Coronary collaterals and graft failure

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Chapter 33: Coronary collaterals and graft failure

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Abstract:
In this chapter, we recall the role of the coronary collateral circulation in severe obstructive coronary diseases, and, based on the literature review, we try to provide an answer to the question: when the patients undergo aorto-coronary bypass graft surgery, does good collateral flow reduce the risk of graft disease or, on the contrary, does it increase the risk of graft disease? In order to get additional arguments, a review of the numerical models and simulations addressing this problem is also included in the chapter.

Keywords: coronary artery disease / collateral circulation / bypass grafts / graft failure / numerical simulations

List of abbreviations:
PCI = Percutaneous Coronary Intervention
MACCE = Major Adverse Cardiac and Cerebrovascular Events
CABG = Coronary Artery Bypass Graft
MGF = Mean Graft Flow
CTO = Chronic Total Occlusion
OPCAB = Off-Pump Coronary Artery Bypass
CC = Coronary Collaterals
ITA = Internal Thoracic Artery
PTCA = Percutaneous Transluminal Coronary Angioplasty
CFD = Computational Fluid Dynamics
IMA = Internal Mammary Artery
LMCA = Left Main Coronary Artery
LAD = Left Anterior Descending Artery
LCx = Left Circumflex Branch
RCA = Right Coronary Artery
AMI = Acute Myocardial Infarction
SV = Saphenous Vein

I – Description of the problem: Coronary disease / collaterals / CABG / graft failure

The right and left coronary systems are connected via collateral vessels and anastomoses of their terminal branches. Coronary collateral vessels measuring 100 μm or less in diameter are a normal finding at post-mortem. They are thin-walled, vein-like, anastomotic channels that connect either a proximal to a distal section of the same coronary artery or one coronary artery to another. Although anatomically present, collateral flow is minimal when there is normal antegrade flow in the artery receiving the collateral vessel. However, if there is a stenotic lesion or occlusion of this artery, the resultant decrease in distal coronary pressure produces a pressure gradient across the collateral network leading to a marked increase in collateral blood flow and vessel diameter [1, 2, 3, 4]. This remodeling develops over time in progressive coronary disease and chronic occlusion. Greater severity of coronary disease is often associated with increased presence of collateral vessels. At the extreme, in case of total coronary occlusion, myocardial flow is provided only via collaterals.

The coronary collateral circulation thus provides an alternative source of blood supply to areas of poorly perfused myocardium. It can limit the extent of myocardial ischaemia and cell death, and is better developed in patients with long-standing ischaemic symptoms and arterial stenoses greater than 70%. The protective role of collaterals in hearts with coronary obstructive disease has been demonstrated by many authors, showing smaller infarcts, less aneurysm formation, and improved ventricular function compared with patients in whom collaterals were not visualized [3, 4]. The more extensive is the collateral network, the less severe is the regional dysfunction [5, 6]. Nonetheless, it is important to note that there is marked variability in the amount of collateral flow between different patients with coronary artery disease: some patients develop collaterals at a substantially higher rate than others [4].

The process of collateral vessels recruitment is mainly driven by the creation of a transanastomotic pressure gradient. However, it may be also affected by other factors, such as the size and status of the distal arterial lumen, coronary vascular resistance, blood viscosity, myocardial contractility, physical activity of the subject and comorbidities such as diabetes [3].

Moreover, it is difficult to measure collateral flow clinically, which leaves room for divergent interpretations of the relationship between coronary collaterals and adverse cardiac events [7, 8]. Detection by angiography of collateral flow only provides an estimate of the absolute collateral flow, since only collaterals > 100 μm in diameter are identified through this imaging modality [6]. Besides, the presence of visible collateral vessels does not indicate whether these vessels are effective or not. Other techniques for collateral flow detection, such as myocardial contrast echocardiography, radionuclide techniques, and pressure-derived collateral flow index, are indirect methods with better quantification of collateral flow. Unfortunately, these methods are not easy to incorporate into routine clinical practice and the most widespread evaluation of the collateral circulation remains the one proposed by Rentrop et al. [9] in 1985.

Consequently, there is continuing controversy over whether coronary collateral vessels are protective with respect to future cardiac events or not. It is substantially related to common methodological problems such as relatively low numbers of individuals included in the

studies, short observation periods, and use of surrogate end points for adverse cardiac events such as systolic left ventricular function [7]. Contradicting results may also be caused by a different selection of patients (different pathological situations), by inconsistencies in the definition of collateral circulation, or by the existence of coronary steal when the collateral pathways are altered. At the same time, obviously, more diseased patients are at an increased risk of events irrespective of collateral presence. To estimate the true protective impact of collaterals, adjustment for indicators of disease severity such as degree of stenosis, number of vessels involved, history of the disease and of the medical treatment appears indicated [10].

Another important controversy is related to the best way to restore adequate perfusion to the ischemic myocardium. In aorto-coronary bypass grafting surgery, the graft supplies blood distally to a critical coronary stenosis. Ongoing large clinical trials, for example the SYNTAX study [11, 12], compare surgery and percutaneous coronary intervention (PCI). One major finding was that, after a 5 years follow up, the estimates of MACCE (Major Adverse Cardiac and Cerebrovascular Event) were 26.9% in the CABG group and 37.3 % in the PCI group. Estimates of myocardial infarction (3.8% in the CABG group versus 9.7% in the PCI group) and repeat revascularization (13.7% versus 25.9%) were significantly increased with PCI versus CABG. All cause death (11.4 % in the CABG group vs 13.9% in the PCI group) were not significantly different between groups. They conclude that CABG should remain the standard of care for patients with complex lesions and that PCI is an acceptable alternative for patients with less complex disease. The same recommendation can be found in the *Guidelines on Myocardial Revascularization* [13]. The main advantages of CABG compared with percutaneous coronary intervention (PCI) include lower rate of repeat procedures, greater success rates with chronically occluded coronary arteries, and the protection of the entire vessel proximal to the anastomosis of a mammary artery graft. Optimal surgical results are obtained in the long term with extensive employment of arterial conduits (namely, the Internal Thoracic Artery, ITAs). The greater saphenous vein (GSV) represents a complementary conduit for CABG, although it has been associated with lower patency-rates in the long term. Surgery may also have some disadvantages, and several post-surgical complications have to be taken into consideration (e.g. intimal thickening hyperplasia, restenosis, surgical injury, long term graft failure).

