

# Efficacy of Retrograde Filling on Antegrade Flow of Coronary Artery with Significant (High Grade) Stenosis

M Shabestari, L Alizadeh, M Nikdoust, F Mirblouk, H Mehdikhani, M Fadavi, J Mahmoodi

## Citation

M Shabestari, L Alizadeh, M Nikdoust, F Mirblouk, H Mehdikhani, M Fadavi, J Mahmoodi. *Efficacy of Retrograde Filling on Antegrade Flow of Coronary Artery with Significant (High Grade) Stenosis*. The Internet Journal of Cardiology. 2008 Volume 7 Number 2.

## Abstract

### Objectives–

of this study was to evaluate effects of retrograde filling on the patency of significant (high-grade, >90%) coronary arterial stenosis.

### Methods–

The basis of our study was a comparison between the first and the second angiography of 102 patients with at least a 3-month interval between the two angiographies. Seventy-four of the patients were male (72.5%) and twenty-eight were female (27.4%). The patients were between the ages of 40 and 75, and the mean patient age was 61. Patients were not classified in order of risk factors, and none of them had diabetes mellitus. All 102 patients were classified in two groups (A and B) in regard to the presence or absence of retrograde filling. Group A (34 patients) consisted of patients with retrograde flow of grade 3 (complete perfusion) or 2 (partial collateral flow), whereas patients with retrograde filling grade 1 (barely detectable collateral flow) or 0 (no collateral flow) were put into group B (68 patients).

### Results–

In the second angiography, total occlusion occurred in the target vessels of 30 patients (88.24%) in group A and 12 patients (17.65%) in group B. Ninety percent occlusion and existence of antegrade flow was seen in 4 (11.76%) and 56 (82.35%) patients of group A and B, respectively. Results were analyzed through a Chi-square test. Total occlusion occurred in the patients with retrograde collateral flow significantly more than in patients without retrograde collateral vessels. ( $P=0.001$ )

### Conclusion

– As the severity of obstruction leads to retrograde collateral development, significant retrograde collaterals cause earlier total vessel occlusion

## INTRODUCTION

A drop in post-stenotic pressure caused by flow-limiting stenosis is known to stimulate the development of collateral circulation from other coronary artery beds. <sup>1</sup> The supply of collateral (vascular channels that interconnect to the epicardial artery) blood flow increases post-stenotic pressure, thus improving the coronary flow reserve and increasing the ischemic threshold. <sup>2</sup>

Preexisting collaterals are thin-walled structures ranging in diameter from 20 to 200 ( $\mu\text{m}$ ). <sup>3</sup>

Since no pressure gradient exists between the arteries which collaterals connect, they are normally closed and non-functional. The transformation of preexisting collaterals into mature collaterals is called arteriogenesis. This occurs in three stages: <sup>4,5</sup>

The initial stage, i.e. the first 24 hours, involves a passive widening of the preexisting channels. The second stage, i.e. 1 day to 3 weeks, is characterized by inflammation and cellular proliferation. The third stage of collateral maturation, i.e. 3 weeks to 6 months, involves the

thickening of vessel walls due to deposits of extra cellular matrix and further cellular proliferation. <sup>456</sup>

Collateral blood flow may also develop by vessel neoformation, but in dogs this mechanism contributes only less than 5 percent of total collateral flow. <sup>2</sup>

Blood flow through these anastomoses begins as a consequence of the flow-limiting stenosis when a pressure gradient develops between their origin and termination. <sup>2</sup>

## **METHODS**

Initially, we found changes in the antegrade flow of stenotic vessels in patients with coronary artery disease who had been referred for percutaneous coronary intervention (PCI). Those changes persuaded us to focus more on the flow of stenotic arteries and presence of collaterals (retrograde filling).

