Scientific letter

Diagnostic value of coronary flow reserve determined by echo dipyridamole stress in homozygous familial hypercholesterolemia

Valor diagnóstico de la reserva de flujo coronario mediante eco-dipiridamol en la hipercolesterolemia homocigota familiar

To the Editor,

Hypercholesterolemia is a major risk factor for cardiovascular disease. Homozygous familial hypercholesterolemia (HoFH; OMIM #143890) is a rare disease caused by mutations in the low-density lipoprotein-cholesterol receptor gene. It is characterized by extremely elevated plasma low-density lipoprotein (LDL), tendon and skin xanthomas, and progressive atherosclerosis and results in death before 30 years of age if not treated.[1] HoFH patients show varying cardiovascular disease risk and undoubtedly represent a particular cohort of cardiovascular disease patients. Accordingly, the standard algorithm for assessing cardiovascular risk, atherosclerotic burden, and inducible cardiac ischemia may not be suitable.[1]

Indeed, it is also clear that myocardial perfusion scintigraphy should be prescribed with caution to limit the lifetime radiation exposure. On the other hand, cardiac magnetic resonance stress testing is not widely available or well-standardized.

Based on these considerations and on previous work,[2] we decided to perform the myocardial ischemia follow-up of 4 HoFH siblings by using dual-imaging stress echocardiography to measure the wall motion and Doppler-derived coronary flow reserve (CFR) of the mid-distal left anterior descending artery (LAD) during dipyridamole stress echocardiography (DiSE-CFR).

CFR can be measured by several invasive and noninvasive techniques, quantitatively by positron emission tomography or by Doppler flow wire during coronary angiography or as coronary blood flow velocity during DiSE. Of these techniques, transthoracic echocardiography allows the highly accurate recording of flow velocity in the mid-distal LAD. CFR in the LAD during DiSE has excellent concordance with invasive Doppler flow wire readings and good reproducibility.[3] For this reason, it is now more commonly used in the stress echo laboratory; the intra- and interobserver variabilities for Doppler recording measurements are $< 10\%$.[4]

CFR has been proven to exhibit powerful and additive prognostic value in large-scale multicenter studies involving patients with known or suspected coronary artery disease.[3] A CFR reduction can indicate significant epicardial coronary artery stenosis (typically when the CFR is < 1.8) or coronary microvascular disease[2,4] and therefore probably constitutes a further prognostic index.[3,4]

In the present study, we examined 4 HoFH siblings who were compound heterozygotes for LDL receptor gene mutations[5]: 1 woman (patient 1), 2 twin sisters (patients 2 and 3), and 1 man (patient 4), who were 26, 24, and 18 years old, respectively, on admission to our lipid clinic in 2009. They all had xanthomas in the Achilles tendon since adolescence that was overlooked until they were 19 years old. They had been treated, at best, with dietary approaches and multidrug therapy until 2013 when, upon the addition of evolocumab to high-intensity statin therapy, a satisfactory lipid profile was obtained (table 1).

All patients were asymptomatic for angina and/or dyspnea. However, they showed slight alterations in ventricular repolarization (slight ascending ST-segment in DII-DIII-aVF and from V4 to V6 rapidly regressing during the recovery phase) in ergometric stress testing while being negative for inducible myocardial ischemia. We thus followed up these patients with serial DiSE-CFR to evaluate both myocardial ischemia and CFR in the LAD.

At the first DiSE, patient 4 was positive for myocardial ischemia (left ventricular hypokinesia of the apical segments and of the middle anterior wall) and for CFR alterations (absence of detectable coronary blood flow in the LAD under rest conditions). Subsequent coronary angiography revealed the presence of chronic occlusion of the anterior descending artery and $> 70\%$ stenosis in the first diagonal branch with a Rentrop 1 collateral circle; these lesions were treated with percutaneous coronary revascularization (percutaneous transluminal coronary angioplasty/stenting of the LAD artery and of the first diagonal branch). DiSE-CFR performed at 10 months follow-up failed to detect inducible ischemia and the CFR was "normal" (2.22).

At the first DiSE-CFR, patient 1 showed no inducible ischemia, based on wall motion criteria, but a slight CFR reduction (1.90) compatible with coronary microvascular disease. The addition of evolocumab to statin therapy achieved a satisfactory lipid profile (table 1). Tests able to identify the presence of high-risk plaque[6] were delayed because the patient was asymptomatic for angina and dyspnea. At 2 years follow-up, the same test showed a LAD blood flow with increased velocity and inverted direction, suggesting a collateral coronary circulation. Subsequent coronary angiography revealed the presence of chronic occlusion of the LAD in the presence of valid (Rentrop 3) coronary collateral flow (figure 1). The patient was treated with percutaneous coronary revascularization (percutaneous transluminal coronary angioplasty/stenting of the LAD).

