Intracoronary blood flow velocity for evaluation of percutaneous interventions and collateral vascular dynamics

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Introduction
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General Introduction

A Doppler tipped guide wire (Flowire) was introduced a decade ago, facilitating blood flow velocity measurements distal of coronary narrowings. Before this technical refinements of guide wires, blood flow measurements were only possible proximal to a coronary lesion using a Doppler equipped guiding catheter or 3F Doppler tipped catheters. The Doppler tipped guidewire allows assessment of epicardial flow velocity providing information of the functional significance of coronary narrowings and enables evaluation of the coronary microcirculation in normal and pathological conditions. The most important areas of interest for studying the coronary circulation are:

- assessment of the function severity of a coronary lesion, in particular relevant in intermediate lesions
- guidance of balloon angioplasty or stent implantation
- evaluation of the dynamics of the collateral circulation
- assessment of the endothelial function

The thesis focusses on guidance of balloon angioplasty or stent implantation and evaluation of the dynamics of collateral circulation.

Guidance of Percutaneous Coronary Interventions

Balloon angioplasty was the initial technique of percutaneous revascularization in patients with significant obstructive coronary artery disease. The relative high incidence of restenosis (30-50%) was an important drawback of initial balloon angioplasty procedures. This process of restenosis starts already directly after balloon deflation due to (sub-) acute recoil. Several studies demonstrated better angiographical and clinical outcomes following an optimal initial angiographic result after balloon angioplasty (<30% DS). This finding contributed to a altered therapeutic strategy, the so-called “the bigger, the better” doctrine. New techniques were developed to further decrease residual luminal obstructions after PTCA such as directional atherectomy and subsequently stent implantation. The deployment of a stent prevented sub-acute recoil resulting in a larger initial lumen after the procedure. The incidence of coronary restenosis following conventional balloon angioplasty was reduced by stent implantation in particular due to its favourable effect on epicardial remodelling following PTCA (15-20%). Stent implantation became the treatment of choice to treat coronary narrowings, due to a reduction in the incidence of procedural complications (dissections), its simplicity in use and a favourable long-term clinical outcome. However, the occurrence of in-stent restenosis is a major drawback that is, at present, still difficult to treat. This resulted in an increase of interest in provisional stent implantation, i.e. to use stent implantation only in those patients with an suboptimal result after balloon angioplasty. Angiography (a planar two-dimensional silhouette of the lumen) alone is insufficient to assess an optimal result after percutaneous interventions,
as the severity of a coronary lesion consists of an anatomic and a functional component, that requires more adequate visualization using intra coronary ultrasound imaging or a physiological parameter to assess the functional improvement after the percutaneous intervention.

Therefore, several applications (intravascular ultrasound (IVUS) imaging\(^4^6\), coronary flow velocity reserve (CFR)\(^7^10\), or pressure-derived fractional flow reserve (FFR)\(^11\)) were used to guide balloon angioplasty towards optimal (or “stent-like”) results. IVUS provides morphologic information of a coronary narrowing without physiological assessment of the coronary narrowing. Guidance with IVUS provides better information of the true lumen after the intervention, making it possible to upsize balloons safely\(^4^12\), and after intervention, making it possible to correlate the true residual lumen to clinical outcome\(^4^6^13\).

Several studies used the CFR to assess the functional severity of a residual lesion to guide balloon angioplasty. An observational multicenter trial, Doppler Endpoints Balloon Angioplasty Trial Europe 1 (DEBATE-1)\(^7\), revealed a combination of two predictors for a better 6-months clinical outcome after successful balloon angioplasty in patients with single vessel disease; i.e. residual diameter stenosis ≤35% combined with distal CFR >2.5 after balloon angioplasty. Patients with an optimal result showed a 16% incidence TLR at 6 months follow-up, which was significant better as the 34% of those patients with a DS >35% and/or a CFR ≤2.5.