102 patients, who had been referred for angioplasty to the catheterization lab of Razavi Hospital in Mashhad, Iran were studied. Seventy-four of the patients were male (72.5%) and twenty-eight were female (27.4%), the male to female ratio being 2.64/1. Patients were between ages of 40 and 75, and the mean patient age was 61. Cases were chosen completely randomly, so they were not classified in order of risk factors. Suffering from single-vessel disease (SVD) with a patency of at least 90%, they had been referred between the years 2003 to 2005. Demographic data are shown in Table I. Our study was performed regardless of the type of stenotic vessels, sex and age. Because of the profound impact of diabetes mellitus on collateral perfusion, diabetic cases were excluded from our study. The patients did not have any history of PCI or coronary artery bypass graft surgery (CABG). They did not have left main disease or multi-vessel diseases, and they had at least 90 percent stenotic lesions.

These patients had been candidates for PTCA (percutaneous transluminal coronary angioplasty) in the previous 3 months, and had no acute coronary events during these 3 months. The patients had been treated with-blockers, nitrates, ticlopidine and aspirin. They underwent angiography again and PTCA was done at the same time. Although most patients were referred during the first month (73 patients), 29 patients were referred during the second and third months from the first angiography. Our study was based on the comparison between the first angiography and the second one. All of the patients were evaluated and labeled according to the presence of collateral vessels.

Our coronary collateral grading consisted of a classification system. <sup>7</sup> Patients who had complete perfusion or partial collateral flow and in whom contrast material entered the target epicardial vessel in the angiographic study and opacified the vessel completely (grade 3) or partially (grade 2) were put into grade 3 (excellent collateral flow) and grade 2 (good collateral flow), respectively. Patients with poor collateral flow were put into grade 1. They had barely detectable collateral flow and contrast medium passed through collateral channels but failed to opacify the epicardial vessel at any time. Patients without any contrast flow and no visible flow were classified in grade 0. No collateral vessels were seen in the patients of this group (Table I).

### **Figure 1**

Table I. Demographic data of the 102 cases who underwent angiography

Sex	Age	Coronary artery	Interval to second angiography
m/f	40-60/ 60-75	LAD/ LCX/ RCA	1 <sup>st</sup> mo/ >1 <sup>st</sup> mo
74/28	34/28	61/11/30	73/29

In the second angiography, we evaluated and compared the presence of collateral vessels (retrograde filling) with the amount of antegrade flow observed.

## **RESULTS**

Thirty-four of the 102 patients who had been referred with severe stenotic lesions (90% or more) for PCI, had significant collateral vessels (Grade 2 or 3) and retrograde filling of epicardial vessel in the first angiographic study (called group A). The other 68 patients had severe stenotic lesions and near total occlusion, but collateral vessels did not develop and no retrograde filling of epicardial vessels was observed (Grade 0 or 1). We called this group 68 patients group B (Table II).

**Figure 2**

Table II. Perfusion grading distal to coronary stenosis.

Grade	TIMI	Collateral Flow	Rentrop Collateral Grade
3	Prompt antegrade flow and rapid clearing	Excellent	Complete perfusion
2	Slow distal filling, but full opacification of distal vessel	Good	Partial collateral flow
1	Small amount of flow but incomplete opacification of distal vessel	Poor	Barley detectable collateral flow
0	No contrast flow	No visible flow	No collateral flow

In the second angiographic study performed less than 3 months after the first one, total occlusion occurred in 30 patients (88.24%) of group A, but only 4 patients (11.76%) of this group showed 90% occlusion and antegrade flow of the target artery; and the target lesion was unchanged. In group B, total occlusion occurred in only 12 patients (17.65%). Ninety percent (90%) occlusion and existence of antegrade flow of coronary artery was seen in 56 patients (82.35%). Total occlusion occurred most often in patients with retrograde collateral flow-88.24% vs. 17.65% (P=0.001).

**STATISTICAL ANALYSIS**

Results were analyzed via a Chi-square test Expected values were obtained for both groups through the test (Table III).

**Figure 3**

Table III. Degree of occlusion in 102 patients classified into groups A and B with regard to the presence or absence of collaterals.

	with collateral Group A	without collateral Group B	total
<b>total occlusion</b>	30	12	42
<b>90% occlusion</b>	4	56	60
<b>total</b>	34	68	102

Measuring Chi-square total value, we used the Chi formula, shown below:

$$X^2 \text{ (Chi-square)} = (\text{Observed} - \text{Expected})^2 / \text{Expected}$$

Through the formula, the total value turned out to be 46.63 (Table IV). On the basis of Chi-square, P value was 0.001.

