Physiological and morphological aspects of coronary revascularisation

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Cornelis Josefus Bernard Maria Botman

Wijsheid van Jezus Sirach 6;18-37

*“Mijn kind, laat je van jongs af aan onderrichten,
dan vind je nog wijsheid wanneer je grijze haren hebt.
Benader haar als iemand die ploegt en zaait,
wacht op haar goede vruchten.
Haar verwerven kost je wel enige moeite,
maar al vlug zul je van haar vruchten eten.
Hoe hard is de wijsheid voor wie niets geleerd heeft,
een dwaas houdt het niet bij haar uit.
Ze drukt op hem als een steen die zijn kracht beproeft,
hij zal niet aarzelen die van zich af te gooien.
De wijsheid is wat haar naam inhoudt,
haar betekenis is niet voor iedereen te doorzien.
Luister, mijn kind, aanvaard mijn inzicht,
wijs mijn raad niet af.
Doe de boeien van de wijsheid om je voeten,
leg haar juk op je nek.
Zet je schouders onder haar en til haar op,
laat je niet hinderen door haar boeien.
Benader haar met hart en ziel,
volg met al je kracht haar wegen.
Zoek haar, spoor haar op, dan leer je haar kennen.
Heb je haar in bezit, laat haar dan niet gaan.
Tenslotte zul je rust bij haar vinden
en zal ze jou tot vreugde worden.
Haar boeien bieden je een machtige bescherming,
haar juk wordt een sierlijk gewaad.
Want haar juk is een gouden tooi,
haar boeien zijn een purperen weefsel.
Als een sierlijk gewaad trek je haar aan,
als een vreugdekrans zet je haar op je hoofd.
Mijn kind, als je wilt zul je onderricht krijgen,
als je je inspant zul je verstandig worden.
Als je van luisteren houdt zul je inzicht krijgen,
als je je oren gebruikt zul je wijs worden.
Begeef je onder oude mensen,
hang aan de lippen van de wijzen onder hen.
Luister met genoegen naar elk gesprek over God
en laat geen wijze spreuk je ontgaan.
Als je een verstandig mens leert kennen,
zoek hem dan in alle vroegte op
en laat je voeten de dorpel van zijn deur verslijten.
Richt je aandacht op de voorschriften van de Heer
en denk bij alles wat je doet aan zijn geboden.
Hij zal je sterken en je de wijsheid schenken waarnaar je verlangt.*

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Cover design by Kees-joost and Hilde Botman.
The hands of our children binding together symbolising among other things the indissolubility of cardiothoracic surgeons and interventional cardiologists.

Physiological and Morphological Aspects of Coronary Revascularisation

Proefschrift

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de Rector Magnificus, prof.dr.ir. C.J. van Duijn, voor een commissie aangewezen door het College voor Promoties, in het openbaar te verdedigen op dinsdag 11 december 2007 om 16.00uur

door

Cornelis Jozefus Bernard Maria Botman

geboren te Hoorn

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prof.dr. N.H.J. Pijls
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prof.dr.ir. F.N. van de Vosse

Copromotor:
dr. J. Schönberger

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Chapter 1
Introduction

History of coronary bypass surgery

Coronary bypass surgery was initiated in 1964. It was a remarkable case of interpolation of an autogenous saphenous vein between the aorta and a coronary artery performed by Michael DeBakey on November 23, 1964. This was the first successful aorto-coronary bypass grafting procedure. A seven year follow-up study revealed the graft to be widely open. The concept behind this effort was that the symptoms and events associated with coronary artery disease were related to stenotic lesions that could be identified by coronary angiography, and if those lesions could be treated with bypass grafting, unfavorable symptoms and events would be less common. Experience has shown the correctness of this concept, but it also has shown that atherosclerosis is a progressive disease.

Venous bypass grafts

Early bypass operations were almost entirely performed with aorta-to-coronary saphenous vein grafts. Patency rates were influenced by the coronary artery size , surgical technique and grafted artery (better patency when the left descending artery was grafted). Angiographic follow up studies showed a late attrition rate of 2 to 5 percent per year after operation. (1,2) The late attrition appears to be related to intrinsic pathologic changes in those grafts. During the first year after surgery thrombosis and/or fibro-intimal proliferation predominates.(3) It is important to realize that despite the imperfection of vein grafts , many of these grafts provide substantial long-term benefit.

Internal thoracic artery grafts

Early patency rates of internal thoracic artery grafts are slightly better than vein grafts but, more important, the late attrition is extremely low.(1,4) The most common cause of internal thoracic artery graft failure appears to be competition in blood flow through a native coronary artery that is only moderately stenotic. That may produce a functional closure or "string sign". It is said that atretic internal thoracic artery grafts may increase in size if the stenosis of the non-significant native coronary artery becomes more significant in time but no systematic studies have been performed to investigate this phenomenon. It has been claimed that patency rates of internal thoracic artery grafts are the highest when the left anterior descending-diagonal system is grafted, although Dion restudied 135 internal thoracic artery to the left circumflex artery and noted a 95% patency rate after 13 months as well.(5) Not much is known about internal thoracic artery graft to the right coronary artery. Up till now, the left internal thoracic artery to left descending artery graft is the most effective and longest lasting treatment of coronary artery disease.

