The coronary collateral circulation-clinical predictors

The coronary arteries were once thought of as functional end-arteries. Indeed, most of the time they are, as illustrated by myocardial ischemia in coronary artery disease. However, there are interconnecting branches between the main arteries which can prevent such ischemia despite coronary artery occlusion in many patients (1). In some cases, patients can even suffer total left main artery occlusion without myocardial infarction or with only very mild symptoms (2). These interconnecting networks of branches, which can be observed and graded by angiography, represent the coronary collateral circulation; an alternative route for the myocardial perfusion. The clinical relevance of this circulation is clear from recent analyses. A meta-analysis of 12 studies including 6,529 patients showed that patients with a well-developed collateral network had a 36% reduced risk of mortality (3). This may be because the collateral circulation protects against ischemic changes during repolarization, so avoiding fatal ventricular arrhythmias in the event of an acute coronary artery occlusion (4, 5). Another large analysis including 7 studies and 1425 patients showed that a well-developed collateral circulation was a risk factor for restenosis after coronary revascularization (6). The relationship observed here may be causal or it may simply be a function of disease severity. Either way, the collateral circulation apparently has significant prognostic implications.

A better understanding of the factors influencing the development of the coronary collateral circulation is essential. For this reason, Zorkun et al. (7) performed a retrospective study of 74 patients with greater than 90% occlusion of the left anterior descending artery. They assessed the association of multiple clinical and laboratory markers with the degree of collateralization and found, despite limited statistical power, male gender (OR 4.73, p=0.010), prior statin use (OR 4.70, p=0.021) and high hs-C-reactive protein levels (OR 0.94, p=0.048) as independent predictors of well-developed collaterals. These findings are somewhat surprising. A previous large study of 450 patients with coronary artery disease that considered patient history, cardiovascular risk factors, medication use and angiographic data showed that the only independent determinant of adequate collateral circulation was the degree of coronary artery stenosis (8). In patients without coronary artery disease, the baseline heart rate has been described as the main predictor of collateralization (9). There is also evidence that genetic factors play a role (10). Interestingly, even transplanted hearts maintain their collateral network without any impairment, despite immunosuppressive therapy (11).

We have to be aware of some of the limitations of this study. The statistical power with only 74 patients enrolled in this study is rather low for a multivariate analysis. Furthermore, collaterals were assessed angiographically, which is a semi-quantitative method with significant drawbacks. For correlation analyses using collaterals as a predictor variable, this is especially critical. While some (random) measurement error is acceptable for the dependent variable, standard statistical regression models assume the predictor variable to be measured without error. However, the angiographic “quantification” of the collateral circulation is not error free. The Rentrop scoring approach, as used by the others, does not agree perfectly with the gold standard, the hemodynamic assessment of collaterals (collateral flow index, CFI) (12). However, the authors acknowledge most of these limitations in their discussion; this study provides interesting information, which could help to find therapeutic options to encourage the development of the collateral circulation.

Such therapeutic approaches are currently being explored. The collateral vessels are induced by sheer stress on the endothelium by the process of arteriogenesis (note the distinction with angiogenesis which occurs in response to hypoxia). In arteriogenesis, monocytes probably have a key paracrine function releasing chemokines and growth factors to encourage new vascular growth. G-CSF, which targets monocytes is one proposed agent which could leverage this process for clinical benefit (13). Another option would be to increase sheer stress, which can be done via external counter-pulsation (14) or via physical exercise (15).

All these mentioned trials were small proof-of-concept studies; larger confirmatory trials need to follow (16). Greater a knowledge of the determinants of a good coronary collateral circulation is key to an understanding of the pathogenesis of coronary heart disease. Moreover, in the search for better and more targeted therapies in the management of coronary heart disease, the collateral circulation is a promising area for future advances in clinical practice.
Rahul Bahl, Adam Timmis†, Pascal Meier
University College London, Department of Cardiology,
London-UK
†The London Chest Hospital, London-UK

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References