Prognosis of coronary flow reserve: a new therapeutic target?

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This editorial refers to 'The prognostic impact of coronary flow-reserve assessed by Doppler echocardiography in non-ischaemic dilated cardiomyopathy'† by F. Rigo et al., on page 1319

Coronary circulation, as in other vascular territories, is able to maintain its constant flow even with changes in the myocardial perfusion pressure. This physiological adaptation mechanism is defined as autoregulation. The concept of coronary flow reserve (CFR) is related to the ratio between the coronary blood flow after maximum vasodilatation, and the coronary blood flow at rest.1

The highest CFR is in the subepicardial layer of the myocardium. The CFR is lower in the subendocardial layer, so in relation to a decrease in myocardial flow, the subendocardial CFR is exhausted first. It is well known that in the absence of macroscopic coronary artery disease, the decrease of the CFR can be attributed to alterations in the microvascular circulation.2

CFR can be measured by magnetic resonance imaging, positron emission tomography, coronaryography, and transthoracic echocardiography. The last technique is especially useful because of its disposability, low costs, and the absence of radiation exposure.

The lower limit of CFR proposed by Dimitrow et al.3 using different methods in control groups is 3.0. A reduction in CFR can be found in some diseases associated with coronary microvascular dysfunction such as hypertrophic cardiomyopathy (CFR 2.21 ± 0.2), dilated cardiomyopathy (DCM) (CFR 1.9 ± 0.2), and Syndrome X (CFR 2.27 ± 0.3).4

The assessment of CFR has been also used to assess the prognostic value of different cardiac scenarios. Marks et al.5 described an increased mortality in patients with abnormal CFR (by means of invasive measurements) and normal coronary angiograms. Coronary microvascular dysfunction is also responsible of unfavourable outcome in hypertrophic cardiomyopathy. In such patients, CFR assessed by PET, was an independent predictor of clinical deterioration and death. It has also been documented that CFR, in normal to mildly diseased arteries, is an independent predictor of long-term prognosis of atherosclerosis within the next decade.6

Rigo et al.7 offer a very interesting article regarding the prognostic value of echo-Doppler-derived CFR in patients with non-ischaemic DCM. This study reports the utility of CFR, assessed by transthoracic dipyridamole stress echocardiography on LAD territory, for predicting prognosis in 129 patients (from four institutions) with DCM. All patients had an ejection fraction <40% and angiographically normal coronary arteries, with New York Heart Association class < III. All patients were followed for a median of 22 months. Patients with congenital, valvular, hypertrophic cardiomyopathy, myocardiitis, pericarditis, and thyroid disease were excluded. Events were defined as death for all causes, cardiac death, development or progression of heart failure. They defined abnormal CFR as <2.0. The authors concluded that a reduced CFR during vasodilator stress is an independent prognostic marker of unfavourable outcome. The final analysis was above 129 patients (46 patients had normal and 83 had abnormal CFR). The worst prognosis was observed in those patients with an abnormal CFR compared with those having a normal CFR (70 vs. 22%). In the multivariable analysis, severity of mitral insufficiency (HR, 1.9; 95% CI, 1.06–2.87), abnormal CFR (HR, 4.0; 95% CI, 1.1–15.6), rest Wall Motion Score Index (HR, 6.9; 95% CI, 1.5–30.7) were independent predictors of survival.

Although this result supports the increasing interest of CFR in the prognosis of cardiac patients, there are a few aspects that should be considered before interpreting the final conclusions. The different groups are not really homogeneous in their basal conditions. The diuretic use, left ventricular end-diastolic volume, ejection fraction at rest, and at peak stress, left ventricular mass index and the wall motion score index at rest and at peak stress shows differences between both groups. Some of the mentioned parameters are also markers of unfavourable outcome itself, and all of them are more prevalent (in the unfavourable direction) in the abnormal CFR group. Nevertheless, the multivariate analysis clarifies the independent relationship between low CFR and prognosis. In addition, stress echocardiography was performed and analysed at each local participating centre. This is for sure a potential bias to the results taking into account that we do not have intercenter variability data.

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It has been described how much CFR adds to other predictors of survival in patients with DCM. Before this study, Neglia et al.\textsuperscript{8} reported a worse prognosis in patients with DCM and low CFR assessed by PET at rest and after intravenous dipyridamole. A reduction in myocardial blood flow was associated with an increase in the relative risk of death, development, or progression of heart failure of 3.5 times over other more common clinical and functional variables. The results were independent of the degree of LV functional impairment. Rigo’s results are in the same line as this one, giving confidence to CFR assessed by echo, more applicable to the routine clinical practice.

A final step of CFR potentials is related to studies demonstrating that the reduction in CFR is reversible. In this direction there are few trials. CFR could improve in hypercholesterolaemic patients after statin treatment.\textsuperscript{9} Also it has been described an increase in CFR in hypertensive patients after reaching blood pressure goals. This has been reported with several drugs giving the impression that reaching the goals is more important than using a specific drug. Hilddick-Smith and Shapiro\textsuperscript{10} investigated 35 patients with pure aortic stenosis, LV hypertrophy, and normal coronary arteriograms. Patients underwent adenosine transthoracic echocardiography on two occasions (immediately before or after aortic valve replacement and 6 months postoperatively), concluding that CFR increases after aortic valve replacement for aortic stenosis simultaneously with regression of LV hypertrophy.

The conclusion that improving CFR in certain diseases with coronary microvascular dysfunction would influence positively the prognosis, could be logically concluded from the last studies. The demonstration of a relationship between an increase in CFR after treatment with a favourable outcome in DCM, or any disease with myocardial blood flow impairment, is nowadays a dare for future studies. Looking at the results of Rigo et al. and other studies, CFR may serve in the near future as a goal for treatment, becoming a new therapeutic target. Also may detect patients with unfavourable prognosis in whom a more aggressive therapy should be done. In this scenario, echocardiography and non-invasive modalities will be positioned as the election techniques.

Conflict of interest: none declared.

References