Intracoronary blood flow velocity for evaluation of percutaneous interventions and collateral vascular dynamics
van Liebergen, R.A.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 10

Summary and Interpretation of the Findings

Outlined in the Present Thesis
The major theme of this thesis is the application of intracoronary blood flow velocity measurements as indications for diagnosis and success of therapy.

**Guidance of Percutaneous Coronary Interventions**

Patients with an impaired CFR after balloon angioplasty may benefit from additional stent implantation; i.e., a better long-term clinical and angiographical follow-up. For this reason, assessment of the CFR and/or rCFR directly after angiographically satisfactory balloon angioplasty can be a cost-effective tool for decision making regarding adjunctive stenting. **Chapter 2** demonstrates an overall immediate improvement of absolute and relative CFR toward normal values after balloon angioplasty. Despite the additional lumen enlargement as determined by angiographic variables, there was no further improvement of the absolute and relative CFR after stent implantation. Impaired CFR immediately after successful balloon angioplasty or stent implantation was related to an increase in baseline blood flow velocity. Individual values of distal CFR changed at follow-up in patients without restenosis; i.e., initial high values decreased and low values increased toward values of the reference CFR. Normalization of impaired CFR at follow-up in patients without restenosis after balloon angioplasty or stenting was associated with a reduction of the baseline blood flow velocity toward values seen in patients without impaired CFR, supporting the contention that this phenomenon is predominantly related to a slow recovery of autoregulation of the microvascular bed. A temporary increase in baseline blood flow velocity after percutaneous interventions may be the result of microembolization. Herrman et al demonstrated an increase in baseline blood flow velocity after PTCA (from 17±10 to 36±18) in patients with an elevation in cardiac markers of infarction within 24 hours after PTCA (positive cTnT-test)\(^1\). This was related to thrombemboli dislodging into the microcirculation causing microinfarcts. In contrast to an epicardial coronary arterial obstruction, baseline blood flow into the microembolized area is not reduced, but may actually be enhanced, secondary to an adenosine-related hyperemia of the myocardium surrounding the embolized microregions\(^2,3\). Biochemical markers of myocardial damage were not determined in the present study. Therefore, it cannot be excluded that microembolization may have been operative to explain the temporary increase in baseline blood flow velocity.

Another technique to guide optimal balloon angioplasty is intravascular ultrasound (IVUS) imaging. **Chapter 3** demonstrated for the first time that adjunctive IVUS-guided balloon angioplasty induces an additional increase in hyperemic blood flow velocity related to a reduction of residual lumen obstruction. Subsequent stent implantation resulted in a further increase of coronary luminal dimensions, while the hyperemic blood flow velocity parameters remained unchanged, indicating an absence of a functional residual lumen obstruction after IVUS-guided balloon angioplasty. This suggests the presence of a plateau-phase in the optimal hemodynamic result following IVUS-guided balloon angioplasty. The SIPS trial demonstrated a lower rate of target lesion revascularization at six months follow-up in patients treated with IVUS-guided balloon angioplasty as compared to patients treated with standard balloon angioplasty period\(^4\). Haase et al also reported in an observational study a similar clinical
SUMMARY AND INTERPRETATION

outcome after IVUS-guided balloon angioplasty compared to stent implantation. Moreover, Abizaid et al revealed similar promising long-term outcomes regarding the target lesion revascularization rate and event-free survival after IVUS-guided balloon angioplasty as compared to provisional stent implantation. In conjunction, the data from these clinical trials suggest that IVUS-guided balloon angioplasty may serve as an alternative for stent implantation resulting in a similar clinical outcome. Furthermore, this study confirms an earlier report showing that IVUS allows the safe use of balloons traditionally considered oversized with respect to the occurrence of coronary dissections.