Radial artery grafts

A widely used alternative arterial graft is the radial artery. The radial artery is a long graft and somewhat larger in size than the internal thoracic artery. As with other arterial grafts , the radial artery is less effective in situations with competitive flow. Radial artery grafts are not as reliable as internal thoracic artery grafts but may be superior to venous grafts over the long term if they prove to be resistant to late graft atherosclerosis. Over the short term, if "string sign" is seen as graft failure, the patency rate of the radial artery graft is lower than the patency rate of the vein graft. In contrast to the vein graft, radial artery graft patency is also related to the site of anastomosis.(6)

Stenosis severity and graft patency

It has been suggested that grafting of less critical stenosis, which may imply lower flow rates through the bypass graft, may be a risk factor of early dysfunction of the bypass graft.(7) This important hypothesis has never been studied in a mathematical model , nor in a vitro-model, nor prospectively in a human study.

In regular clinical practice , coronary arteries eligible for surgical re-vascularisation are selected on a subjective basis: visual estimation of the stenosis severity on the coronary angiogram.

The shortcomings of coronary angiography for correct assessment of functional stenosis severity are well known for decades and are even more pronounced after coronary bypass surgery. (8).

For this reason, cardiologists have searched for more accurate functional methods to indicate the impact of a stenosis on blood flow.

Functional assessment of bypass grafts

Fractional flow reserve calculated from coronary pressure measurements permits reliable assessment of the functional severity of a stenosis in a coronary artery. At this moment, fractional flow reserve is the gold standard for functional stenosis severity of a lesion in a coronary artery, with a threshold of 0.75 to detect ischemia. (9).

Fractional flow reserve can also be considered as an inverse measure of resistance of a particular conduit. If there is no resistance at all along the conduit, the pressure in the distal and proximal part of the conduit should be equal, even at maximum blood flow. With increasing resistance, the decline of pressure will be more pronounced.

Until recently, only few data have been available about fractional flow reserve in bypasses. It has been suggested that resistance in an internal thoracic artery would be higher than in vein grafts. In earlier studies, it has even been suggested that resistance in an internal thoracic artery would be so high that ischemia could result, especially shortly after surgery before hyperplasia had occurred and when a large myocardial territory was depending on the graft.

In a recent study, the functional capacity of bypass grafts 6 months after surgery was investigated by FFR measurements.(10) It was shown that even in a left internal thoracic artery bypass graft, placed on a normal viable anterior wall, the resistance to blood flow under maximal hyperaemic conditions is small, although not negligible. A value of fractional flow reserve of 0.90 indicates, although mild resistance is present, the function of the graft is far above the treshold at which myocardial ischemia might occur.

In that study, it was shown that normal venous bypass grafts had a resistance that is almost completely negligible (0.96) and therefore comparable to a normal coronary artery.(10) This means that if the native coronary artery is occluded, fractional flow reserve can be used to assess bypass graft function in the same way as in native coronary arteries.

Objectives of this thesis

The objectives of this thesis are: 1. to acquire more insight in the mutual influence of native artery blood flow and bypass function, both from the theoretical point of view and in a prospective clinical study; 2. to compare functional methods, especially FFR with anatomic standards (both invasive as non-invasive) in subsets of patients after bypass surgery; and 3. to investigate the usefulness of FFR in patients with multivessel disease to stratify them in one arm suitable for PCI and another arm more suitable for CABG (so-called ‘tailored-approach’).

Outlines of this thesis

The thesis starts with an outline about the different invasive and non-invasive methods to evaluate coronary artery disease either morphologically and functionally.

(Chapter 2.)

To study the flow through a bypass graft in relation to functional stenosis severity in a native vessel, we developed a mathematical resistance model and a sophisticated, physiologically representative in vitro model mimicking the epicardial coronary arteries, bypass grafts and microcirculation. **(Chapter 3.)**

In these models we tested the hypothesis on decrease of flow in several types of bypasses in relation to the functional stenosis severity in the native coronary artery, both for bypass grafts with a smaller diameter (i.e. left internal thoracic artery) and bypass grafts with a larger diameter (i.e. venous bypass graft). Next, this hypothesis was tested in patients in a prospective clinical trial **(Chapter 4.)**: In 164 patients admitted for coronary bypass surgery, not suitable for percutaneous intervention and with at least one intermediate lesion, fractional flow reserve (FFR) was measured in all vessels that were intended to be grafted, in such a way we tried to establish if a lesion was functionally significant or not. The surgeon was blinded to these results and performed the surgery based on classical angiographic data. One year after surgery, repeated coronary angiography was performed to establish bypass graft patency.

