The coronary collateral circulation-clinical predictors

Koroner kollateral dolaşım-klinik öngördürücüler

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.

Address for Correspondence/Yazışma Adresi: Dr. Pascal Meier, Assistant Professor Adjunct Yale Medical School and Senior Lecturer University College London, Cardiology University College London Hospitals London-*UK* Phone: +44 20 3456 7898 E-mail: pascalmeier74@gmail.com

Accepted Date/Kabul Tarihi: 07.11.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 07.12.2012

doi:10.5152/akd.2013.040

Rahul Bahl, Adam Timmis[1], Pascal Meier
University College London, Department of Cardiology, London-*UK*
[1]The London Chest Hospital, London-*UK*

Conflict of interest: None declared.

References

1. Seiler C. The human coronary collateral circulation. Eur J Clin Invest 2010; 40: 465-76. [CrossRef]
2. Meier P. The sword of damocles: an illustrative example of the life-saving effect of the collateral circulation. J Invasive Cardiol 2011; 23: E47-8.
3. Meier P, Hemingway H, Lansky AJ, Knapp G, Pitt B, Seiler C. The impact of the coronary collateral circulation on mortality: a meta-analysis. Eur Heart J 2012; 33: 614-21. [CrossRef]
4. Meier P, Gloekler S, de Marchi SF, Zbinden R, Delacretaz E, Seiler C. An indicator of sudden cardiac death during brief coronary occlusion: electrocardiogram QT time and the role of collaterals. Eur Heart J 2010; 31: 1197-204. [CrossRef]
5. Meier P, Seiler C. Sudden cardiac arrest during acute coronary occlusion - who is at risk? Cardiology 2010; 117: 124-7. [CrossRef]
6. Meier P, Indermuehle A, Pitt B, Traupe T, de Marchi SF, Crake T, et al. Coronary collaterals and risk for restenosis after percutaneous coronary interventions: a meta-analysis. BMC Med 2012; 10: 62. [CrossRef]
7. Zorkun C, Akkaya E, Zorlu A, Tandoğan İ. Determinants of coronary collateral circulation in patients with coronary artery disease. Anadolu Kardiyol Derg 2012; 12: 146-51.
8. Pohl T, Seiler C, Billinger M, Herren E, Wustmann K, Mehta H, et al. Frequency distribution of collateral flow and factors influencing collateral channel development. Functional collateral channel measurement in 450 patients with coronary artery disease. J Am Coll Cardiol 2001; 38: 1872-8. [CrossRef]
9. de Marchi SF, Gloekler S, Meier P, Traupe T, Steck H, Cook S, et al. Determinants of preformed collateral vessels in the human heart without coronary artery disease. Cardiology 2011; 118: 198-206. [CrossRef]
10. Meier P, Antonov J, Zbinden R, Kuhn A, Zbinden S, Gloekler S, et al. Non-invasive gene-expression-based detection of well-developed collateral function in individuals with and without coronary artery disease. Heart 2009; 95: 900-8. [CrossRef]
11. Rutz T, Gloekler S, de Marchi SF, Traupe T, Meier P, Eshtehardi P, et al. Coronary collateral function in the transplanted heart: propensity score matching with coronary artery disease. Heart 2011; 97: 557-63. [CrossRef]
12. van Liebergen RA, Piek JJ, Koch KT, de Winter RJ, Schotborgh CE, Lie KI. Quantification of collateral flow in humans: a comparison of angiographic, electrocardiographic and hemodynamic variables. J Am Coll Cardiol 1999; 33: 670-7. [CrossRef]
13. Meier P, Gloekler S, de Marchi SF, Indermuehle A, Rutz T, Traupe T, et al. Myocardial salvage through coronary collateral growth by granulocyte colony-stimulating factor in chronic coronary artery disease: a controlled randomized trial. Circulation 2009; 120: 1355-63. [CrossRef]
14. Gloekler S, Meier P, de Marchi SF, Rutz T, Traupe T, Rimoldi SF, et al. Coronary collateral growth by external counterpulsation: a randomised controlled trial. Heart 2010; 96: 202-7. [CrossRef]
15. Zbinden R, Zbinden S, Meier P, Hutter D, Billinger M, Wahl A, et al. Coronary collateral flow in response to endurance exercise training. Eur J Cardiovasc Prev Rehabil 2007; 14: 250-7. [CrossRef]
16. Schaper W. Collateral vessels reduce mortality. Eur Heart J 2012; 33: 564-6. [CrossRef]