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FRACTIONAL FLOW RESERVE OF INTERMEDIATE LESIONS ON COLLATERAL DONOR CORONARY ARTERIES AFTER MYOCARDIAL INFARCTION

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Abstract: Fractional flow reserve (FFR) is the gold standard for the functional assessment of coronary arteries. The aim of this study was to evaluate the relation between angiography, QCA and FFR in borderline lesions on collateral donor coronary arteries. In addition, FFR is compared with the angiographic appearance of collaterals to infarction-related arteries and echocardiographically assessed viability of infarct related the LV wall. In 60 patients with previous IM and occluded IRA, functional assessment of borderline coronary stenosis (30-70% DS) on collaterals donor artery was performed. We have not found statistically significant differences in these parameters between groups with different angiographic appearances of collaterals and different viability of distal myocardium. However, we found higher FFR values in diabetic patients (p=0.018). Higher FFR values in diabetic patients reveal the negative effects of diabetes on collateral growth and myocardial viability.

*Key words***:** FFR, collaterals, intermediate stenosis, diabetes mellitus

Abbreviations: FFR – Fractional Flow Reserve, QCA – Quantitative Coronary Angiography, DS – Diameter of stenosis, IRA – Infarct Related Artery, LCA – Left Coronary Artery, LAD – Left Anterior Descending Artery, LCX – Left Circumflex Artery, RCA – Right Coronary Artery, MI – Myocardial Infarction, IHD – Ischemic Heart Disease, DM – Diabetes Mellitus, CCC – Coronary Collateral Circulation, VEGF – Vascular Endothelial Growth Factor, PAI -1 – Plasminogen Activator Inhibitor.

INTRODUCTION

The development of fractional flow reserve and its establishment as a recognized technique for determining ischemic lesions (De Bruyne et al, 1993; Pijls et al. 1993) have allowed its application in various clinical settings and collateral blood flow physiology being such a case (Pijls et al., 1995). As FFR is a functional parameter determining the relation between lesion severity (calculated as a pressure drop distally to lesion) and viability of the myocardium, there is enough evidence to support the prognostic value of the method after MI (Beleslin et al., 2008) in residual lesions.

The contribution of collateral circulation in patients that survived MI and have a re-canalized lesion of the coronary artery in a functional improvement of the left ventricle during rehabilitation has been documented (Vukcevic et al., 2009). FFR obtained during the occlusion of an infarcted artery during PCI is moderately correlated to visible collateral blood flow (during angiography). Its functional contribution cannot be disregarded, even in

angiographically invisible collaterals. FFR is higher in patients with ST elevation during artery occlusion and in patients with a verified viable myocardium in infarcted areas. FFR has not been examined in donor arteries for collateral blood flow, especially in borderline lesions.

MATERIALS AND METHODS

We examined the fractional flow reserve in arteries with borderline stenosis (30-70%), supplying collateral blood flow for occluded MI-related arteries in 60 patients. In all patients the regional wall motion was examined by a standard echocardiogram.

Quantitative collateral circulation grading

The extent of collateralization to the coronary artery of interest is described using the Rentrop Score (Rentrop et al., 1985): 0 = no visible collateralization, 1 = faint filling of only side branches of coronary artery of interest, 2 = partial filling of artery of interest, and 3 = complete filling of artery of interest.

Quantitative Coronary Angiography for coronary stenosis evaluation

QCA (Hermiller et al., 1992; Gronenschild et al., 1994) was performed using catheter calibration. The angiograms were evaluated using the Siemens Axiom Artis system. The following data were recorded for each coronary artery segment: percentage of segment diameter reduction and minimum lesion diameter.