**Figure 4**

Table IV. Expected values obtained by Chi-Square test.

	with collateral Group A	without collateral Group B
<b>total occlusion</b>	18.29	9.14
<b>90% occlusion</b>	12.8	6.4

**Figure 5**

Table V. Chi-Square test values in detail. Chi-square total value of 46.63 was obtained, so P value of 0.001 was calculated.

	with collateral Group A	without collateral Group B	total
<b>total occlusion</b>	14	28	42
<b>90% occlusion</b>	20	40	60
<b>total</b>	34	68	102

**DISCUSSION**

There are several mechanisms which are said to be responsible for promoting collateral growth. It seems that shear stress or mechanical forces determine the size of collateral channels in the early minutes and hours. It is also thought that inflammation induces activation of inflammatory cells and is a rich source of growth factors for the development of coronary collateral vessels.

There are more than 15 growth factors that stimulate collateral growth. Among these known growth factors, VEGF (vascular endothelial growth factor) and FGF (fibroblast growth factor) are believed to play the most important roles in in-vivo studies.

Tissue hypoxia is associated with regulation of VEGF. Severity of the obstruction is a critical determinant of the development of coronary collateral channels in patients. Coronary collaterals do not develop until a coronary stenosis of at least 70 percent diameter narrowing is present. Beyond this threshold value, the growth of collateral channels is directly related to the severity of stenosis.

Patients with coronary risk factors such as diabetes mellitus have an impaired ability to develop collateral blood vessels.

Our results demonstrated two observations:

(1) Probability of total vessel stenosis in the presence of retrograde collaterals during the maximum period of three months could be forecast, and (2) Presence of retrograde collaterals with grade 3 will accelerate the vessel occlusion.

Patients with severe coronary artery disease are varied in terms of collateral growth and collateral blood flow; however, it is not entirely clear why some patients develop effective collateral vessels distal to a severe stenosis and others do not, though it is said that the causes of these individual differences in coronary collateral circulation are likely to be related to genetic factors.<sup>17</sup> Presence of high-grade collaterals will accelerate atherosclerosis and will lead to total vessel occlusion.

According to what is said above, patients with 90 percent stenosis and high flow collaterals (Grade 3) after a maximum of 3 months had total occlusion ( $P=0.001$ ). Contrary to these findings, in patients with 90 percent stenosis and low-grade collaterals after 3 months, antegrade flow was present.

It seems that VEGF, which increases secondarily to the severe stenosis, causes the progression of atherosclerosis, in severe stenotic vessels. VEGF, which is injected intra-coronary for angiogenesis or increases naturally and secondarily to hypoxia and severe stenosis, will accelerate and amplify the atherosclerotic phenomenon and promote atherosclerotic plaque.<sup>14</sup> Collateral presence will reduce repeated ischemia in patients.<sup>17</sup>

According to the relationship between the accelerating atherosclerosis phenomenon and atheroma plaque development and the presence of collaterals, it seems that there is a relation between collateral growth and severe obstruction of the coronary artery, which is followed by post-stenotic pressure decrease.

## CONCLUSION

In severe coronary artery disease, i.e. patients with at least 90 percent obstruction of one vessel, the presence of collaterals (retrograde filling) will cause total obstruction of the vessel in at least 3 months.

Conversely, in the absence of collaterals, after 3 months the antegrade flow was still present. As the severity of stenosis has an effect on the collateral growth, the presence and quick

development of collaterals will accelerate coronary artery occlusion ( $P=0.001$ ).

These findings were observed regardless of the type of vessel, sex and age of the patients, and we did not consider major coronary risk factors. None of the patients had diabetes mellitus. We highly recommend another study in regard to type of involved vessel, sex, age and risk factors to determine effects of these factors especially diabetes on collateral vessels.