The reliability of CABG as a therapeutic strategy lasts as long as the graft remains patent. An appreciable number of grafts may occlude within a few years of implantation, causing the failure of the procedure. Graft patency may deteriorate over time on the basis of chronic atherosclerotic evolution. At a given follow up time-point, grafts may be perfectly patent, may present mild or severe stenoses, or be occluded. Generally speaking, more than mild stenosis implies graft failure, which needs to be prevented to improve the patient's outcome. Sherwin et al. report a loss of patency in 50 percent of vessels over a ten-year period [14]. Many authors have suggested that local haemodynamics and graft quality may play a role in such atherogenic process. Blood flow velocity, shear stresses, turbulent flow, or, on the contrary, low flow rates and blood stasis may be related to atherosclerotic plaque development and affect the long term patency of the bypass grafts [7, 15]. Regions with flow separation or recirculation (for example, the heel, toe, and bed of an anastomosis) are believed to be atherogenic factors. Once plaque develops and encroaches into the lumen, further flow disturbances are inevitable [14, 16].

The surgical significance of collateral circulation has not been extensively studied. On one hand, collateral circulation maintains conditions which are favorable for the long term success of coronary bypass grafting, by preserving both left ventricular contractility and patency of

the distal coronary segments. On the other, there may be cases in which the auto-revascularization by collateral circulation is sufficient to obviate the necessity of surgical revascularization [1]. Once formed, collaterals may well be less likely to occlude spontaneously than a saphenous vein bypass graft. Postoperative angiography has shown that in some cases coronary bypass may lead to loss of previously well developed collaterals. Thrombosis of a vein graft may also obstruct the collaterals through distal embolization, leaving the patient with a much more severe perfusion deficit.
The question addressed in this chapter is whether good collateral flow may reduce the risk of bypass graft disease or, on the contrary, increase such risk.
In Section II (resp. III), we will present some studies which conclude that collateral flow has a detrimental (resp. beneficial) effect on graft patency. In Section IV, we will present the studies concluding that collateral flow does not influence the graft patency. In regard to these different conclusions, numerical simulations are introduced in Section V, in order to help understanding such contradictions. Section VI recalls that graft failure can be due to many other causes than collateral flow. A new therapeutic direction, aiming at promoting collateral growth in patients with Coronary Artery Disease (CAD) who cannot be revascularized neither by PCI nor by CABG is briefly described in the last Section of the chapter.

II - Studies that conclude that good collateral flow has a detrimental effect on graft patency

There are few papers reaching this conclusion; globally, these argue that the underlying mechanism is related to flow competition.
Kaku et al. [17] investigated whether a well-developed collateral circulation distal to chronically occluded left anterior descending artery competes with the flow of a distally anastomosed graft. Their patients were divided into three groups: Poor collaterals, Group P (Rentrop grade 0 or 1); Moderate collaterals, Group M (Rentrop grade 2); Rich collaterals, Group R (Rentrop grade 3). They show that the intraoperatively measured MGF (Mean Graft Flow) is lower for higher Rentrop grades : 50.4 ± 26.3 ml/min for the patients of group P, 43.1 ± 24.1 ml/min for the patients of group M, and 32.6 ± 14.4.3 ml/min for the patients of group R. They conclude that, when collateral perfusion distal to a Chronic Total Occlusion (CTO) is well developed (high Rentrop grade), there is potential competition between the collateral flow and left ITA graft flow. However, they also performed post-operative coronary angiography and observed that the collateral feeding arteries distal to CTO that had been detected pre-operatively in Group M and R were not observed post-operatively in all patients. The left ventricular ejection fraction, long-term survival and freedom from cardiac events were comparable among the three groups in the following 5 years. They conclude that retrograde collateral circulation could regress over time after revascularization and the competition itself might become not clinically significant in the long term.

Some other papers deal with the flow competition between the collaterals and the antegrade blood flow through dilated native vessels, in patients undergoing PCI. These studies are listed in the Section “Revascularization of stenostic lesions and risk of restenosis” of the review paper by Stoller and Seiler [18]. They conclude that well developed collaterals to a revascularized region are a risk factor for restenosis of the treated lesion. By the way, other authors have pointed out that recanalization of a chronic total occlusion through PCI with drug-eluting stents is associated with a rapid decline in distal collateral function which may expose the patient to higher risk of adverse cardiac events in case of later restenosis [19, 20, 21]. Nonetheless, the discussion of the effects of PCI on the distal collateral circulation is beyond the scopes of the present chapter.

In some cases, worse long term graft patency may not be directly related to flow competition with the collateral circulation, but to the altered microvascular status of the distal territory. For example, Pohl et al. [22] report that two-thirds of their patients do not have enough collateral flow to prevent myocardial ischemia during coronary occlusion. In the study of Bexell et al. [23], a significant correlation is demonstrated between stenosis severity, scar extent in the myocardial territory distal to the affected coronary artery, and collateral flow. Patients with hemodynamically significant stenoses (>70%) exhibited significantly greater collateralization and scar extent than patients with < 70% stenosis. Also, greater stenosis severity and mean scar extent were found in patients with collaterals than in patients without collaterals…

III - Studies that conclude that good collateral flow will improves long-term graft patency

Already in 1974, Levin [1] claimed that the likelihood of a successful outcome after coronary bypass grafting is enhanced if good flow is demonstrated angiographically in the distal segment of an obstructed coronary artery (as a result of antegrade filling, collateral circulation or both). This can be interpreted in the light of the protective effect of the collateral circulation. In the setting of coronary artery disease, it can play a crucial role in limiting the burden of myocardial ischemia, thereby reducing the incidence and magnitude of myocardial injury. Lower distal microvascular resistances would allow higher flow rates in the grafts, thereby reducing the risk of restenosis.
This finding was confirmed by Ozdemir et al. [24]. These authors used transthoracic Doppler ultrasonography to assess left ITA patency and flow after coronary artery bypass grafting. They aimed to show the early effects of preoperative collateral vessels supply to the left anterior descending artery over left ITA graft flow. Thirty-four patients were enrolled in the study: 19 patients with angiographically evident collateral vessels and 15 without collaterals. They concluded that patients with well-developed collaterals to the left anterior descending artery have better flow in the left internal mammary graft and more significant improvement in left ventricular function after coronary bypass. The same conclusion can be found in [25]. In case of an occluded infarct-related artery, Steg et al. [26] have demonstrated that collateral flow to the artery-related territory may be associated with improved clinical outcomes after acute myocardial infarction, and may also determine the benefit of subsequent recanalization of this territory.

Moreover, the presence of collaterals has a particular implication for patients undergoing off-pump coronary surgery (OPCAB), as these collaterals can provide perfusion to the ischemic myocardium intraoperatively during periods of coronary occlusion [4]. During off-pump CABG, the anastomoses are constructed on the beating heart while the target coronary is occluded for about 15 minutes. It is hypothesized that collaterals may protect patients against perioperative myocardial damage during off-pump CABG. The beneficial effects of coronary collaterals on short-term and mid-term outcome in the setting of OPCAB have also been demonstrated by Nathoe et al. [27]. This group demonstrates that Kaplan-Meier estimates of event-free survival at 1 year were 87% in patients with and 69% in those without collaterals after off-pump CABG. The presence of collaterals was associated with a significantly lower rate of any first adverse event in the off-pump but not in the on-pump group. Induction of

complete cardiac arrest during on-pump CABG attenuates and even prohibits the potential protective role of collaterals, if present.