Further on, we conducted two studies to evaluate the physiologic and anatomic result after surgical angioplasty of the left main coronary artery. In the first study in 31 patients, anatomic evaluation of surgical left main angioplasty was performed after 8 years follow up by angiography and IVUS and compared to functional evaluation by FFR. **(Chapter 5.)**

In the second study, the results of coronary angiography and MRI as well as FFR measurements were compared in 18 patients 8 years after surgical angioplasty of the left main coronary artery. **(Chapter 6.)**

Finally, we tested a patient-tailored approach of revascularization in 150 patients with anatomic 3-vessel disease guided by FFR measurements: In patients with functional 3-vessel disease, bypass surgery was performed and in patients with functional 1- or 2-vessel disease (not including the proximal left anterior descending artery) PCI was performed. Outcome in both groups was compared during a 24-months follow-up. **(Chapter 7.)**

References

1. Lytle BW, Loop FD, Cosgrove DM, et al. Long-term (5 to 12 years) serial studies of internal mammary artery and sapheneous vein coronary bypass grafts. J Thorac Cardiovasc Surg 1985;89:248-58
2. Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass fate and patient outcome: Angiographic follow-up of 5056 grafts related to survival and re-operation in 1388 patients during 25 years. J Am Coll Cardiol 1996;28:616-26
3. Bourassa MG, Campeau L, Lesperance J. Changes in grafts and coronary arteries after coronary bypass surgery. Cardiovasc Clin 1991;21:83-100

4. Loop FD, Lytle BW, Cosgrove BM, et al. Influence of the internal mammarial-artery on 10-year survival and other cardiac events. N Eng J Med 1986;314:1-6
5. Dion R, Etienne PY, Verhelst R, et al. Bilateral mammary grafting. Clinical, functional, and angiographic assessment in 400 consecutive cases. Eur J Cardiothorac Surg 1993;7:287-94
6. Desai ND, Cohen EA, Naylor CD, et al. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. N Eng J Med 2004;351:2302-9
7. Wilson RF, Marcus ML, White CW. Effects of coronary bypass surgery and angioplasty on coronary blood flow and flow reserve. Prog Cardiovasc Dis 1988;31:95-114
8. Zir LM, Miller SW, Dinsmore RE, et al. Interobserver variability in coronary angiography. Circulation 1976;53:627-30
9. Pijls NHJ, de Bruyne B, Peels K, et al. Measurements of fractional flow reserve to assess the functional severity of coronary artery stenosis. New Eng J Med 1996;334:1703-8
10. Glineur D, Poncelet A, El Koury G, et al. Fractional flow reserve of pedicled internal thoracic artery and saphenous vein grafts 6 months after bypass surgery. Eur J Cardiothorac Surg 2007;31:376-82.

Chapter 2

Physiological and morphological methods to assess coronary artery disease

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Introduction

To evaluate the condition of native coronary arteries and venous and arterial bypass grafts, several methods can be used. These methods can be divided in morphological and physiological methods.

In this chapter coronary angiography, intra-vascular ultrasound (IVUS), magnetic resonance imaging (MRI), multi-slice computed tomography (MSCT), fractional flow reserve (FFR) measurement and intra-vascular Doppler are discussed .

The discussion will be focused on their utility to evaluate coronary artery disease.

Invasive morphological methods

Coronary angiography.

History. Throughout the 1960s and 1970s, cardiac catheterisation was primarily a diagnostic procedure that was used to evaluate hemodynamics, ventricular function, and coronary anatomy. However, the introduction of interventional devices in the 1980s made catheterisation an important tool in the treatment of coronary artery disease.

Till the present time, coronary angiography remains the standard to which all morphologic methods of diagnosing coronary artery disease are compared.

It is the primary method of defining coronary anatomy in human.

Coronary angiography not only provides an anatomic map of the coronary arteries but also the characteristics of distal vessels in terms of size, atherosclerotic disease and identification as well as function of collaterals.

Sones ushered in the modern era of coronary angiography in 1958 when he developed a safe and reliable method of selective coronary angiography by using an antecubital incision over the brachial artery. (1).

Percutaneous arterial catheterisation, described in 1953 by Seldinger, was first used to study coronary arteries in 1962 (2). Modification of catheters were made by Amplatz and Judkins in 1967 (3,4).

At the present time also the radial approach is used in coronary angiography (5).

Angiographic views and interpretation. The viewing and interpretation of coronary angiograms is of vital interest to cardiologists and cardiac surgeons if they have to make informed decisions about their patients.

Filming is done in a number of projections so that all coronary arteries can be visualized throughout their length and significant disease can be detected and quantified. In most laboratories 5 standard views are used to visualize the left coronary artery and 2 to visualize the right coronary artery.

Limitations of coronary angiography. Despite significant improvements in the quality of coronary angiography, a number of limitations are inherent to this method. Film interpretation is subjective, different angiographers may interpret stenosis severity quite differently, although correlation of angiography with post mortem findings has been acceptable (6). Underestimation and overestimation of lesions is a problem that in most cases can be resolved with filming in more views (7).