Subsequently, several multicenter randomized trials were performed to compare provisional versus direct stent implantation. Both the French Randomized Optimal Stenting Trial (FROST)\(^8\) and the Doppler Endpoint STenting INTernational Investigation (DESTINI)\(^10\) trial adopted the cutoff value for DS (35%) from the DEBATE-1 trial as a predictor for clinical outcome. However, the FROST and DESTINI study used lower cutoff values for CFR after balloon angioplasty (2.2 and 2.0, resp.) due to the inclusion of patients with multivessel, more diffuse, coronary artery disease. Stent implantation was performed in 48% of the patients in the FROST study and in 57% of the patients in the DESTINI trial who were randomized to provisional stent implantation. Major adverse events after provisional stenting was similar to the events after direct stent implantation in both the FROST (15.1% vs 16%, resp.) and DESTINI (12% vs 14%). The DEBATE-2 trial demonstrated similar results after provisional and primary stent implantation in patients with single vessel disease (14.4% vs 13.4% MACE, resp.). However, this trial showed that provisional stent implantation was more expensive and adjunctive stent implantation after optimal balloon angioplasty demonstrated a very low incidence of MACE (6.5%).

In conjunction, these multicenter studies underscored the clinical significance of CFR measurements for guidance of percutaneous coronary interventions. Despite the relevant contribution of CFR measurements for patient management, the mechanisms responsible for an optimal or suboptimal CFR following percutaneous coronary interventions are poorly understood.

**Evaluation of the Hemodynamics of the Coronary Collateral Circulation**

Pathomorphological studies in the 1950’s, using cast-corrosion techniques, had clearly shown the existence of numerous anastomoses in all myocardial layers\(^14^15\). The collateral
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circulation appeared to be present at birth and increases, independent of a person’s gender, in accordance with the physiological growth of the coronary vascular tree. These observations were confirmed by Fulton’s cautiously performed angiographic studies. The abundance of collateral vessels in all myocardial layers in the normal heart indicated that the adaptive changes of the collateral circulation in obstructive coronary artery disease are a result of enlargement of preexisting arterial anastomosis rather than neovascularization.

Pathomorphological studies reported that myocardial infarct size was frequently smaller than the size of the diseased vascular bed. Likewise, numerous investigations have reported that myocardial damage is frequently absent in spite of a total coronary occlusion. These observations, relating collateral vascular supply to myocardial infarct size, constitute major arguments in favour of the functional importance of collateral vessels.

The introduction of coronary arteriography at the end of the 1960’s generated a large number of studies that confirmed the conclusions of the pathomorphological studies. The initial angiographic studies demonstrated that collateral vessels only become angiographically present in subtotal obstructive lesions and in particularly in total coronary occlusions.

Subsequently, the introduction of balloon angioplasty created a model to study the collateral circulation during acute coronary occlusion. Rentrop et al. demonstrated a marked discrepancy between spontaneous and recruitable collateral vessels, using contralateral contrast injection during balloon occlusion. This illustrates that the angiographical appearance of collateral vessels considerably depends on the pressure gradient exerted on the vascular bed. This observation underlines the importance of recruitable vessels, indicating that in previous studies, which did not acknowledge these vessels, may have classified their patients incorrectly. Furthermore, these investigations demonstrated that a coronary wedge pressure >30 mm Hg is indicative of angiographical appearance of collateral vessels during coronary occlusion. Presence of collateral vessels during brief coronary occlusion, documented by assessment of recruitable collateral vessels or coronary wedge measurements, coincides with the reduction of electrocardiographic signs of ischemia and left ventricular dysfunction.

Numerous reports have underlined the functional significance of the coronary collateral circulation in obstructive coronary artery disease. Despite these important observations, there was limited information on the factors associated with collateral vascular responses in humans. Initial angiographical studies using the angioplasty model showed that duration of angina and coronary severity are important factors promoting collateral vascular growth. Moreover, the knowledge regarding the dynamic behaviour of the human collateral circulation was based exclusively on angiographic studies. Few studies have been performed to express the development of the collateral circulation in terms of flow and resistance. Several studies demonstrated that alterations of coronary blood flow velocity in the contralateral donor artery during angioplasty can be used as a novel method to assess collateral flow. In these studies, coronary blood flow velocity analysis was performed using a 3F Doppler catheter.