IV - Studies that conclude that collateral flow does not influence the long-term graft patency

IV.1 - Several studies directly compare the graft flow and graft patency between patients with or without a good collateral circulation.

In 1972, Smith et al. [*28*] studied the effects of CABG and coronary collaterals (CC) on myocardial blood flow (MBF) in 24 patients undergoing 29 CABGs (all with saphenous vein graft). The vessels receiving bypass grafts were classified angiographically as follows: group A, vessels with less than 80% obstruction and no collaterals; group B, those with greater than 80% obstruction and no collaterals; group C, those with greater than 80% obstruction and collaterals; group D, those with total obstruction and distal vessel filled by collaterals only. MBF after CABG was compared to pre-existing MBF by intraoperative injection of xenon via distal bypass grafts, the proximal portion of the grafts being occluded or patent. Pressure gradients across bypassed obstructions were measured. The results were correlated with pre-operative coronary arteriograms to determine the effects of CC on MBF and postobstruction perfusion pressures. For the total series, mean MBF was increased by CABG from 32 ± 6 ml/min per 100g (graft occluded) to 118 ± 13 ml/min per 100g (graft open). Vessels with less than 80% stenosis by angiography had pressure gradients less than 20 mmHg across obstructions, high post-obstruction perfusion pressure (75 ± 7 mmHg), and normal MBF (87 ± 6 ml/min per 100g) even during graft occlusion. In this group, the pre-existing pressures and flows were high, and the net contribution of bypass grafts to myocardial blood flow in the rest state was minimal. Vessels with stenosis greater than 80% or total occlusion by angiography presented significant pressure gradients with marked reduction of post-obstruction MBF. No significant difference in postobstruction MBF was found when vessels with CC (Coronary Collaterals) (21 ± 4 ml/min per 100g, for the group D, with the graft clamped) were compared to those without CC (17 ± 4 ml/min per 100g, for the group B, with the graft clamped) . The authors note that, however, collateral flow is low in all vessels studied.

Shimizu et al. [*29*] studied ninety patients who had CABG because of coronary stenosis or occlusion. They divided the patients into two groups: the “collateral group” (angiographically evident collateral circulation) and the “non-collateral group” (without collateral circulation). They concluded that the differences in graft patency and graft flow between the two groups were not statistically significant. However, the surgical mortality was higher (5.4%) in the “non-collateral group” than in the “collateral group” (0%). Left ventricular ejection fraction and myocardial perfusion were significantly improved after CABG in the “collateral group”.

More recently, Caputo et al. [30] assessed the prognostic effect of coronary collaterals on early and midterm clinical outcomes in patients undergoing first-time isolated off-pump coronary artery bypass surgery (OPCAB). They established that coronary collaterals were associated with improved myocardial protection during OPCAB surgery. Although patients with coronary collaterals had more extensive coronary artery disease, poor left ventricular function, and more cardiac risks factors than patients without collaterals, the early and midterm clinical outcome after OPCAB surgery was comparable between the two groups

IV.2 - Additional studies suggest that regression of the collateral network, loss of collateral function, and even inverted direction of collateral flow can be observed after CABG or after removing the obstruction in the collateralized artery. In these circumstances, no flow

competition with the graft can occur and, the pre-operatively established collateral flow has no influence on the graft patency.

Actually, the collateral flow is driven by the pressure gradient between the donor and the recipient artery (the stenosed or even occluded artery). When the obstruction in the recipient artery is removed or bypassed, the pressure gradient is also removed, or even reversed. Some authors have indeed shown that the human collateral channels can serve as a bidirectional functional conduit [31]

In 1978, Uflacker and Enge [32] investigated the behavior of collateral pathways after CABG, since the status of the collateral circulation may be decisive in establishing the suitability of reoperation if occlusion of the graft develops. When the graft was patent, they could not visualize the collateral circulation which had been demonstrated pre-operatively. When the graft was occluded, the collateral circulation observed before surgery was frequently found. They concluded that collateral circulation regresses if bypass grafting is successful, but that collaterals probably are recruited or develop again if grafts become occluded or function poorly. This idea was then supported by Boodhwani [4] who explains that coronary collaterals that are visible prior to CABG disappear in the presence of a patent bypass graft and can reappear if the graft occludes.

In the study of Wang et al. [33], collateral flow was present on preoperative angiography in 19 patients and absent in 25 patients. Baseline collateral flow disappeared after CABG in 12 of 14 patients after bypass of the RCA but persisted in all patients without such intervention.

As explained in Section II, Kaku et al. [17] found that retrograde collateral perfusion tends to be surmounted by ITA graft flow and disappears over time, since collateral channels are supposedly much smaller, providing greater resistance to flow than the ITA graft. Furthermore, ITA graft flow can increase over time, as collateral perfusion declines, since the ITA can autoregulate its flow depending on the demand and resistance of distal myocardial territories.

Similarly, several groups have suggested that collateral flow may disappear after PCI and may reappear if a recurrent occlusion increases again the pressure gradient between donor and recipient artery [5, 31, 34, 35].

V - Numerical simulations that can help to understand what happens

As demonstrated in Sections II, III, and IV, the conclusions of the clinical studies are very different. However, the methodologies employed are also heterogeneous, the baseline patients' characteristics can be difficultly compared, and the methods to estimate the amount of collateral flow are different. Additionally, many other causes than flow competition may be involved in the determinism of graft failure. For these reasons, numerical models and simulations are quite useful and interesting, because they can help understanding the influence of each factors separately, and they can provide a better knowledge of the collateral circulation and of the mechanism of graft failure.

Computational Fluid Dynamics (CFD) methods could enable prediction of changes in coronary flow and pressures after therapeutic interventions (PCI, CABG). For example, computed blood velocity may allow evaluation of shear stresses, and of flow stagnation or, on

the contrary, turbulent flow within bypass grafts. The mechanical properties of the vascular walls may be taken into account. Correlations between local haemodynamic phenomena and atherogenesis or intimal hyperplasia can thus be established. Moreover, advances in numerical methods and three-dimensional imaging techniques have enabled the quantification of cardiovascular mechanics in subject-specific anatomic and physiologic models. Patient-specific modeling has enabled innovative applications of cardiovascular mechanics, namely predicting outcomes of alternative therapeutic interventions for individual patients [36].

V.1 - Models of the coronary circulation.