As with any invasive procedure, small risks are associable with coronary angiography. The magnitude of the risk is influenced by certain factors as skill of the angiographer and instability of clinical symptoms, but primarily by the extent of the disease found at angiography (8).

For clinical decision making, however, the major disadvantage of coronary angiography is the often poor correlation between anatomic severity of abnormalities on the coronary angiogram and their functional severity in terms of blood flow impairment.

It is well known that both symtoms and prognosis of patients with coronary artery disease are in most cases strongly related to the presence and extent of inducable ischemia. The latter is directly related to decreased blood flow rather that to anatomic abnormalities.

For these reasons, functional assessment of both native coronary arteries and bypass grafts has become increasingly important and often mandatory for optimum decision making with respect to revascularization.

Intra-vascular ultrasound (IVUS).

Rationale for IVUS. As visual interpretation of coronary angiograms exhibits significant observer variability and angiography often underestimates the extent of atherosclerosis, misinterpretation often occurs (9,10). IVUS has several unique properties in the detection and quantitation of coronary artery disease (11). In contrast to regular angiography, not only the lumen of the vessel is imaged but also the wall. In the development of atherosclerosis, mostly considerable, disease is present in the arterial wall, IVUS assesses and quantifies this "burden of disease" much more reliable. Moreover, the cross-sectional perspective of IVUS permits visualisation of the full 360 degree circumference of the vessel wall. Accordingly, measurement of the lumen area can be determined by planimetry independent of the angiographic projection or magnification (11,12). The tomographic perspective of IVUS enables evaluation of vessels difficult to assess by angiography including diffusely diseased segments, bifurcation lesions and ostial lesion. After stent implantation, IVUS enables careful control of adequate deployment of all struts.

Limitations and artefacts. IVUS devices generate artefacts that may adversely affect image quality, alter interpretation or reduce quantitative accuracy (13).

Since the minimum size of the current devices is 0.9mm, some stenosis cannot be crossed and not be visualized .

Geometric distortion can result in an elliptical rather than circular imaging plane (14).

Mechanical devices may exhibit cyclical oscillations in rotational speed resulting in non-uniform rotational distortion (NURD), arising from mechanical friction within the catheter drive shaft (14). Finally, IVUS is expensive, somewhat time-consuming and requires quite a bit of experience to be optimally used.

Safety of IVUS. Although IVUS requires intra-coronary instrumentation, the incidence of complications is low, 1.1 percent in data from European centres. The most frequent encountered complication is focal coronary spasm. Other complications that are related to instrumentation in the coronary artery are vessel dissection or perforation and guidewire entrapment (15-17).

Non-invasive morphological methods

Magnetic resonance imaging (MRI)

Coronary artery imaging. Coronary artery MRI is considered a very challenging area. Coronary arteries are small structures and follow a tortuous course, and are intimate with many surrounding structures, making them difficult to visualize (18).

Moreover, the rapid movements of coronary arteries during a heartcycle influence the imaging of these structures.

The blind prospective detection of coronary artery lesions with coronary MRI is being evaluated with several techniques. So far, no single technique has emerged that can provide the sensitivity and specificity of catheter-based x-ray contrast angiography (19-21).

Coronary bypass grafts. MRI has been used to evaluate bypass grafts. The more stationary position and straight path of the internal thoracic artery and the venous bypass contribute to the relative ease at which these vessels may be visualized by MRI.

A major obstacle for bypass graft imaging is the local signal loss and artefact with implanted metallic objects as homeostatic clips. In addition grafts with tight stenosis may result in insufficient contrast penetration to characterize graft patency (22-24).

Also for imaging of the rather large and stationary left main coronary artery, MRI may be suitable and was evaluated in chapter 5 and 6 of this thesis.

Multi-slice computed tomography (MSCT)

Native coronary arteries. MSCT can be used as non-invasive technique to visualize the epicardial coronary arteries. It requires the injection of intra-venous contrast material. A scout scan is performed to localize the position of the heart in the chest. Thereafter, contrastagent is administered at a rate of 4 ml/s. Due to the worse temporal solution of MSCT, beta-blockers are often given to decrease the heart rate. The radiation exposure of MRI is extremely high.

The sensitivity and specificity to detect significant stenosis is 96 and 91 percent (25). This is encouraging, however several points must be emphasized: MSCT cannot assess 20% of all coronary arteries due to technical factors such as respiration artefact, the presence of calcification and motion artefacts. The motion artefacts predominantly occur in the right coronary artery and the circumflex artery.

In general, MSCT can best assess the proximal and middle segments of the coronary arteries. Due to limited spatial resolution, distal segments and side branches less than 2 mm in diameter cannot be adequately visualized, and MSCT cannot quantify stenosis severity.

Bypass grafts. MSCT can be used to visualize coronary artery bypass grafts and to assess their patency. The specificity is 78% and the sensitivity more than 90%. The accurate detection of internal thoracic arteries was somewhat lower than for venous grafts, as was the detection of distal anastomotic sites (26).