The operators of the DEBATE-2 trial pursued an aggressive approach to obtain an optimal angiographic (DS) and hemodynamic result (CFR) as demonstrated by the percentage diameter stenosis after balloon angioplasty. Chapter 4 study shows that intracoronary hemodynamic guidance of a coronary intervention on top off angiography results in an additional improvement of clinical outcome. Approximately 50% of the patients in the guided balloon angioplasty arm of the DEBATE II study showed to have an unsatisfactory result despite guided balloon angioplasty, which is in accordance with the DESTINI and FROST trials. This subset of patients requires stent implantation to improve the direct hemodynamic and late clinical outcome. However, this indicates that the remaining 50% of the patients showed a good "stent-like" clinical outcome after optimal balloon angioplasty. From a clinical point of view this is an important observation, since a restenotic lesion can be treated easily with a stent, while the treatment of in-stent restenosis is still cumbersome. Furthermore, the provocative low percentage of target lesion revascularization in the subgroup of patients with an optimal result after balloon angioplasty followed by additional stent implantation is in favour of hemodynamic guidance of stent implantation, in contrast to the current clinical practice of primary stenting.

The results of this analysis of the DEBATE II study demonstrate that the clinical benefit of stent implantation following suboptimal and optimal balloon angioplasty is related to a reduction of residual lumen obstruction as determined by angiographic and Doppler flow indices.

The completion of the DEBATE-1 and DEBATE-2 trials provided a large cohort of patients with single vessel disease in which angiographic and hemodynamic measurements were performed before and after percutaneous interventions. This large cohort of patients allows a new analysis to assess more powerful predictors for an optimal clinical outcome after balloon angioplasty. Chapter 5 identified several potential predictors of MACE at 6 months follow-up after univariate analysis in the large cohort of patients with single vessel disease treated with balloon angioplasty. After multivariate logistic analysis, a powerful predictive model for MACE was developed that included Doppler variables before balloon angioplasty (baseline-APV, CFR) and residual stenosis after balloon angioplasty as independent predictors. The risk model was simplified by using the number of risk factors as new predictor for clinical outcome. This model demonstrated a large difference in clinical outcome between patients with a low risk and a high risk. The risk factors for MACE at 6 months follow-up determined in the present study allow easy stratification of patients directly following the procedure. This study indicates approximately 50% of the patients can be identified after balloon angioplasty showing a similar clinical outcome as compared to primary stent implantation.
In conjunction, CFR after balloon angioplasty in combination with residual diameter stenosis are good predictors for clinical outcome. The present thesis demonstrated that an optimal balloon angioplasty guided by CFR may result in a stent-like result while there is accumulating data indicating that this can also be achieved by IVUS-guided balloon angioplasty. Patients in the DEBATE-2 study treated with guided balloon angioplasty to optimal results demonstrated an improvement of CFR after adjunctive stent implantations. This finding contrasts with the results of chapter 2, where CFR after balloon angioplasty remains similar after adjunctive stent implantation. The patients in this single center study described in chapter 2 underwent a more optimal balloon angioplasty in contrast to the patients enrolled in the multi-center study. Moreover, this discrepancy can be explained by the difference in the number of patients included. The remarkable low incidence of cardiac events after optimal balloon angioplasty followed by adjunctive stent implantation is in favour of hemodynamic guidance of coronary stent implantation. However, it cannot be excluded that the selection of patients, predominantly single vessel disease and probably minimal microvascular disease, may also have contributed to the excellent clinical outcome.

When using the new defined risk factors determined in chapter 5, clinical outcome after balloon angioplasty in patients with no risk factors is almost equal as following the aforementioned superior clinical outcome after adjunctive stent implantation, while the presence of only a single risk factor yields a clinical outcome similar to primary stent implantation.