Coronary angiography and FFR

Multi-directional coronary angiography was performed using Judkin's technique in all patients. A luminal diameter narrowing of 30-70% was considered to represent intermediate stenosis. In all patients, intracoronary pressure was measured for the vessels that were angiographically suspected as donors of collaterals. A 0.014-inch guidewire with a premounted pressure sensor (PressureWire™, Radi Medical Systems; Uppsala, Sweden) was placed across the lesion with the pressure sensor at least 2 cm distal to the examined lesion. To induce a maximal hyperemic vascular response, 150 μg of intracoronary nitroglycerine was given to reduce spasm. Soon after, 140 or 60 μg of LCA or RCA, respectively, of the intracoronary adenosine serving as a vasodilator of resistance vessels (arteriole and capillaries), was injected. Under conditions of maximal hyperemia, the pressure distally to the stenosis, was measured by the wire pressure sensor, and the pressure proximal to the stenosis, was measured at the tip of the catheter and recorded. The calculated gradient ratio was expressed as the FFR (Pijls et al., 1995).

Statistical analysis

Data are generally expressed as the means ± SD. ANOVA was used for comparison of means between populations. A value of $p<0.05$ was considered as indicative of significant difference. Computation was performed using the SPSS software.

RESULTS

Most patients were males with a high incidence of diabetes (Table I). No significant collaterals (Rentrop classification grade 3) were found. We also did not observe any difference between angiographically assessed percentages of stenosis, QCA-derived and

Table 1. Baseline characteristics

Age (years)	61±7
M/F	39/21
Coronary risk factors	
Arterial hypertension	42 (70%)
Hypercholesterolemia	34 (56,6%)
Smoking	32 (53,3%)
Family history of CAD	30 (50%)
DM	24 (40%)

Values are presented as numbers (%) or mean ±standard deviation.

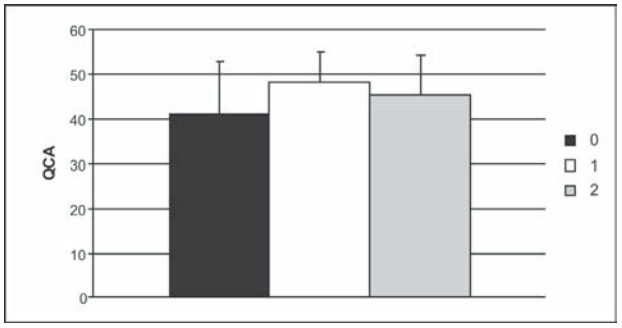

Fig. 1. Mean values of QCA DS% among different Rentrop groups (p=0.296).

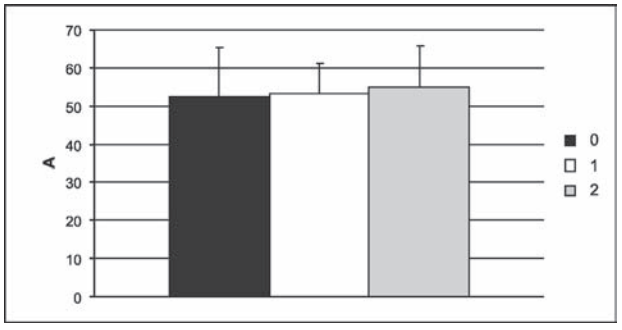

Fig. 2: Mean values of angiographically (A-DS%) assessed stenosis in different Rentrop groups (p=0.848).

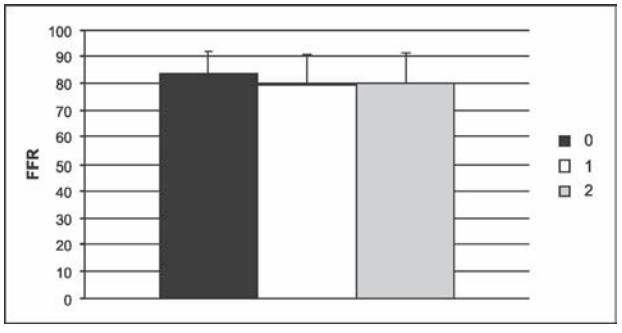

Fig. 3. Mean FFR values in different Rentrop groups (p=0.772).