Some models are based on the use of lumped parameters only [15, 37]. These models use the well-known analogy between hydraulic networks and electric circuits [38]. Other models, for example those developed by the group of Ch. Taylor [39, 40], couple three-dimensional finite elements simulations of the flow in the aorta and arterial system and lumped parameter elements representing the inlet and outlet boundary conditions for the coronary flow. They can thus take into account the interactions between the heart and arterial system, and they can study interactively the changes in cardiac properties, arterial system and coronary arteries. They predict realistic coronary flow and pressure waveforms, and they can study how the degree of a stenosis in the left anterior descending coronary artery affects these waveforms. The significance of coronary lesions is also predicted with a computed model developed by Hose and colleagues [41]. This model combines 3D arterial anatomy reconstruction (from rotational coronary angiography) and Computational Fluid Dynamics (C.F.D.).

V.2 - Simulation of the flow in the graft or in the anastomoses.

Arterial bypass grafts tend to fail after some years due to the development of intimal thickening (restenosis) [42]. Literature findings suggest that factors that influence the progression of the restenosis include:
- individual blood rheology [16, 43],
- local arterial geometry, ratio of the graft to the host artery diameter, placement of the junctions, suture length, anastomotic angle [44, 45, 46]. The velocity profile disturbances are mostly evident in the vicinity of anastomoses. At the heel of the anastomosis, fluid acceleration is observed leading to non-uniform velocity and wall shear stress distributions. On the contrary, low velocity profiles were computed at the toe. In these regions, the simulations showed recirculation zones and flow separation. Such flow behavior is extensively proposed in the literature as the cause for the occurrence of thrombosis [16, 47].
- graft surface characteristics and mechanical properties [15, 46, 48]. It is known that arterial grafts such as the ITA and radial artery grafts provide, in general, better patency than vein grafts. Approximately, 15-30% of saphenous vein grafts occlude within the first year of surgery, with the rate increasing to over 50% after 10 years.
- compliance mismatch between the graft and the coronary artery, that has been suggested as an initiating factor for progress of wall thickening along the suture line. For example, the effect of the wall distensibility on the anastomotic flow and on the intramural stress distribution has been considered by Leuprecht et al. [49]

However, none of the above numerical studies does deal with some eventual presence of collateral flow.

V.3 – Hydraulic / Electric Analogy

Our group has proposed a model of the coronary circulation based on the hydraulic/electric analogy, for patients with three-vessel disease (stenoses of the left main coronary artery (LMCA), left anterior descending artery (LAD), and left circumflex artery (LCx), and with chronic occlusion of the right coronary artery (RCA)), undergoing off-pump coronary surgery. [50, 51, 52]. The simulations provide quantitative estimations of the distribution of flow and pressures across the coronary network for these patients and they allow to study the influence of the severity of native artery stenoses, of the degree of collateral supply developed by the patients and of the revascularization status (no grafts, left grafts only, complete revascularization). This model is less sophisticated than others. Nonetheless, as an element of novelty, it takes simultaneously into account the effect of revascularization, of the grade of native arteries stenoses and of the collaterality. The results seem to be clinically relevant. For example, the simulated values we obtain for the total collateral flow rate, the collateral resistance, the pressure after the RCA occlusion (P_w) are in total agreement with those measured by Goldstein et al. [53] (Q_{col} = 13 ml/min, R_{col} = 450 mmHg.s/ml, and the ratio (P_w / aortic pressure) about 0.5), for the same type of patients and a comparable surgical procedure (the measurements of these authors were performed after the saphenous vein graft was anastomosed distally to the diseased coronary artery but before the graft was connected to the aorta). Goldstein et al. [53] found that patients with greater extension of coronary collaterals (Grade 4) have significantly greater mean values of retrograde flow (15.7 ml/min) and significantly smaller mean collateral resistance (306 mmHg.s/ml). We confirm such trend in our simulations.

The most important features shown by the calculations can be summarized as follows:

a) The values of the distal capillary resistances and of the collateral resistances have a major overall impact on the pressures and flow rates, including the graft flow rates [54, 55]. Such a correlation between graft flow and perfusion of the area depending from the graft has also been demonstrated by Hirotani et al. [56]. Flow rates in the native branches or in the grafts are higher when the distal capillary resistances are lower. In other words, the status of the distal supplied territory influences the graft flow [57].

b) Concordantly with several other authors (see Section I of this Chapter), we find that well-developed collaterals exert a beneficial effect on myocardial viability and ventricular function after acute coronary occlusion. The microvascular damages are reduced [58]. On the contrary, when myocardial ischemia had occurred, for example, for patients who had an AMI (Acute Myocardial Infarction), the perfusion of the right capillary territory is lower (in comparison with the patients who did not have an AMI), due to lower collateral flow rates and higher microvascular resistances. As explained by Nijveldt et al. [59], despite successful recanalization of the infarct-related artery (which corresponds to the cases (1G) (right graft only) and (3G) (all grafts operating) in our study), the perfusion of the ischemic myocardium may not be completely restored in patients with AMI due to microvascular obstruction.

c) In the presence of the left-sided grafts, the flows in the proximal native stenosed arteries become lower. When the LAD graft or LCx graft are present, the pressure drops across the LAD or LCx stenosis are reduced, due to the increased distal pressure induced by the graft. Since the hydraulic resistances of these stenosed arteries remain globally the same, the flow rate drops. Some sort of flow compensation appears between the graft and the native artery, especially if the native artery is not too severely obstructed. Overall, the perfusion of the LAD territory and of the LCx territory is improved in the presence of the left-sided grafts, but this

improvement remains moderate. This feature has been previously documented by other groups. Shimizu et al. [60] demonstrated small graft flows in patients with low-grade native coronary stenosis. Lust et al. [61] suggested that the two flow sources (native artery and graft) interact with each other in the physiological maintenance of distal perfusion requirements, rather than competing against each other. Kawasuji et al. [62] also found that 96% of patients with stenosis > 90% showed graft-dependent flow. Conversely, in another group with stenosis between 76 and 90%, 9% of patients showed native-dominant flow, 29% balanced flow, and 62% graft-dependent flow. This finding indicates that the graft could thus promote progression of native disease (because of the decreased transtenotic flow).

d) In some situations (depending on the relative severity of the LMCA, LAD and LCx stenoses and on the relative values of the capillary and collateral resistances compared to the resistance of the native stenosed artery), some retrograde flow may occur. Under such circumstances, the blood coming from the left-sided graft will preferentially flow through the native stenosed coronary artery rather than through the collateral vessels or towards the distal microvascular territory, since the resistance of the native artery is smaller. We thus obtained a negative flux in the native artery. This phenomenon is less important in the case of severe stenoses on the left-sided coronary branches, since the resistance of the stenosed branch and of the collateral and capillary beds are comparable.

e) In all cases, the amount of collateral flow remains rather low (< 20 ml/min). This result is in agreement with data from the literature [28, 53, 63].

f) When all grafts are operating, the collateral flows between the left and right coronary arteries are negligible. This is due to the fact that the pressure gradient across the collateral network drops to almost zero. Loss of collateral flow after revascularization has been previously discussed in Section IV.2 of this Chapter.

g) Reverse collateral flow may even exist when the right coronary graft is present, especially when the left-sided grafts are not operating: due to the presence of the right graft, the right territory is better perfused and the pressures in the right area become higher than those of the left territories. This has been also demonstrated by other authors: Miyamoto et al. [31] have shown that revascularization of the target artery can reverse the pressure gradient across the collateral network, establishing collateral flow in the opposite direction. …

Overall, in [58], we conclude that patients with a good collaterality (Rentrop Score = 3) or patients without anterior myocardial infarction have i) less severe stenoses of the LMCA, ii) lower microvascular resistances, iii) higher graft flow rates when the revascularization is performed, iv) higher collateral flow rates towards the territory of the occluded artery, v) better perfusion of this area, vi) better total perfusion of the heart.