Evaluation of the Hemodynamics of the Coronary Collateral Circulation

The establishment of the time period required for maturation of pre-existing collateral vessels in humans has important clinical implications. Experimental studies have indicated that myocardial infarct size is determined by the size of the myocardium at risk, the duration of coronary occlusion and collateral flow to the jeopardized myocardium\(^9,10\). Clinical studies have demonstrated that a short period of preceding angina (24-48 hours) exerts a protective effect as documented by an approximately 25-30% reduction in myocardial infarct size. Chapter 6 demonstrates that such a time period is too short for effective collateral vascular development. The protective effect does not seem to be exerted by collateral flow but is most likely due to ischemic preconditioning, presumably related to stimulation of adenosine-A1 receptors and opening of ATP-dependent potassium channels. Chapter 6 illustrates that a patient without preceding angina runs a high risk of developing a large myocardial infarction following abrupt coronary occlusion due to the fact that collateral vessels are absent and a protective effect related to ischemic preconditioning is lacking. Furthermore, clinical studies have demonstrated that the time window for reperfusion therapy can be increased in the presence of collateral flow to the jeopardized myocardium\(^11-13\). Finally, clinical studies using myocardial contrast echocardiography following the acute phase of myocardial infarction have demonstrated that collateral vascular supply to the occluded vascular bed is associated with an improved left ventricular function after revascularization\(^14,15\).

Chapter 6 indicates that the clinical information on the duration of angina and the use of nitrates
SUMMARY AND INTERPRETATION

allows the prediction of spontaneously visible and recruitable vessels with a 75% overall accuracy. Furthermore, the clinical and angiographical variables predict recruitability of collateral vessels with an 80% overall accuracy. These findings are important for risk stratification of patients undergoing interventions for ischemic coronary syndromes.

The results of Chapter 7 indicate that the presence of recruitable vessels during acute balloon coronary occlusion reduces signs of ischemia, often through transiently increased flow in the donor coronary resulting in increased collateral flow in the recipient coronary artery due to a reduced collateral vascular resistance. This study expands previous preliminary findings by combining measurements in both the donor and recipient coronary arteries. Blood flow velocity measurements in the donor and recipient coronary arteries allows exploration of the dynamics of the collateral circulation during acute coronary occlusion. Analysis of blood flow velocity in the donor artery yields a similar predictive value for recruitability of collateral vessels as blood flow velocity measurements in the recipient coronary artery, while this latter analysis has a better predictive value for the development of electrocardiographic signs of ischemia. Furthermore, collateral flow in the recipient artery and the coronary wedge/aortic pressure ratio were better predictors for ischemia than collateral flow assessed in the donor artery or angiographic grading of collateral vessels. This study underlines the importance of physiological parameters for the evaluation of the function of recruitable collateral vessels.

The coronary blood flow velocity analysis of the donor or recipient coronary artery in combination with coronary wedge pressure measurements in the setting of coronary angioplasty allow to determine flow and resistance of the collateral vascular bed. The methods described provide an important potential tool to gain insight into the coronary hemodynamics in humans. Furthermore, these techniques facilitate the study of the pharmacological responsiveness of the collateral circulation in obstructive coronary artery disease.

The pharmacological responsiveness of the collateral circulation in conscious humans has only been studied in an indirect fashion16-18. Collateral flow was determined directly in Chapter 8 using blood flow velocity analysis of the recipient coronary artery during balloon coronary occlusion. Coronary collateral blood flow can be increased by adenosine and nitroglycerin in a selected cohort of patients with 1-vessel disease and spontaneously visible collateral vessels in contrast to patients with recruitable collateral vessels. This effect of these vasodilators is a result of a reduction of the collateral vascular resistance and the peripheral vascular resistance of the recipient coronary artery.

It is possible that the pharmacological responsiveness of spontaneously visible collateral vessels, documented in the present study constitutes the background for the observed endorsement of thrombolytic therapy by nitroglycerin treatment in the presence of collateral vessels5. Although the present study indicates that recruitable collateral vessels are not responsive to vasodilatory therapy, these vessels become spontaneously visible, and potentially responsive to pharmacological modulation, in a relatively short time span of 10-14 days in sustained coronary occlusion19. Consequently, the pharmacological responsiveness of collateral vessels in this situation may alleviate cardiac symptoms or improve left ventricular function. These findings may stimulate further research for evaluation of other pharmacological agents that are effective in modulating coronary collateral vascular resistance.
Furthermore, a recent study suggests that the collateral flow increase after administration of vasodilators in patients with a chronic coronary occlusion may be positively related to the functional integrity of the myocardium as reflected by the left ventricular function\(^{20}\). Although this relationship was evaluated in a limited number of patients, the potential impact requires further analysis before and after revascularization. In addition, the observed large variation in the collateral flow response in patients with spontaneously visible collateral vessels requires further study as it may be important to select patients who may benefit from conservative therapy or who are candidates for revascularization.

