm of the left anterior descending (LAD) and of left circumflex arteries (*D*) with prompt regression after intracoronary nitroglycerin (NTG) with evidence of a non-significant lesion in the proximal LAD (arrow) (*E*).

atypical chest pain after a non-conclusive exercise ECG testing. He had no history of previous myocardial infarction and baseline echocardiography showed no wall motion abnormalities at rest. He underwent DASE (dobutamine infusion with 3 min dose increments starting from 5 μg/kg and increasing to 10, 20, 30, 40 μg/kg followed by atropine 1.00 mg to reach 85% of target HR), with no evidence of inducible ischaemic ECG changes nor of alterations in wall motion. Three minutes following administration of propranolol, 5 mg intravenously in repeated portions of 1 mg, he abruptly experienced severe chest pain with concomitant ST-segment elevation in leads DII, DIII, and aVF and akinesia of the left ventricular (LV) infero-lateral segments. He was therefore referred for emergent coronary angiography that showed a non-significant coronary artery disease (CAD) with a $<$60% stenosis in the mid-portion of the RCA with no evidence of vessel thrombosis, myocardial bridging, or spasm (no changes observed after intracoronary nitroglycerin). We decided to perform a functional evaluation of the stenosis by using a pressure wire (PressureWire Radi Medical Systems), retrieving a fractional flow reserve (FFR) value of 0.90 after intracoronary adenosine, consistent with a functionally non-significant lesion. Accordingly, we did not proceed to any interventional treatment and a post-discharge dypiridamole single-photon emission computed tomography (SPECT) provided a further confirmation of the absence of inducible ischaemia in the RCA territory. His subsequent clinical course on long-term diltiazem has been uneventful up to the latest available follow-up in April 2010.

Case 3

A 65-year-old woman with high blood pressure, diabetes mellitus, and a history of chronic ischaemic heart disease was admitted to out department in March 2010 because of new onset angina at rest. A recent dypiridamole SPECT, performed prior to symptoms initiation, had shown no evidence of reduced coronary reserve with a mildly reduced global systolic performance (LV ejection fraction, 46%). She underwent DASE (dobutamine infusion with 3 min dose increments starting from 5 μg/kg and increasing to 10, 20, 30, 40 μg/kg followed by atropine 0.75 mg to reach 85% of target HR), with no evidence of inducible ischaemic ECG changes from baseline (*Figure 2A*) nor of alterations in wall motion. Five minutes following administration of propranolol, 5 mg intravenously in repeated portions of 1 mg, she began complaining of severe chest pain with associated diaphoresis and