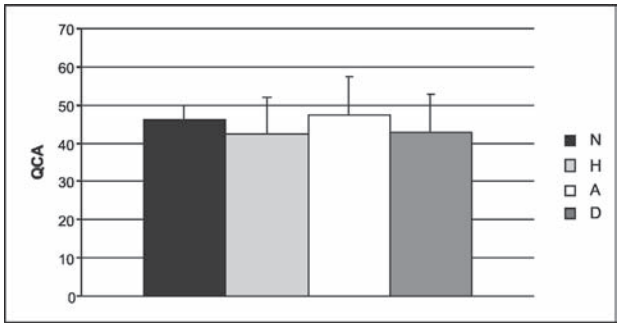

Fig. 4. Mean values of QCA DS% in collateral flow donating arteries between groups with different wall motion values (N-normokinetic, H-hypokinetic, A-akinetic, D-diskinetic (p=0.595).

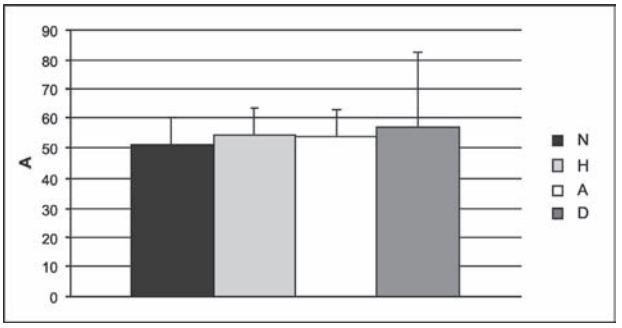

Fig. 5. Mean values of angiographically assessed percentages of stenosis (A-DS%) in donor arteries in groups with different wall motion values (p=0.904).

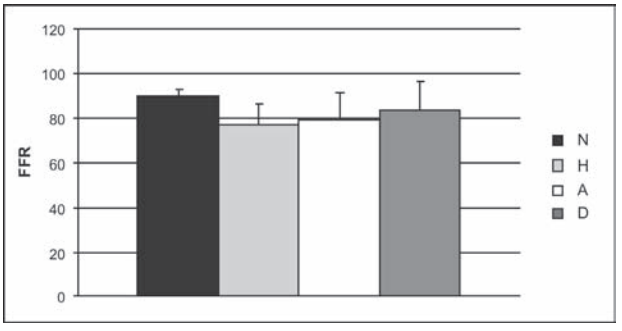

Fig. 6. Mean values of FFR in collateral flow donating arteries between groups with different wall motion values (p=0.226).

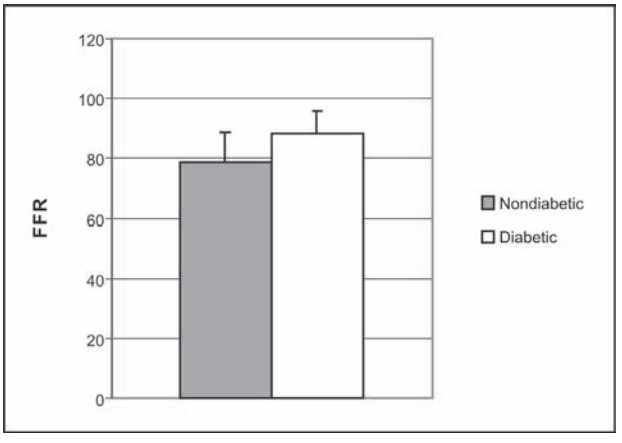

Fig. 7. Mean values of FFR in diabetic vs non diabetic (p=0.018) patients.

FFR values (Fig. 1, 2 and 3) in groups with different Rentrop grades. Likewise, no difference was found between groups with different wall motion after MI (Fig. 4, 5 and 6). The only significant difference was observed between groups of diabetic compared to non-diabetic patients (Fig. 7).