The introduction of a Doppler tipped guide wire permitted assessment of collateral flow in the ipsilateral recipient artery distal to the balloon. This unique approach for assessment of collateral flow is easy to perform in the setting of coronary angioplasty and allows detection of collateral flow from other sources than the contralateral coronary artery. Blood flow velocity
measurements distal of the occluded balloon quantified collateral flow by means of the mean collateral peak velocity integral. During balloon occlusion, collaterals were able to supply $\pm 30\%$ of the flow provided antegrade after successful PTCA$^{51,52}$.

Initial reports evaluated hemodynamic estimates (pressure or blood flow velocity) of the collateral vascular circulation in relation to the angiographic grading of collateral vessels according to Rentrop's classification before balloon coronary occlusion without classifying recruitable collaterals during coronary occlusion.

The introduction of the Doppler Flowwire made it possible to measure blood flow velocity and wedge pressure during balloon occlusion. The coronary occlusion wedge pressure was measured at the tip of the balloon catheter through the fluid-filled lumen during balloon inflation. The collateral vascular resistance can be assessed by combined measurement of collateral flow velocity and coronary wedge pressure in the recipient coronary artery. However, no previous studies were performed using both pressure and flow-derived variables which are of crucial importance for the evaluation of the hemodynamics of collateral vascular circulation.

Moreover, the pharmacological responsiveness of the collateral circulation in humans remains uncertain. Several clinical studies reported improvement in myocardial perfusion due to enhanced collateral flow after the intravenously administration of vasodilators, although this beneficial effect could be related also to the alterations in preload or afterload$^{53-55}$. The results of studies that evaluated the hemodynamics of collateral circulation after intracoronary administration of vasodilators were subject to criticism for the technique applied to assess collateral flow$^{56}$.

In conjunction, both contralateral contrast injection during balloon occlusion to assess angiographic presence of recruitable collateral vessels and combined pressure-flow velocity measurements are necessary for appropriate evaluation of collateral vascular growth in response to epicardial narrowing in coronary artery disease.

Aims of the Present Thesis

The present thesis is strongly driven by the development of sensor equipped guidewires. The application of these wires allows functional evaluation of the coronary circulation in normal and pathological conditions. The thesis focusses on the following main themes:

**guidance of balloon angioplasty or stent implantation**

- To study the immediate and long-term effects of PTCA on the distal coronary flow velocity reserve balloon angioplasty with coronary stent implantation.
- To determine the physiological gain after standard balloon angioplasty and adjunctive IVUS-guided balloon angioplasty and stent implantation by serial measurements of distal hyperemic blood flow velocity.
- To evaluate hemodynamic alterations after stent implantation following suboptimal or optimal balloon angioplasty.
- To identify more powerful independent predictors of major adverse cardiac events (MACE) within 6 months follow-up after balloon angioplasty by means of a multivariate
analysis to guide optimal balloon angioplasty and stent implantation.

evaluation of the hemodynamics of the coronary collateral circulation
- To determine clinical and angiographical predictors for recruitability of collateral vessels during acute coronary occlusion.
- To evaluate the dynamic responses of the collateral circulation in both the donor and recipient vascular bed during acute transient coronary occlusion.
- To determine the predictive values of physiological variables for recruitability of collateral vessels during acute coronary occlusion.
- To evaluate the pharmacological responsiveness of the coronary collateral circulation in patients with recruitable and spontaneously visible collateral vessels
- To evaluate the relationship between angiographic presence of collateral vessels, hemodynamic variables of the collateral vascular circulation and signs of ischemia during balloon coronary occlusion.

References


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