Apart from the suboptimal imaging of coronary arteries by the non-invasive methods, especially when compared to coronary angiography, the poor relation between (apparent) morphologic abnormalities and their functional significance remains a major problem, as will be discussed later.

Physiological methods

Coronary Flow Reserve (CFR)

Coronary flow reserve (CFR) is defined as the ratio of hyperemic blood flow in a coronary artery to resting (baseline) flow. (46). The concept of CFR has contributed to the understanding of coronary physiology in an unequaled way. However, for clinical use and decision making, CFR has a number of considerable limitations. First, there is a wide range of normal value, ranging from 2.0-6.0, depending on age, patient, gender, etcetera. No sharp cut-off value is available to decide which vessels are normal.

Second, CFR varies with hemodynamic loading conditions, blood pressure, heart rate and contractility. An identical stenosis may result in completely different CFR value with different blood pressure or heart rate.

Finally, CFR strongly depends on resting flow which is almost never obtained in the catherization laboratory.

Technically, a major limitation of CFR is that direct blood flow measurement in the catherization laboratory is very hard and mostly surrogate measures of the CFR are used by Doppler measurements or temperature measurement (mean transit time ratio's).

For all of those reasons, a more practical index for assessment of funcional stenosis severity had to be developed, as discussed in the next paragraph and frequently used in this thesis: Fractional flow reserve.

Fractional Flow Reserve (FFR)

For over 40 years, the technique of coronary angiography has played a pivotal role in the diagnosis and treatment of patients with ischemic heart disease (1,4). However, as explained above, coronary angiography has several well recognized limitations (9,10). Most importantly the pathophysiological significance of a stenosis cannot be judged reliably from the angiogram alone, whereas both for quality of life and prognosis of a patient, inducibility of ischemia as reflected by the functional significance of a stenosis is most important (29). In this respect it is important to define that a stenosis is called functionally significant, hemodynamically significant or physiologically significant if it is able to limit maximum achievable blood flow (induced by adenosine, given intra-venously) to such a degree that ischemia of the myocardium supplied by that particular stenotic artery can be induced if the patient is sufficiently stressed.

A number of studies confirmed a poor correlation between anatomic estimation of coronary narrowings and physiologic measures of coronary function, especially in ranges of 50-90% diameter stenosis (30). It was shown repeatedly that in patients with angiographically significant coronary disease, outcome was clearly related to the extent of inducible ischemia and not to the anatomic degree of narrowing (31,32).

In that respect, it is important to realize that the physiological impact of a coronary artery stenosis on blood flow is determined by interaction with several other factors such as aortic pressure, central venous pressure, collateral flow, and resistance and size of the depending myocardial bed (33,34). To overcome these limitations of coronary angiography, and to obtain more information on blood flow and to improve clinical decision making, additional techniques have been developed such as intracoronary pressure measurements.

Concept and practical set-up. The exercise tolerance of patients with stable coronary artery disease is determined by maximum achievable myocardial blood flow. In the presence of a stenosis, the exercise level at which ischemia will occur is directly related to the maximum coronary blood flow that is still achievable by the stenotic vessel. Therefore, not *resting flow* but only *maximum achievable blood flow* to the myocardium at risk is the best parameter to determine the functional capacity of the patient. Expressing myocardial blood flow in absolute dimensions, however, has some disadvantages because this is dependent on the size of the distribution area which is unknown and will differ between patients, vessels and distribution areas. It is therefore better to express maximum achievable (stenotic) blood flow in relation to normal maximum blood flow. Therefore, the ratio between maximum achievable stenotic blood flow and maximum achievable normal blood flow was introduced and this index was called fractional flow reserve (FFR) (35-37). Fractional flow reserve is defined as the maximum achievable blood flow to a distribution area in the presence of a stenosis as a ratio to the normal maximum achievable blood flow to that distribution area in the hypothetical situation the supplying vessel would be completely normal. In other words, fractional flow reserve expresses maximal blood flow in the presence of a stenosis as a fraction of normal maximum blood flow. This index is not dependent on resting flow and is therefore not subject to many of the limitations related to the concept of coronary flow reserve.

How to determine FFR. Under circumstances generally present in the coronary catheterization laboratory it is impossible to determine the ratio of maximum flow in the presence of a stenosis in relation to normal maximum coronary blood flow directly. However, by using a pressure-monitoring guidewire at maximum hyperemia it is possible to calculate this ratio of flows by a ratio of pressures. This is explained in figures 1 and 2.