DISCUSSION

Coronary collaterals, or "natural bypasses," are anastomotic connections between portions of the same coronary artery and between different coronary arteries (Popma and Bittl, 2001.). Collateral circulation potentially offers an important alternative source of blood supply when the original vessel fails to provide a sufficient blood supply (Sasayama and Fujita, 1992). In patients with chronic IHD, coronary collateralization maintains myocardial viability in the collateral-fed distribution (Piek et al., 1997), and is associated with smaller myocardial infarctions (Habib et al., 1991), ventricular aneurysm formation, improved left ventricular function, lower arrhythmias and better survival, compared to patients that do not develop collaterals (Regieli et al., 2009). Timely enlargement of collaterals may even prevent transmural myocardial infarction (MI) and death in symptomatic patients (Shaper et al., 1988). Fukai et al. (2000) found that well-developed coronary collaterals might minimize the infarct area and predict the presence of a viable myocardium in patients with a history of anteroseptal MI. Angiographic studies had shown the first appearance of collaterals within 2 weeks after acute MI (Schwartz et al., 1984; Rentrop et al., 1989). Recurrent and severe myocardial ischemia is assumed to stimulate the development of coronary collateral circulation. The ischemic episode has to exceed a specific threshold value in order to produce clinical events such as sudden MI or even sudden cardiac death. This threshold value depends on the sensitivity of the myocardium to ischemia, which is determined by, among other factors, its level of protection by collateral circulation. However, the growth of collateral arteries through arteriogenesis is not dependent on ischemia (Buschmann and Schaper, 2000). Collateral arteries develop in non-hypoxic tissue. Whereas angiogenesis (the formation of new capillaries by sprouting from post-capillary venules) is induced by hypoxia, arteriogenesis (the transformation of pre-existing arterioles into functional (muscular) collateral arteries with vasomotor properties) is induced by an increase in shear stress. Mechanisms of coronary arteriogenesis have been well investigated, and signal cascades initiated by increased fluid shear stress at the site of pre-existent collateral vessels have been elucidated in animal models (Schaper and Buschmann, 1999).

Fulton and Royen (2004) demonstrated that in patients with obstructive CAD, functional coronary collaterals develop by the enlargement of pre-existing coronary anastomoses. The main stimulus to vessel enlargement was the collateral blood flow generated by differential pressure gradients resulting from coronary artery occlusion or stenosis. The extent of coronary artery collateralization was related to angina duration (Fulton, 1964). It is now clear that long-standing high-grade coronary stenosis is mainly responsible for collateral vessel growth (Pohl et al., 2001). Severe coronary narrowing results in myocardial ischemia, and a pressure gradient between the providing and receiving coronary arteries across the collateral network. The new establishment of a pressure gradient leads to the recruitment of collateral blood flow and increased shear stress at the site of pre-existing collateral vessels. Thus, severe coronary narrowing is inevitably accompanied by two potential stimuli for the development of collateral circulation: myocardial ischemia and shear stress.

Coronary collaterals develop over time after an acute myocardial infarction. Collateral resistance rapidly decreases and collateral flow reaches 90% of maximal capacity in the first four weeks after acute occlusion, and coronary collaterals can be seen angiographically (Patterson et al., 1983). The various chemokines and growth factors involved in both processes also differ (Van Royen et al. 2001).

Coronary angiography is the standard method to identify coronary collateral arteries. Angiography with ordinary visual detection has limited resolution. Arterioles <100 μm are invisible in angiographic examination (Gensini and Da Costa, 1969) and visible collaterals typically have a diameter of 0.5 mm (Rockstroh and Brown, 2002).

In our study, we expected a clear negative correlation between FFR and the Rentrop collateral grade due to a larger vascular zone. According to our data,

no clear correlation was found. In the interpretation of our findings, several limitations must be considered. First, our study included a small number of patients. Second, angiography may not detect most collaterals situated intramurally. Therefore, the collaterals visualized by angiography may not accurately quantify collateral circulation. We may have underestimated the presence of collateral flow by measuring only spontaneously visible coronary collaterals (Berry et al., 2007; Meier et al. 2007). Third, we did not perform echocardiographic viability or nuclear perfusion tests to assess the viability of the distal myocardium. Instead, a number of different cardiologists performed conventional echocardiographic exams; inter-operator variability may be a possible source of the nonuniformity of our results. The last may be the most important limitation of our study. Finally, the present study is a retrospective, observational one.