VI - Other causes of graft failure that are not related to collateral flow

In this Section, we present some clinical studies reporting over graft failures. Some of the clinically identified causes for graft failure are the same as predicted by the numerical simulations, including the target vessel diameter (lower graft patency was shown for smaller vessels), the harvesting technique (because of mechanical damages that may be inflicted during harvesting), the quality of the graft itself, some technical errors with anastomoses, scarce outflow territory and high resistance in distal vessels, … Nonetheless, the cause for

poor blood flow in the graft is not always straightforward [64]. Nakajima et al. [65] suggest that flow insufficiency may be defined as < 15-20ml/min during intraoperative transit-time flowmetry, with more than half of all bypass grafts with < 15 ml/min occluding within several months.

VI.1- Technical problems with the graft or the anastomoses

The causes of early graft failure are often related to technical defects in the proximal or distal anastomoses [66]. Excessive turbulence at the anastomosis site, or kinking or twisting of the graft, have to be avoided [67].

VI.2 - Microvascular damages of the targeted territory

In many cases, a poor graft outcome is related to the microvascular status of the target territory [59, 67, 68, 69]; however, the assessment of the status of the microvascular beds remains challenging.

VI.3 - Mechanical properties of the grafts

The quality of the conduit is obviously crucial: for example, excessively narrow or dilated saphenous vein segments and significantly atherosclerotic grafts should be avoided.

It is also known that inner pressure applied to the saphenous vein graft during harvesting might alter its mechanical properties and thereby decrease its patency in the long-term. Such process may be mediated by mechanotransduction of excessive inner pressure into altered endothelial function [70]. Distending pressures even as low as 50 mmHg can increase the stiffness of the graft and thus impair the graft's function under its new hemodynamic conditions [71, 72].

Besides, significant flow differences exist between arterial and venous grafts. Although arterial grafts have much better long-term patency than venous grafts, they also have a limited ability to supply blood flow at peak myocardial demand. Blood flow through saphenous vein grafts may be 2 to 3 times higher than blood flow through ITA grafts to the same target area. [73].

In [57], Glineur et al. provide a comparative study of the hydrodynamic performances of the left and right ITAs (Internal Thoracic Arteries). The resistance of the left ITA appears significantly higher than that of the right ITA or of the SVG. Several factors could contribute to this finding: i) the territory of the LAD (on which the left ITA is preferentially implanted) is likely to require a larger blood flow supply than other territories for which SV or right ITA are more often used, ii) differences in the 3-dimensional configuration of various types of grafts could affect the transmission of the pressure wave, iii) differences in length and inner diameter of grafts conduits directly affect their resistance to flow. Nonetheless, ITA grafts display dynamic properties that allow chronic adaptation of their flow rates to the features of the distal myocardial territory, based on its extension and microvascular resistances, as well as on the resistance of the target coronary artery.

Clinical practice has associated specific grafts conduits with specific territories: SV graft preferentially used for distal RCA, right ITA for LCx territories, and left ITA for the LAD territory. However, in most studies, grafts used for the right coronary artery usually show the lowest patency rates, regardless of the conduit chosen; targeting the LAD, on the other hand, produces the highest patency rates [67]. Redzek et al. [74] also report that the patency of internal thoracic artery and vein grafts depends on the revascularized coronary artery properties. In their Fig. 1 and 3, they compare the patency (% of patent grafts after several

years) of ITA grafts and venous grafts, according to the degree of coronary artery stenosis (< 75% or > 75%), and in their Fig. 2 and 4, they show the same type of comparison, according to the peripheral diameter of target coronary artery (<1.5 mm or > 1.5 mm). The rates of occluded or patent grafts are different in each case.

VI.4 - Animal studies aimed at improving the comprehension of the mechanism of flow competition.

To determine the impact of LAD-dependent competitive flow (LAD-CF) on distal coronary flow (LAD – DF) and on left internal mammary artery graft flow (LIMA-GF), Karapanos et al. [75] performed a quantitative blood-flow analysis in a swine model of a LIMA-to-LAD coronary artery bypass-graft (CABG). They fixed five levels of LAD-CF: 100%, 75%, 50%, 25% and 0% (corresponding to a progressive occlusion of the native artery) . The reduction of the LAD-competitive flow resulted in a significant increase of LIMA-graft flow, and simultaneous increase of LAD distal flow. They observe that the sum of LAD-CF and LIMA-GF demonstrates no significant change throughout the study, for all the CF (competitive flow) levels. They notice that, in their protocol, the anastomoses were performed on a healthy coronary artery with normal run-off and normal microvascular bed, and no collaterals.

In a previous work, Lust et al. [61] performed CABG in 15 mongrel dogs using the pedicled left ITA anastomosed to the normal, fully patent circumflex coronary artery. After 8 weeks, 2 grafts occluded as a result of poor technical anastomotic construction. In the 13 remaining animals, all grafts were widely patent at all time points. The data suggest that ITA grafts are dynamic and may remain patent despite significant residual flow in the native vessel. Temporary occlusion of either the proximal native vessel or the ITA graft produces reciprocal flow increases in the other vessel, such that distal perfusion was constantly maintained. Rather than competing against each other, the two flow sources seem to interact in the physiologic maintenance of distal perfusion requirements. This study, however, could not provide data over the maintenance of such mechanism in the long term.

VII – New therapeutic direction: promotion of collateral growth in patients with CAD that cannot be revascularized either by PCI or by CABG

This research is advanced by some groups, for example, the group of Ch. Seiler in Bern (Switzerland) [76, 77]. They suggest that approximately one-fifth of patients with CAD cannot be revascularized by percutaneous coronary intervention neither by bypass grafting, and that the therapeutic promotion of collateral growth may be a valuable treatment strategy in those patients. This new approach should aim at stimulating the growth of large conductive collateral arteries (arteriogenesis). Potential arteriogenic approaches include the treatment with granulocyte colony–stimulating factor, physical exercise training, and external counterpulsation.

VIII – Conclusion

Gathering the results of the currently available clinical and computational studies, we may conclude that the collateral circulation has a rather beneficial impact on the outcome of coronary grafts.