The 2 female twins (patients 2 and 3) showed no abnormal values in the DiSE-CFR tests.

The feasibility of stress echocardiography is undermined by its poor acoustic window and the specific contraindications to dipyridamole (presence of severe conduction disturbances, asthma, and a resting systolic blood pressure < 100 mmHg). Furthermore, we specifically measured the CFR of the LAD. The 3-coronary artery approach would undoubtedly be more fruitful but it remains too technically challenging. In addition, we must also consider the lifetime radiation exposure. However, the combination of wall motion and CFR into a single test with transthoracic echocardiography enables the simultaneous imaging of LAD flow and regional wall motion.

In the clinical setting for HoFH, stress echocardiography wall motion criteria and CFR may be considered a valid tool to assess inducible myocardial ischemia, LAD stenosis, and coronary microvascular dysfunction.[4]

The patients described here underline the need for the individualized follow-up of HoFH patients aimed at updating the risk of acute cardiovascular disease events and balancing the

Table 1
Lipid profile and lipid-lowering therapy in 4 siblings who are compound heterozygotes for LDL receptor gene mutations

Year	Total cholesterol, mg/dL	Triglycerides mg/dL	HDL-C, mg/dL	LDL-C, mg/dL	Lp(a), mg/dL	Lipid-lowering therapy
Patient 1						
2009	384	64	51	320	-	None
2013	266	69	61	191	10	Rosuvastatin 20 mg OD
2016	146	71	57	75	8	Rosuvastatin 20 mg OD + Evolocumab 420 mg QM
2019	168	47	67	92	7	Rosuvastatin 20 mg OD + Evolocumab 420 mg QM
Patient 2						
2009	427	80	58	353	-	None
2013	315	81	45	250	7	Atorvastatin 40 mg OD
2016	148	68	45	89	5	Atorvastatin 40 mg OD + Evolocumab 420 mg QM
2019	149	65	54	82	5	Atorvastatin 40 mg OD + Evolocumab 420 mg QM
Patient 3						
2009	558	131	66	460	-	None
2013	305	65	76	216	10	Atorvastatin 40 mg OD
2016	178	75	67	96	10	Atorvastatin 40 mg OD + evolocumab 420 mg QM
2019	169	76	61	93	9	Atorvastatin 40 mg OD + evolocumab 420 mg QM
Patient 4						
2009	302	97	61	221	-	None
2013	246	42	57	181	6	Atorvastatin 40 mg OD
2016	144	37	63	74	4	Atorvastatin 40 mg OD + evolocumab 420 mg QM
2019	129	97	47	63	4	Atorvastatin 40 mg OD + evolocumab 420 mg QM

HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein(a); OD, once a day; QM, every 4 weeks.