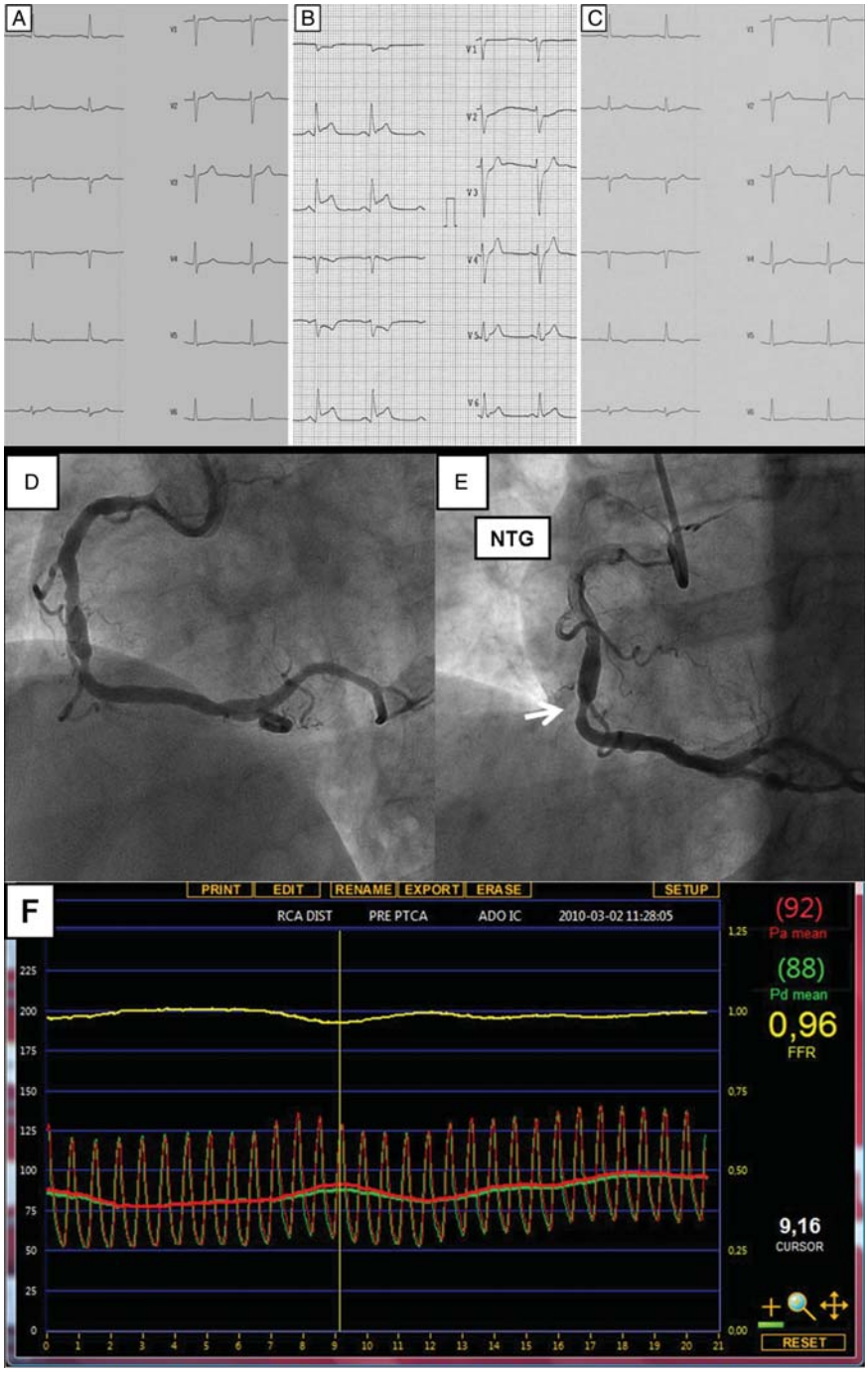

Figure 2 Twelve-lead ECG recorded at baseline (*A*), in the recovery phase of stress-echocardiography following beta-blocker administration showing ST-elevation in the inferior leads (*B*), and in the cath-lab with regression of ST-elevation (*C*). Coronary angiograms showing a 50% stenosis in the mid-portion of the RCA (*D*) with no changes after intracoronary nitroglycerin (*E*); assessment of fractional flow reserve through pressure wire as displayed on the analysing system with a measured value of 0.96 (*F*).

concomitant ST-segment elevation in leads DII, DIII, and aVF (*Figure 2B*) and akinesia of the LV infero-lateral segments. She was given sub-lingual nitroglycerin and immediately transferred to the cath-lab. Coronary angiography showed diffuse non-significant stenoses (~25%) in the LAD and CFx systems, and a 50% stenosis in the mid-portion of the RCA (*Figure 2D*) with no evidence of coronary thrombosis, myocardial bridging, or spasm (no changes observed after intracoronary nitroglycerin—*Figure 2E*). Notably, at the time of the first available coronary angiogram the ST-segment elevation had resolved (*Figure 2C*) and the chest pain nearly completely regressed. We decided to perform a functional evaluation of the stenosis by using a pressure wire,

retrieving a FFR value of 0.96 after intracoronary adenosine (60 μg bolus), consistent with a functionally non-significant lesion (*Figure 2F*). This patient, like the previous one, was discharged home being prescribed long-term calcium channel blockade with diltiazem.

Discussion

Transmural myocardial ischaemia with development of ST-segment elevation has been described as an extremely rare complication potentially occurring during the recovery phase of DASE[1–4]. Among nearly 10 000 DASE performed at our centre in the study time frame, this complication occurred in 0.1% of cases, in line with that reported by Lamisse *et al.*[2] Coronary findings in patients experiencing such complication had ranged from normal coronary arteries to severe coronary stenoses. Although in many of the reported cases, no critical atherosclerotic lesions were documented in the ischaemia-related vessel[1–4] in others the presence of extensive significant disease was documented in the whole coronary tree.[5]

During incremental dosing, dobutamine may likely provoke transmural myocardial ischaemia via, at least, two different mechanisms: (i) coronary spasm in predisposed patients with coronary spastic angina in the absence of significant CAD[6]; (ii) increased myocardial oxygen demand and/or myocardial blood flow maldistribution in the presence of severe CAD[7]. However, the mechanisms underlying transmural myocardial ischaemia in the recovery phase of DASE are unclear. Coronary vasospasm occurring in mildly diseased vessels has been proposed, on a speculative basis, as a possible determinant likely being triggered by a paradoxical exacerbation of α1-mediated coronary vasoconstriction elicited by beta-blocker administration.[8]

We believe that the early finding of a prone-to-spasm coronary vasculature in the first patient along with the more contemporary observations of a functional non-significance of the stenoses in the ischaemia-related vessels as assessed with FFR in the latter patient, provide the first, although indirect, evidence confirmative of coronary spasm as the most plausible mechanism accounting for transmural ischaemia developing after beta-blockers administration during DASE in patients with mild CAD.

The study of the coronary physiology as currently feasible in the cath-lab through different means including FFR may help unravelling the mechanisms underlying long-known yet not fully elucidated pathophysiological phenomena.

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