Before the revascularization, the collateral flow reduces the microvascular damages in the territory distal to the obstruction, which improves the chances of success of the bypass grafting. When the bypass graft is operating, the collateral flow regresses (it could disappear, or even reverse in the opposite direction). Therefore, no competition occurs between the

collateral flow and the graft flow, and consequently the collateral flow may not be considered as responsible for graft failure. Graft failure, if any, may be due to other causes.
Clinical studies addressing the mid- and long-term patency rates of coronary bypass conduits according to the baseline angiographically evident degree of collaterality, will be needed to finally clarify this issue. Future investigations in this perspective should compare the long-term behavior of arterial and venous grafts with respect to the pre-operative degree of collaterality and to the late recruitment of collaterals in case of graft failure. This could provide additional useful criteria for graft choice in the clinical practice.

IX- References

[1] Levin D. "Pathways and functional significance of the coronary collateral circulation" Circulation, 1974, Vol.50, p831-837.

[2] Samady H., Ragosta M., Beller G. " Coronary collaterals, stenoses, and stents" Jour. Am. Coll. Cardiol. , 2002, Vol. 40(9), p 1551-1554.

[3] Berry C., Balachandran K., L'Allier Ph., Lespérance J., Bonan R., Oldroyd K. "Importance of collateral circulation in coronary heart disease" European Heart Journal, 2007, Vol.28, p278-291.

[4] Boodhwani M."Invited commentary" Ann. Thor. Surg., 2008, Vol.85, p79.

[5] Sabia P., Powers E., Jahaweera A., Ragosta M., Kaul S. "Functional significance of collateral blood flow in patients with recent acute myocardial infarction. A study using myocardial contrast echocardiography" Circulation, 1992, Vol.85, p 2080-2089.

[6] Elsman P., Van't Hof A., de Boer M., Hoorntje J., Suryapranata H., Dambrink J., Zijlstra F., on behalf of the Zwolle Myocardial Infarction Study Group. "Role of collateral circulation in the acute phase of ST-segment-elevation myocardial infarction treated with primary coronary intervention" Eur. Heart Jour., 2004, Vol.25, p854-858.

[7] Billinger M., Kloos P., Eberli F., Windecker S., Meier B., Seiler C. "Physiologically assessed coronary collateral flow and adverse cardiac ischemic events: a follow-up study in 403 patients with coronary artery disease" Jour. Am. Coll. Cardio., 2002, Vol.40(9), p1545-1550.

[8] Spaan J., Kolyva Ch., Van Den Wijngaard J., Ter Wee R., Van Horssen P., Piek J., Siebes M. "Coronary structure and perfusion in health and disease" Philosophical Transactions of the Royal Society A, 2008, Vol.366, p3137-3153.

[9] Rentrop K., Cohen M., Blanke H., Phillips R. « Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J. Am. Coll.Cardiol., 1985, Vol. 5, p587-592.

[10] Regieli J., Jukema J., Nathoe H., Zwinderman A., Ng S., Grobbee D., Van Der Graaf Y., Doevendans P."Coronary collaterals improve prognosis in patients with ischemic heart disease" Int. Jour. Cardiol. , 2009, Vol.132, p257-262.

[11] Kappetein A., Feldman T., Mack M., Morice M. Cl., Holmes D., Stahle E., Dawkins K., Mohr F., Serruys P. and Colombo A. "Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three vessel disease: 3-year follow up of the SYNTAX trial" Eur. Heart Jour., 2011, Vol.32, p 2125-2134.

[12] Mohr F., Morice M. Cl., Kappetein A., Feldman T., Stahle E., Colombo A., Mack M., Holmes D., Morel M.A., Van Dyck N., Houle V., Dawkins K., Serruys P. "Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three- vessel disease and left main coronary disease: 5-year follow up of the randomized, clinical SYNTAX trial" Lancet, 2013, Vol.381, p 629-638.

[13] Guidelines on myocardial revascularization. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur. Heart Jour., 2010, Vol. 31, p2501-2555.

[14] Sherwin S, Shah O., Doorly D., Peiro J., Papaharilaou Y., Watkins N., Caro C., Dumoulin C. "The influence of out-of-plane geometry on the flow within a distal end-to-side anastomosis" Jour. Biomech. Engin., 2000, Vol. 122, p 86-95.

[15] Pietrabissa R., Mantero S., Marotta T. and Menicanti L. "A lumped parameter model to evaluate the fluid dynamics of different coronary bypasses" Med. Eng. Physics, 1996, Vol.18, p 477-484.

[16] Chen J., Lu X.Y., Wang W. "Non-newtonian effects of blood flow on hemodynamics in distal vascular graft anastomoses" Jour. Biomechanics, 2006, Vol.39, p1983-1986.

[17] Kaku D., Nakahira A., Hirai H., Sasaki Y., Hosono M., Bito Y., Suehiro Y., Suehiro S. "Does rich coronary collateral circulation distal to chronically occluded left anterior descending artery compete with graft flow?" Interactive CardioVascular and Thoracic Surgery, 2013, Vol.17, p944-949.

[18] Stoller M. and Seiler Ch. "Pathophysiology of coronary collaterals" Current Cardiology Reviews, 2014, Vol 10, p 38- 56.

[19] Zimarino M., Ausiello A., Contegiacomo G., Riccardi I., Renda G., Di Iorio C., and De Caterina R. "Rapid decline of collateral circulation increases susceptibility to myocardial ischemia" Jour. Am. Coll. Cardiol. , 2006, Vol 48(1), p 59-65.

[20] Meier P., Zbinden R., Togni M., Wenaweser P., Windecker S., Meier B., and Seiler Ch. "Coronary collateral function long after drug-eluting stent implantation" Jour. Am. Coll. Cardiol., 2007, Vol 49(1), p 15- 20.

[21] Kern M. "Attenuated coronary collateral function after drug-eluting stent implantation" Jour. Am. Coll. Cardiol., 2007, Vol 49(1), p 21- 22.

[22] Pohl T., Seiler Ch., Billinger M., Herren E., Wustmann K., Mehta H., Windecker S., Eberli F., Meier B. "Frequency distribution of collateral flow and factors influencing collateral channel development" Jour. Am. Coll. Cardiol., 2001, Vol 38(7), p 1872-1878.

[23] Bexell D., Setser R., Schoenhagen P., Lieber M., Brener S., Ivanc T., Balazs E., O'Donnell T., Stillman A., Arheden H., Wagner G., White R. "Influence of coronary artery stenosis severity and coronary collateralization on extent of chronic myocardial scar: insights from quantitative coronary angiography and delayed-enhancement MRI" The Open Cardiovascular Medicine Journal. 2008, Vol.2, p79-86.