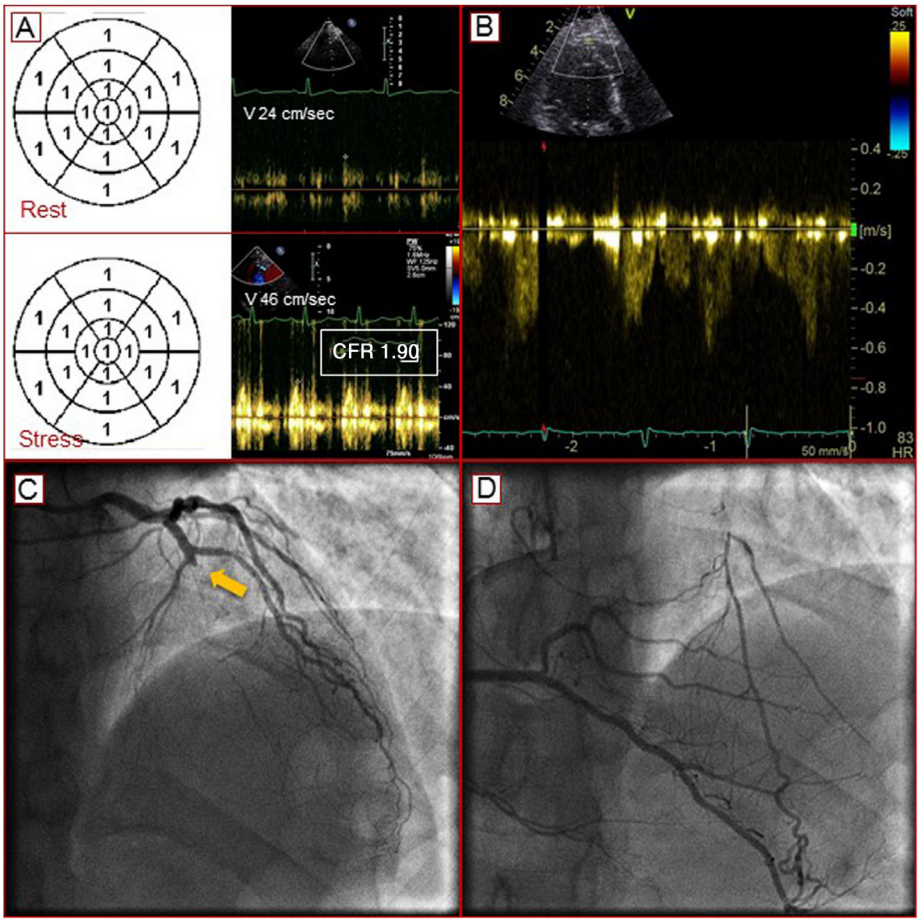

Figure 1. A: normal wall motion in the presence of a slight reduction in coronary flow reserve (CFR) compatible with coronary microvascular disease. B: CFR in the left anterior descending artery with an increased speed and inverted direction due to the presence of collateral coronary circulation. C: chronic occlusion of the anterior descending artery (arrow). D: intracoronary collateral flow.

test cost:benefit ratio with very valid concerns about lifetime radiation exposure.

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A new twist to HeartMate 3 low flow alarms

Un nuevo giro en un caso de alarmas por bajo flujo en una asistencia HeartMate 3

To the Editor,

We read with interest the scientific letter by Couto Mallón et al.[1] reporting a case of early outflow graft stenosis in a HeartWare (Medtronic, United States) left ventricular assist device (LVAD) diagnosed mainly because of an increase in hemolysis parameters and resolved with a percutaneous intervention with stenting.

We would like mention that the clinical presentation and management of an outflow graft obstruction may vary according to the etiology and type of LVAD. To illustrate the latter, we present the case of a 51-year-old woman with a prior history of hypertension, obesity, chronic obstructive pulmonary disease, and end-stage chronic heart failure due to ischemic cardiomyopathy admitted for cardiogenic shock. A HeartMate 3 LVAD (Abbott, United States) was implanted and the patient had an uneventful postoperative course.

Two years later, she was admitted for new-onset low flow alarms. Her blood pressure was well controlled and laboratory tests were unremarkable with no signs of hemolysis. Transthoracic echocardiography showed severe left ventricular dilatation and severely decreased left ventricular ejection fraction. The aortic and mitral valves could not be assessed due to poor visualization. Hypovolemia was initially suspected, so diuretics were discontinued, and intravenous fluids were administered. A few days later, the patient was readmitted for persistence of low flow alarms, and now overt signs of congestive heart failure with shortness of breath were present. A right heart catheterization was performed. With a baseline speed of 5600 rpm, the right atrial pressure was 13 mmHg, the pulmonary artery pressure was 45/27 mmHg with a mean of 33 mmHg, and the pulmonary capillary wedge pressure was 27 mmHg. Cardiac index was 2.18 lpm/m^2. Despite a progressive increase of speed to 6800 rpm, the pump was unable to unload the left ventricle and the pulmonary capillary wedge pressure remained at 26 mmHg. An outflow graft obstruction was suspected, and a chest computed tomography with 3-dimensional reconstruction was performed (figure 1A) and was suggestive of an outflow graft twist. The twist was confirmed by angiography with catheterization of the outflow graft from the ascending aorta (figure 1B and video 1 of the supplementary data). Surgical untwisting of the outflow graft in a clockwise direction was done without complications and a clip was placed to avoid a recurrence (figure 2). Pump flow immediately increased from 2.6 lpm to 5.2 lpm with a rapid improvement in hemodynamics. Intraoperative transesophageal echocardiography also showed a reduction in left ventricular size and mitral regurgitation. The aortic valve, which had opened with every beat, now remained closed (video 2 of the supplementary data).

Twisting of the outflow graft is a late complication appearing in 1.6% of patients supported with early iterations of the HeartMate 3 with a median time of 500 days after implantation.[2] The mechanism behind the twist is a swivel joint connecting the pump with the outflow graft, designed to allow rotation during implantation to ensure a correct placement of the graft. However, it is believed that, in some cases, cardiothoracic movements are transmitted to the pump causing an insidious rotation of the graft leading to a complete twist with significant outflow graft obstruction, which can manifest as persistent low flow alarms. In addition, thrombosis can occur as a result of the twist and lead to a rise in lactate dehydrogenase levels. Of importance, although thrombosis must always be in the differential diagnosis of pump malfunction, this complication is less common in HeartMate 3 than in other types of LVAD. In fact, in the MOMENTUM trial, thrombosis was suspected in 7 of the 515 implants and was confirmed in only