Diabetes mellitus and collaterals

There are contradictory results about the effects of diabetes mellitus (DM) on CCC. Although Banai et al. (1994) reported that collateral circulation does not decrease in DM, Abaci et al. (1999) (who applied the angiographic method) and Nisanci et al. (2002) (who applied the intracoronary pressure measurement method) showed that collateral circulation was decreased in DM.

Insulin is an important regulator of the angiogenesis pathway, and in rat models, insulin resistance is associated with a decreased expression of VEGF, leading to a decreased vascular density in the myocardium in response to ischemia. Adiponectin is an adipocyte-derived cytokine downregulated in patients with DM and known to have angiogenic properties in animals (Ouchi et al., 2004). Adiponectin is considered to promote angiogenesis by promoting endothelial cell proliferation and migration and by suppressing apoptosis (Ouchi et al., 2004). A high concentration of PAI-1 in the blood is one of the features of DM. Decreasing PAI-1 expression in animals stimulates vessel growth in response to myocardial ischemia (Xiang et al., 2004). Our results correlate with the study results of Abaci et al. (1999) who described the negative effects of diabetes on coronary collateral growth and myocardial viability.

REFERENCES

Abaci A., Oguzhan A., Kahraman S. et al. (1999) Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* **99**, 2239-42.

Banai S., Jaklitsch M.T., Shou M. et al. (1994) Angiogenic-induced enhancement of collateral blood flow to ischemic myocardium by vascular endothelial growth factor in dogs. *Circulation* **89**, 2183-89.

Beleslin B., Ostojic M., Djordjevic-Dikic A., Vukcevic V., Stojkovic S., Nedeljkovic M., Stankovic G., Orlic D., Milic N., Stepanovic J., Giga V. and *Saponjski J.* (2008) The value of fractional and coronary flow reserve in predicting myocardial recovery in patients with previous myocardial infarction. *European Heart Journal* **29**, 2617-24.

Berry C., Balachandran K.P., L'Allier P.L. et al. (2007) Importance of collateral circulation in coronary heart disease. *Eur Heart J* **28**, 278-91.

Buschmann I. and *Schaper W.* (2000) The pathophysiology of the collateral circulation (arteriogenesis). *J Pathol* **190**, 338-42.

De Bruyne B., Pijls N.H., Paulus W.J., Vantrimpont P.J., Sys S.U. et al. (1993) Transstenotic coronary pressure gradient measurement in humans: In vitro and in vivo evaluation of a new pressure monitoring angioplasty guide wire. *J Am Coll Cardiol* **22**, 119-26.

Fukai M., Ii M., Nakakoji T. et al. (2000) Angiographically demonstrated coronary collaterals predict residual viable myocardium in patients with chronic myocardial infarction: a regional metabolic study. *J Cardiol* **35**, 103-11.

Fulton W.F.M. (1964). The time factor in the enlargement of anastomoses in arteries in normal and pathologic hearts. *Scott Med* J **9**, 18-23.

Fulton W.F.M. and *van Royen N.* (2004) The coronary collateral circulation in man. In: Schaper W, Schaper J (eds). *Arteriogenesis. Dordrecht: Kluwer Academic*.

*Gensini G.G.*and *Da Costa B.C.B.* (1969) The coronary collateral circulation in living man. *J Am Coll Cardiol* **24**:393-400.

Gronenschild E., Janssen J. and *Tijdens F.* (1994) CAAS II: A second generation system for off-line and on line quantitative coronary angiography. *Cathet Cardiovasc Diagn* **33**, 61-75.

Habib G.B., Heibig J., Forman S.A. et al (1991) Influence of coronary collateral vessels on myocardial infarct size in hu-

mans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators. *Circulation* **83**, 739-46.

Hermiller J.B., Cusma J.T., Spero L.A. et al. (1992) Quantitative and qualitative coronary angiographic analysis: Review of methods, utility, and limitations. *Cathet Cardiovasc Diagn* **25**, 110-31.

Meier P., Gloekler S., Zbinden R. et al.(2007) Beneficial effect of recruitable collaterals: a 10-year follow-up study in patients with stable coronary artery disease undergoing quantitative collateral measurements. *Circulation* **116**, 975-83.