[24] Ozdemir O., Ozdemirel Ozkan D., Soylu M., Duran Demir A., Alyan O., Geyik B., Aras D., Kunt A., Arda K., Sasmaz H., Cobanoglu A. "Effects of previously well-developed collateral vessels on left internal mammary artery graft flow after bypass surgery", Texas Heart Institute Journal , 2005, Vol. 32, p 35-42.

[25] Green D. and Hutton P. "Coronary circulation" Current Anaesthesia and Critical Care, 1999, Vol.10, p70-76.

[26] Steg G., Kerner A., Mancini J., Reynolds H., Carvalho A., Fridrich V., White H., Forman S., Lamas G., Hochman J., and Buller C."Impact of collateral flow to the occluded infarct-related artery on clinical outcomes in patients with recent myocardial infarction: a report from the randomized occluded artery trial" Circulation, 2010, Vol.121, p2724-2732.

[27] Nathoe H., Buskens E., Jansen E., et al. « Role of coronary collaterals in off-pump and on-pump coronary bypass surgery" Circulation, 2004, Vol.110, p1738-1742.

[28] Smith S., Gorlin R. , Herman M. , Taylor W., Collins J. "Myocardial blood flow in man: effects of coronary collateral circulation and coronary artery bypass surgery", The Jour. of Clin. Invest. , 1972, Vol. 51, p 2556-2565.

[29] Shimizu T., Nakajima M., Shimazu K., Sakamoto S., Yuasa K., Aida H., Tsuji S., Takekoshi N., Murakami E. "A comparison of the results of aorto-coronary bypass grafting in collateral and non-collateral groups", The Jour. Cardiovasc. Surg., 1986, Vol. 27(3), p316-322.

[30] Caputo M., Anis R., Rogers Ch., Ahmad N., Rizvi S., Baumbach A., Karsch K., Angelini G., Oberhoff M. "Coronary collateral circulation: effect on early and midterm outcomes after off-pump coronary artery bypass surgery", Ann. Thor. Surg., 2008, Vol. 85, p 71-79.

[31] Miyamoto S., Fujita M., Sasayama S. "Bidirectional function of coronary collateral channels in humans" Int. Jour. Cardiol., 2000, Vol.75, p249-252.

[32] Uflacker R. , Enge I. "The behavior of collateral circulation after coronary artery bypass surgery", Cardiovascular Radiology , 1978, Vol. 1, p 225-227.

[33] Wang J., Filipovic M. , Skarvan K. , Michaux I., Schumann R. , Buser P. , and Seeberger M. "Transesophageal Doppler echocardiographic detection of intramyocardial collateral flow to the right coronary artery and changes in the flow to the inferior left ventricular wall immediately after coronary artery bypass grafting" Am. Jour. Cardiol., 2006, Vol. 98, p1587-1592.

[34] Werner G., Emig U., Mutschke O. , Schwarz G. , Bahrmann Ph. , Figula H. "Regression of collateral function after recanalization of chronic total coronary occlusions " Circulation, 2003, Vol.108, p2877-2882.

[35] Werner G. "The role of coronary collaterals in chronic total occlusions" Current Cardio. Reviews, 2014, Vol.10, p57-64.

[36] Taylor Ch. and Figueroa C. "Patient-specific modeling of cardiovascular mechanics" Ann. Rev. Biomed. Eng., 2009, Vol.11, p109-134.

[37] Geven M., Bohte V., Aarnoudse W., Van Den Berg P., Rutten M., Pijls N. and Van De Vosse F. "A physiologically representative in vitro model of the coronary circulation" Physiol. Measur., 2004, Vol.25, p 891-904.

[38] Olufsen M. and Nadim A. "On deriving lumped models for blood flow and pressure in the systemic arteries" Math. Biosci. Engin., 2004, Vol.1(1), p 61-80.

[39] Kim H., Vignon-Clementel I., Figueroa C., Jansen K., Taylor Ch. "Developing computational methods for three-dimensional finite element simulations of coronary blood flow" Finite Elements in Analysis and Design, 2010, Vol.46, p514-525.

[40] Kim H., Vignon-Clementel I., Coogan J., Figueroa C., Jansen K., Taylor Ch. "Patient-specific modeling of blood flow and pressure in human coronary arteries" Ann. Biomed. Engin., 2010, Vol.38(10), p3195-3209.

[41] Morris P., Ryan D., Morton A., Lycett R., Lawford P., Hose R., Gunn J. "Virtual Fractional Flow Reserve from coronary angiography: modeling the significance of coronary lesions", J.A.C.C.: Cardiovascular Interventions, 2013, Vol.6 (2), p149-157.

[42] Owida A., Do H., Morsi Y. "Numerical analysis of coronary artery bypass grafts: an overview" Comput. Meth. and Prog. in Biomedicine, 2012, Vol.108, p689-705.

[43] Dur O., Coskun S., Coskun K., Frakes D., Kara L., and Pekkan K. "Computer-aided patient-specific coronary artery graft design improvements using CFD coupled shape optimizer" Cardio. Vasc. Engin. Techn., 2011, Vol.2(1), p35-47.

[44] Cacho F., Doblaré M. , Holzapfel G."A procedure to simulate coronary artery bypass graft surgery" Med. Bio. Engin. Comput., 2007, Vol.45(9), p 819-827.

[45] Xiong F., Chong C. "A parametric numerical investigation on haemodynamics in distal coronary anastomoses" Med. Engin. Physics, 2008, Vol.30, p311-320.

[46] Sankaran S., Moghadam M., Kahn A., Tseng E., Guccione J., and Marsden A. "Patient-specific multiscale modeling of blood flow for coronary artery bypass graft surgery" Ann. Biomed. Engin., 2012, Vol.40 (10), p 2228-2242.

[47] Politis A., Stavropoulos G., Christolis M., Panagopoulos F., Vlachos N., Markatos N. "Numerical modeling of simulated blood flow in idealized composite arterial coronary grafts: steady state simulations" Jour. Biomechanics, 2007, Vol.40 (5), p 1125-1136.

[48] Sankaranarayanan M., Chua L., Ghista D., Tan Y. "Computational model of blood flow in the aorto-coronary bypass graft" Biomedical Engineering OnLine, 2005, Vol.4(14), p1-13.

[49] Leuprecht A., Perktold K., Prosi M., Berk T., Trubel W., Schima H. "Numerical study of hemodynamics and wall mechanics in distal end-to-side anastomoses of bypass grafts " Jour. Biomechanics, 2002, Vol.35, p225-236.

[50] Maasrani M., Verhoye J. Ph., Corbineau H., Drochon A. "Analog electrical model of the coronary circulation in case of multiple revascularization" Annals of Biomed. Engin. 2008, Vol.36 (7), p1163-1174.

[51] Maasrani M., Abouliatim I., Ruggieri V.G., Corbineau H., Verhoye, J. Ph., Drochon A. "Simulations of fluxes in diseased coronary network using an electrical model" Proceedings of the IEEE XIX International Conference on Electrical Machines, ICEM 2010, Rome.