## ACKNOWLEDGMENTS

We are extremely grateful to Dr. Mahmood K. Razavi at Stanford Medical Center for his useful comments and worthwhile suggestions.

## References

1. Fuster V, Alexander RW, O'Rourke RA, Hein J, Wellens J. (eds.) In: Hurst's The Heart. 10th ed., New-York, McGraw-Hill Professional, 2001:1109-1121.
2. Maseri A. Ischemic Heart Disease: A Rational Basis for Clinical Practise and Clinical Research. 1st ed., London, Churchill-Livingstone, 1995.
3. Wolf C, Cai WJ, Vosschulte R, Koltai S, Mousavipour D, Scholz D, Afsah-Hedjri A, Schaper W, Schaper J. Vascular remodeling and altered protein expression during growth of coronary collateral arteries. *J Mol Cell Cardiol* 1998; 30: 2291-2305.
4. Schaper W, Ito WD. Molecular mechanisms of coronary collateral vessel growth. *Circ Res* 1996; 79: 911-919.
5. Arras M, Ito WD, Scholz D, Winkler B, Schaper J, Schaper W. Monocyte activation in angiogenesis and collateral growth in the rabbit hind limb. *J Clin Invest* 1998; 101: 40-50.
6. McCourt M, Wang JH, Sookhai S, Redmond HP. Pro-inflammatory mediators stimulate neutrophil-directed angiogenesis. *Arch Surg* 1999; 134: 1325-1331; discussion 1331-1332.
7. Alderman EL, Stadius M. The angiographic definitions of the Bypass Angioplasty Revascularization Investigation. *Coron Artery Dis* 1992; 3: 1189-1207.
8. Chappell DC, Varner SE, Nerem RM, Medford RM, Alexander RW. Oscillatory shear stress stimulates adhesion molecule expression in cultured human endothelium. *Circ Res* 1998; 82: 532-539.
9. Cavaillon JM. Cytokines and macrophages. *Biomed Pharmacother* 1994; 48: 445-453.
10. Pepper MS. Manipulating angiogenesis: from basic science to the bedside. *Arterioscler Thromb Vasc Biol* 1997; 17: 605-619.
11. Henry TD. Therapeutic angiogenesis: *BMJ* 1999; 318: 1536-1539.
12. Shizukuda Y, Tang S, Yokota R, Ware JA. Vascular endothelial growth factor-induced endothelial cell migration and proliferation depend on a nitric oxide-mediated decrease in protein kinase C delta activity. *Circ Res* 1999; 85: 247-256.
13. Schaper W, Buschmann I. Collateral circulation and diabetes. *Circulation*. 1999; 99: 2224-2226.
14. Henry TD, Annex BH, McKendall GR, Azrin MA, Lopez JJ, Giordano FJ, Shah PK, Willerson JT, Benza RL,

Berman DS, Gibson CM, Bajamonde A, Rundle AC, Fine J, McCluskey ER; VIVA Investigators. The VIVA trial: Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. *Circulation* 2003; 107: 1359-1365.

15. Piek JJ, Koolen JJ, Hoedemaker G, David GK, Visser CA, Dunning AJ. Severity of single-vessel coronary arterial stenosis and duration of angina as determinants of recruitable collateral vessels during balloon angioplasty occlusion. *Am J Cardiol* 1991; 67: 13-17.

16. Abaci A, Oguzhan A, Kahraman S, Eryol NK, Unal S, Arinc H, Ergin A. Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 1999; 99: 2239-2242.

17. Schultz A, Lavie L, Hochberg I, Beyar R, Stone T, Skorecki K, Lavie P, Roguin A, Levy AP. Interindividual heterogeneity in the hypoxic regulation of VEGF: significance for the development of the coronary artery collateral circulation. *Circulation* 1999; 100: 547-552.

**Author Information**

**Mahmoud Mohammadzadeh Shabestari, MD**

**Leila Alizadeh**

**Mehri Nikdoust, MD**

**Fardin Mirblouk, MD**

**Hossein Mehdikhani, MD**

**Mahla Fadavi, MS**

**Javad Mahmoodi**