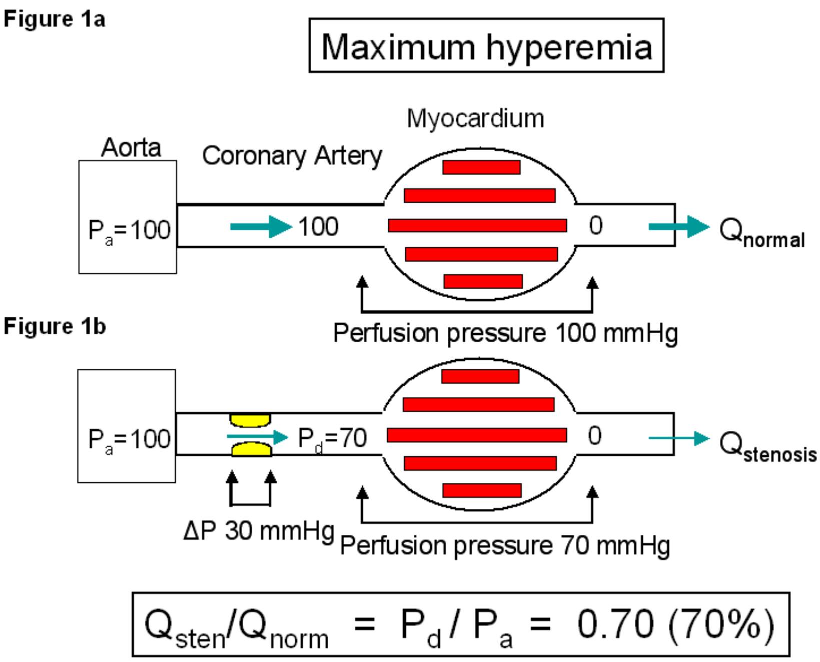


Figure 1a. *Schematic representation of a normal coronary artery and its dependent myocardium, studied at hyperemia. In this normal situation, the (conductive) coronary artery gives no resistance to flow, and thus distal coronary pressure is equal to aortic pressure. Assuming that venous pressure is zero, perfusion pressure across the myocardium is 100 mm Hg.*

Figure 1b.*The same coronary artery, now in the presence of a stenosis. In this situation, the stenosis will impede blood flow and thus a pressure gradient across the stenosis will arise (ΔP=30 mm Hg). Distal coronary pressure is not equal anymore to aortic pressure, but will be lower (P_d=70 mm Hg). Consequently, the perfusion pressure across the myocardium will be lower than in the situation that no stenosis was present (perfusion pressure is now 100-30=70 mm Hg). Because during maximum hyperemia, myocardial perfusion pressure and myocardial blood flow are linearly proportional (see fig. 2), the ratio of maximum stenotic and normal maximal flow can be expressed as the ratio of distal coronary pressure and aortic pressure at hyperemia: FFR=P_d/P_a=70 mm Hg. Importantly, it is distal coronary pressure at hyperemia which determines myocardial flow, and not the pressure gradient across the stenosis.*

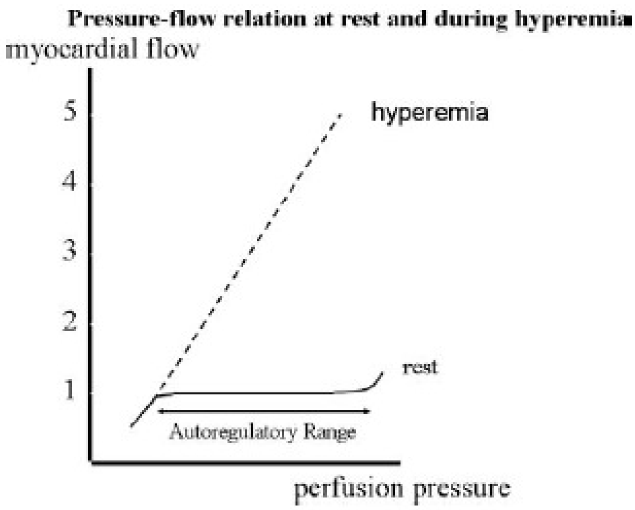


Figure 2. *As opposed to the resting situation, at maximum hyperemia, myocardial perfusion pressure is linearly proportional to myocardial flow.*

Figure 1a represents a normal coronary artery and its dependent myocardium. Suppose that this system is studied at maximum vasodilation. In this situation, myocardial resistance is minimal and constant, and maximum myocardial hyperemia is present, as is the case at maximum exercise. In this situation, as can be seen in figure 2, myocardial perfusion pressure and myocardial flow are linearly proportional, and a change in myocardial perfusion pressure results in a proportional change in myocardial flow. In the case of a normal coronary artery (fig 1a), the epicardial artery only has negligible resistance to flow, and the pressure in the distal coronary artery is equal to aortic pressure. In the example, therefore, myocardial perfusion pressure (defined as distal coronary pressure P_d minus venous pressure P_v) equals 100 mm Hg. In case of a stenosis however (fig 1b), because of this stenosis there will be resistance to blood flow, and distal coronary pressure will be lower than aortic pressure: a pressure gradient across the stenosis exists (in the example Pa-Pd = 30 mm Hg) and myocardial perfusion pressure will be diminished (in the example Pd-Pv=70 mm Hg). In the example, therefore (fig 1b), myocardial perfusion pressure has decreased to 70mm Hg. Because during maximum hyperemia, myocardial perfusion pressure is directly proportional to myocardial flow, the ratio of maximum stenotic and normal maximum flow can be expressed as the ratio of distal coronary pressure and aortic pressure at hyperemia.