**Chapter 9** is the first study evaluating the functional significance of coronary collateral vessels, i.e., absence of ischemia, in relation to pressure and flow-derived variables in a relatively large cohort of patients. The results show a gradual increase in hemodynamic estimates of the collateral vascular conduction in patients without collateral vessels to patients with maximal development of collateral vessels in subtotal or total coronary occlusions. The assessed hemodynamic variables are better markers for the evaluation of functional significance of recruitable collateral vessels than coronary angiography. Furthermore, \(V_{\text{col}}\) and \(P_{\text{w/Pao}}\) are independent predictors for development of myocardial ischemia during brief coronary occlusion emphasizing that the assessment of both variables provides complementary information.

Furthermore, this study documents the maximal collateral vascular circulation in obstructive coronary artery disease represented by a \(P_{\text{w/Pao}}\) of \(-0.45\) and a \(V_{\text{col}}\) of \(-10\) cm in patients with recruitable or spontaneously visible collateral vessels. Obviously, this extent of the collateral vascular circulation is inadequate for myocardial perfusion in order to relieve patients from stress-induced symptoms. Nevertheless, it is possible that symptomatic patients are a selection of patients with inadequate adaptation of the coronary collateral circulation as compared to asymptomatic patients with coronary artery disease. At present the factors determining the maximal collateral vascular circulation are the subject of experimental studies that may lead to new treatment modalities in the near future.

**Future Perspectives**

This thesis has been driven by the rapid development of new techniques of guide wire technology and focused on the functional evaluation of stenosis, restenosis and collateral circulation. The techniques have proven to be very valuable and allowed important conclusions. It also has many promises for the future. The well established protective role of the collateral circulation has stimulated many research groups in modifying and evaluating the protective collateral vascular conductance using growth factors in obstructive arterial disease. This constitutes a potential therapeutic modality for patients not eligible for percutaneous or surgical revascularization. This may be achieved by stimulation of capillary network growth (angiogenesis) or collateral artery growth (arteriogenesis) would be of potential benefit to these patients. Angiogenesis (by VEGF-A or FGF-1) refers to sprouting of endothelial cells leading to capillary networks and promising results have been reported both in peripheral and coronary artery disease\(^{21,22}\). However, these capillary networks are not designed to conduct high volumes of blood as be required for
adequate relief of symptoms in patients with obstructive peripheral or coronary artery disease. Arteriogenesis refers to the growth of preexisting collateral arterioles with a better potential to meet metabolic demands. This process is mediated via increased shear stress and transformation of monocytes into macrophages who produce cytokines and growth factors (MCP-1, TNT-a, b-FGF) involved in arteriogenesis. Promising results concerning arteriogenesis have reported using animal studies. These findings cannot be extrapolated to the human setting without any reserve, as the results in animal studies were performed in acute ligation models that is in marked contrast with patients in whom the atherosclerotic process has progressed for several decades. Moreover, traditional techniques to assess myocardial perfusion such as SPECT and PET-scan have not been validated to quantify alterations in collateral flow. The studies described in this thesis emphasize the dynamic behaviour coronary collateral vasculature and potential modulation of it's resistance assessed by intracoronary physiological parameters. A recent report by Seiler et al demonstrated in humans the potential of growth factor therapy in coronary artery disease evaluated by intracoronary physiological parameters. This emphasizes that the presented validation studies in humans in this thesis demonstrated that these novel techniques are appropriate to assess modifications of collateral vascular growth by novel therapeutic treatment modalities, such as arteriogenesis induced by growth factors.

References


22. Isner JM, Pieczek A, Schainfeld R, Blair R, Haley L, Asahara T, Rosenfield K, Razvi S, Walsh K,