[52] Maasrani M., Abouliatim I., Harmouche M., Verhoye J. Ph., Corbineau H., Drochon A. "Patients'specific simulations of coronary fluxes in case of three-vessel disease" J. Biomed Science and Engineering, 2011, Vol. 4, p 34-45.

[53] Goldstein R., Stinson E., Scherer J., Seningen R., Grehl T., Epstein S., "Intraoperative coronary collateral function in patients with coronary occlusive disease" Circulation, 1974, Vol.XLIX, p298-308.

[54] Maasrani M., Drochon A., Abouliatim I., Harmouche M., Corbineau H., Verhoye J. Ph.. Theoretical study of the flow rate towards the right heart territory in case of total occlusion of the right coronary artery. Medical Engineering and Physics, 2013, **35**, p103-107.

[55] Harmouche M., Maasrani M., Corbineau H., Verhoye J. Ph., Drochon A. Coronary three-vessel disease with occlusion of the right coronary artery: what are the most important factors that determine the right territory perfusion? IRBM (Innovation and Research in BioMedical engineering), 2014, **35**, p149-157.

[56] Hirotani T., Kameda T., Shirota S., Nakao Y. An evaluation of the intraoperative transit time measurements of coronary bypass flow. Eur. Jour. Cardio-Thoracic Surgery 2001; 19(6): 848-852.

[57] Glineur D., Poncelet A., El Khoury G., D'hoore W., Astarci P., Zech F., Noirhomme P., Hanet C. "Fractional flow reserve of pedicled internal thoracic artery and saphenous vein grafts 6 months after bypass surgery" Eur. Jour. Cardio-Thoracic Surgery, 2007, Vol.31, p 376-382.

[58] Abouliatim I., Harmouche M, Drochon A., Maasrani M., Corbineau H., Verhoye J. Ph. Coronary flow in patients with three-vessel disease: simulated hemodynamic variables in relation to angiographically assessed collaterality and history of myocardial infarction. ISRN Vascular Medicine 2011; Article ID 470313, 10 pages.

[59] Nijveldt R., Beek A., Hirsch A., Stoel M., Hofman M., Umans V., Algra P., Twisk J. , and Van Rossum A. "Functional recovery after acute myocardial infarction. Comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury". Jour. Am. Coll. Cardiol., 2008*;* vol. 52, pp 181-189.

[60] Shimizu T., Hirayama T., Suesada H., Ikeda K., Ito S. and Ishimaru S. Effect of flow competition on internal thoracic artery graft: postoperative velocimetric and angiographic study. J. Thorac. Cardiovasc. Surgery, 2000, **120**, 459-465.

[61] Lust R., Zeri R., Spence P.et al. "Effect of chronic native flow competition on internal thoracic artery grafts" Ann. Thorac. Surg,, 1994, Vol.57, p45-50.

[62] Kawasuji M., Sakakibara N., Takemura H., Tedoriya T., Ushijima T. and Watanabe Y. Is internal thoracic artery grafting suitable for a moderately stenotic coronary artery? J. Thorac. Cardiovasc. Surgery, 1996, **112**, 253-259.

[63] Rockstroh J. and Brown B.G. "Coronary collateral size, flow capacity, and growth estimates from the angiogram in patients with obstructive coronary disease". Circulation, 2002, vol. 105, pp 168-173.

[64] Jokinen J., Werkkala K., Vainikka T., Peräkylä T., Simpanen J., Ihlberg L. "Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study" European Jour. Cardio-Thoracic Surgery, 2011, Vol. 39, p 918-923.

[65] Nakajima H., Iguchi A., Tabata M., Koike H., Morita K., Takahashi K., Asakura T., Nishimura S., Niinami H. "Predictors and prevention of flow insufficiency due to limited flow demand" Jour. Cardio. Thor. Surg., 2014, Vol. 9:188.

[66] Kieser T.M., Rose S., Kowalewski R., Belenkle I. "Transit time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts" European Jour. Cardio-Thoracic Surgery, 2010, Vol. 38, p155-162.

[67] Reul R. "Will drug-eluting stents replace coronary artery bypass surgery?" Texas Heart Institute Journal, 2005, Vol. 32, p 323-330.

[68] Fearon W., Shah M., Ng M., Brinton T., Wilson A., Tremmel J., Schnittger I., Lee D., Vagelos R., Fitzgerald P., Yock P., Yeung A. "Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction" Jour. Am. Coll. Cardio. , 2008, Vol.51(5), p560-565.

[69] Spies Ch., Mohrs O., Madison J., Fach A., Nowak B., Voigtlander T. "Limited flow reserve in non-obstructed bypass grafts supplying infarcted myocardium: implications for cardiovascular magnetic resonance imaging protocols " Jour. CardioVasc. Magnetic Reson.. 2006, Vol.8, p373-379.

[70] Chello M., Spadaccio C., Anselmi A., Patti G., Lusini M., Sciascio G., and Covino E."Simvastatin reduces CD40 expression in an experimental model of early arterialization of saphenous vein graft" J. Surg. Res., 2006, Vol. 136, p 302-308.

[71] Ozturk N., Sucu N., Comelekoglu U., Yilmaz B.C., Aytacoglu B.N., Vezir O.. "Pressure applied during surgery alters the biomechanical properties of human saphenous vein graft" Heart Vessels, 2013, Vol.28, p237-245.

[72] Zhao J., Andreasen J., Yang J., Rasmussen B., Liao D., Gregersen H. “Manual pressure distension of the human saphenous vein changes its biomechanical properties – implication for coronary artery bypass grafting” Jour. Biomech., 2007, Vol.40, p2268-2276.

[73] Schmitz C., Ashraf O., Schiller W., Jürgen Preusse C., Esmailzadeh B., Likungu J., Fimmers R., Welz A. “Transit time flow measurement in on-pump and off-pump coronary artery surgery”, Jour. Thoracic Cardio. Vasc. Surg, 2003, Vol. 126, p 645-650.

[74] Redzek A., Mihajlovic B., Kovacevic P., Cemerlic N., Pavlovic K., Velicki L.(2011) « Patency of internal thoracic artery and vein grafts according to revascularized coronary artery properties” Med. Pregl., 2011, LXIV (3-4), p137-142.

[75] Karapanos N., Suddendorf S., Li Z., Huebner M., Joyce L., Park S. “ The impact of competitive flow on distal coronary flow and on graft flow during coronary artery bypass surgery” Interactive CardioVascular and Thoracic Surgery, 2011, Vol.12 , p993-997.

[76] Seiler Ch. “The human coronary collateral circulation”, Heart, 2003, Vol. 89, p 1352-1357.

[77] Seiler Ch., Stoller M., Pitt B., Meier P. “The human coronary collateral circulation: development and clinical importance”, Eur. Heart Jour., 2013, Vol. 34, p 2674-2682.