Therefore:

$$FFR_{myo} = \frac{\text{Maximum myocardial blood flow in the presence of a stenosis}}{\text{Normal maximum myocardial blood flow}}$$

Can be expressed as:

$$FFR_{myo} = \frac{(P_d - P_v)}{(P_a - P_v)}$$

Because generally, central venous pressure is close to zero, the equation can be further simplified to:

$$FFR_{myo} = \frac{P_d}{P_a}$$

As P_a can be measured in a regular way by the coronary or guiding catheter, and P_d is easily obtainable by crossing the stenosis with a sensor-tipped guidewire, it is clear that FFR_{myo} can be simply obtained, both during diagnostic and interventional procedures, by measuring the respective pressures. From the equations above it is also obvious that FFR_{myo} for a normal coronary artery will equal 1.0.

In numerous studies, it has convincingly been shown that treating a coronary stenosis in patients with a fractional flow reserve below 0.75-0.80 improves functional class and prognosis, whereas treating stenoses above that threshold does not improve prognosis and therefore is not recommended (37-39). More specifically, FFR<0.75 has 100% specificity for indicating inducible ischemia associated with that particular stenosis (36,37,39), whereas a FFR>0.80 has a sensitivity of >90% for excluding inducible ischemia.

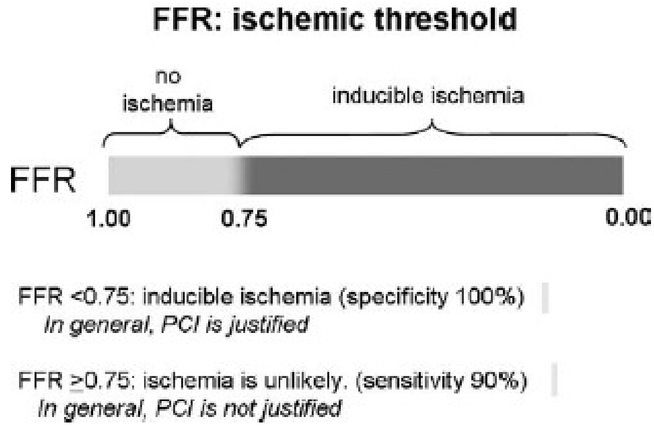


Figure 3. *Schematic representation of the threshold values of FFR. It has been convincingly shown that if FFR is < 0.75, ischemia in this myocardial territory will be inducible, and that in this situation by treating a focal stenosis, the prognosis as well as the complaints of the patient will improve. If FFR is >0.80 on the other hand, it is almost certain that treating an angiographically visible stenosis will not alter the patient's complaints nor prognosis. If FFR is in the small "grey zone" between 0.75 and 0.80, close attention should be paid to individual patient's characteristics (such as site and extent of perfusion abnormalities on noninvasive testing, typical or atypical complaints etc.) to guide sound clinical decision making.*

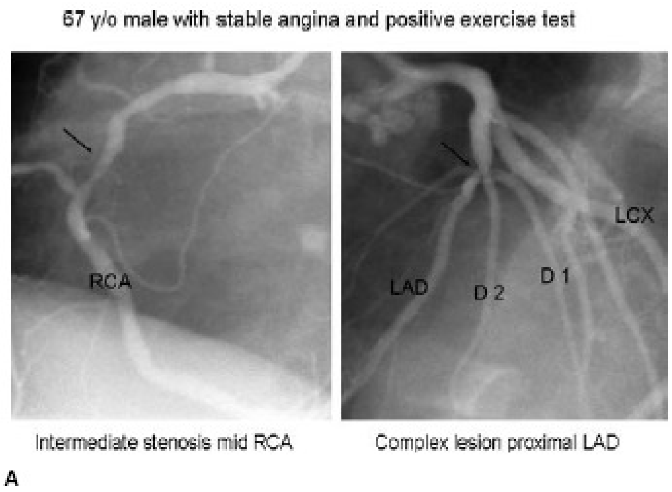
Utility of coronary pressure measurement during coronary interventions. In clear-cut cases of typical chest-pain, positive non-invasive testing and single vessel stenosis, it is not necessary to use any physiologic method to justify a coronary intervention. However, complaints of patients are often not very typical, and non-invasive testing is often equivocal or just not performed. Moreover, coronary disease is often diffuse, complex, affects multiple coronary arteries, and it is often unclear if and to what extent a particular stenosis contributes to ischemia. In such cases, FFR measurements can reliably identify culprit lesions and thus avoid unnecessary interventions which may increase risk without any benefit for the patient. Furthermore, as will be discussed later, FFR measurements can be used to evaluate the result of an intervention and subsequent prognosis. In almost all specific patient groups, the above described threshold values are universally usable, including multivessel disease and previous myocardial infarction. The only situations where FFR should not be used, or with caution, is in the setting of acute coronary syndromes and severe left ventricular hypertrophy.

In other words, FFR accurately distinguishes which coronary stenoses or segments need to be treated and which not.