Nisanci Y., Sezer M., Umman B. et al. (2002). Relationship between pressure-derived collateral blood flow and diabetes mellitus in patients with stable angina pectoris: A study based on coronary pressure measurement. *J Invasive Cardiol* **14**, 118-22.

Ouchi N., Kobayashi H., Kihara S. et al. (2004) Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. *J Biol Chem* **279**, 1304-09.

Patterson R., Jones Collins B., and *Aamod T.* (1983) Differences in collateral myocardial blood flow following gradual vs abrupt coronary occlusion. *Cardiovasc Res* **17**, 207-13.

Piek J.J., van Liebergen R.A., Koch K.T. et al. (1997) Clinical, angiographic and hemodynamic predictors of recruitable collateral flow assessed during balloon angioplasty coronary occlusion. *J Am Coll Cardiol* **29**, 275-82.

Pijls N.H., Van Gelder B., Van der Voort P., et al. (1995) Fractional flow reserve: A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* **92**, 3183-93.

Pijls N.H., van Son J.A., Kirkeeide R.L., De Bruyne B. et al. (1993) Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* **87**, 1354-67.

Pijls N.H.., Bech G.J.., el Gamal M.H. et al. (1995) Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. *J Am Coll Cardiol* **25**, 1522-28.

Pohl T., Seiler C., Billinger M. et al. (2001) 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* **38**, 1872-78.

Popma J.J. and *Bittl J.* (2001) Coronary angiography and intravascular ultrasonography. In: Braunwald E, Zipes DP, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia: W.B. Saunders Company*: 387-418.

Regieli J.J., Jukema J.W., Nathoe H.M. et al (2009) Coronary collaterals improve prognosis in patients with ischemic heart disease. *Int J Cardiol* **132**, 257-62.

Rentrop K.P., Cohen M., Blancke H. et al. (1985) Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* **5**, 587-92.

Rentrop K.P., Feit F., Sherman W. et al (1989) Serial angiographic assessment of coronary artery obstruction and collateral flow in acute myocardial infarction. Report from the second Mount Sinai-New York University Reperfusion Trial. *Circulation* **80**, 1166-75.

Rockstroh J. and *Brown B.G.* (2002) Coronary collateral size, flow capacity, and growth. Estimates from the angiogram in patients with obstructive coronary disease. *Circulation* **105**, 168-173.

Sasayama S. and *Fujita M.* (1992) Recent insights into coronary collateral circulation. *Circulation* **85**, 1197-1204.

Schaper W. and *Buschmann I.* (1999) Arteriogenesis, the good and bad of it. *Eur Heart J* **20,** 1297-99.

Schaper W., Gorge G., Winkler B. et al. (1988) The collateral circulation of the heart. *Prog Cardiovasc Dis* **31**, 57-77.

Schwartz H., Leiboff R.H., Bren G.B. et al. (1984) Temporal evolution of the human coronary collateral circulation after myocardial infarction. *J Am Coll Cardiol* **4**, 1088-93.

Van Royen N., Piek J.J., Buschmann I. et al. (2001) Stimulation of arteriogenesis: a new concept for the treatment of arterial occlusive disease. *Cardiovasc Res* **49**, 543-53.

Vukcevic V., Beleslin B., Ostojic M., Stojkovic S., Stankovic G., Nedeljkovic M., Orlic D., Djordjevic-Dikic A., Stepanovic J., Giga V., Arandjelovic A., Dikic M., Kostic J., Nedeljkovic I., Nedeljkovic-Beleslin B. and *Saponjski J.*. (2009). Quantitative evaluation of collateral circulation in patients with previous myocardial infarction: relation to myocardial ischemia, angiographic appearance and functional improvement of myocardium. *Int J Cardiovasc Imaging* **25**(4), 353-61.

Xiang G., Schuster M.D., Seki T. et al. (2004) Downregulation of plasminogen activator inhibitor 1 expression promotes myocardial neovascularization by bone marrow progenitors. *J Exp Med* **200**, 1657-66.