Multi-vessel coronary interventions. The majority of patients in the catheterization laboratory have multivessel disease.

However, with the expansion of possibilities in interventional cardiology, like the evolution of drug-eluting stents with lower restenosis rates, it is a tendency that more and more patients qualify for interventional treatment and it will become increasingly important to determine which lesions should be stented and which not. It is unwise to implant a large number of stents in the same vessel in these patients, for several reasons. First, the advantage of reducing the reintervention rate using drug-eluting stents will disappear with an increasing number and length of implanted stents. The risk of subacute stent thrombosis is 3-5% in the first year and also because of that reason, unnecessary stents should be avoided. Second, making a metal cast of a coronary artery will disturb flow, affect perforating branches and will have a negative influence on normal physiology. Third, the treatment will become expensive and future bypass surgery becomes less attractive. Moreover, as was demonstrated extensively by several studies, only haemodynamically significant lesions need to be treated and dilation of functionally non-significant lesions should be avoided (32,38).

It is the presence and extent of inducible ischemia which determines the prognosis in these patients, not the angiographic extent of disease. Therefore, for an optimum benefit from drug-eluting stents in patients with complex disease and multiple abnormalities, it is mandatory to make a strategic selection of those arteries and/or locations in which stenting will be the most effective. This means that detailed spatial, focal, and segmental information about the functional impact of all the abnormalities is required. Coronary pressure measurements give a detailed answer to all these questions. For a typical example of the usefullness of FFR in these patients, see figure 4.



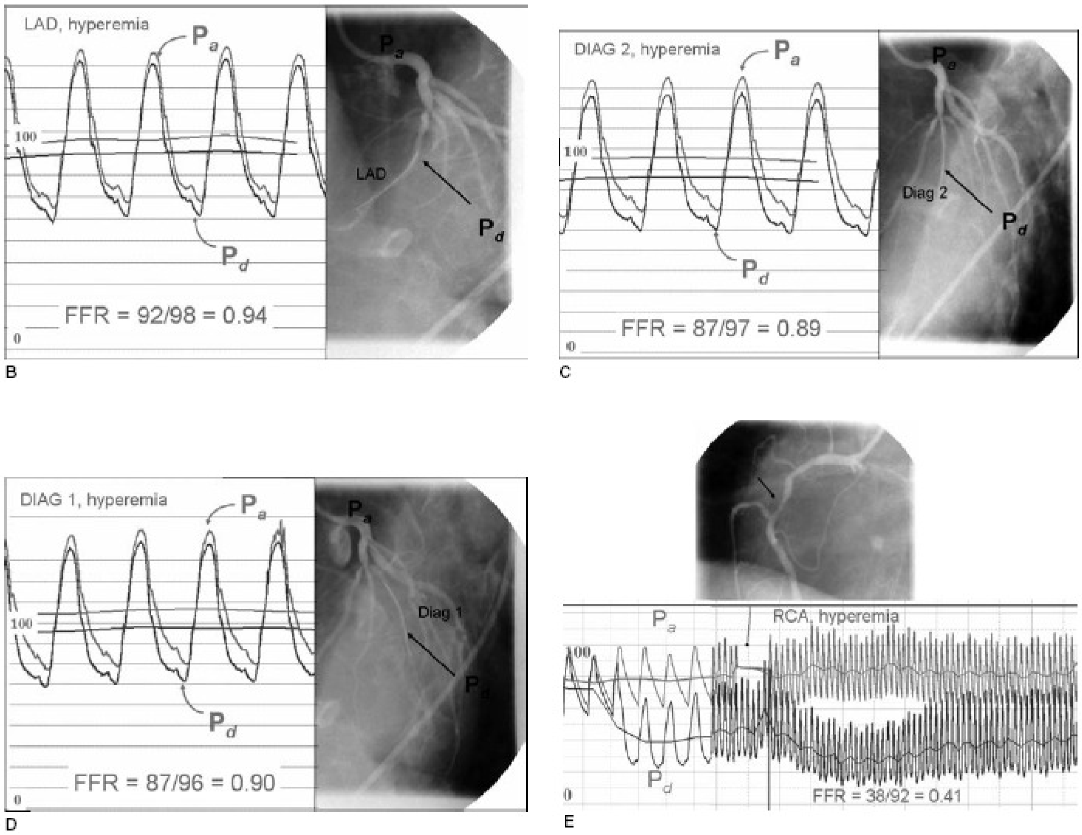


Figure 4. *Example of the usefulness of FFR in a patient with multivessel abnormalities. This 67 year-old patient had typical angina and a positive exercise test. At angiography, a complex lesion at the proximal LAD was found, as well as an intermediate stenosis in the mid RCA. To guide clinical decision making, FFR was measured in the LAD and in both diagonals, as well as in the RCA. As the pressure tracings show, the complex and angiographically severe lesion in the proximal LAD was not hemodynamically significant, as opposed to the angiographically mild RCA lesion. The RCA lesion was treated percutaneously and thus an unnecessary CABG or hazardous PCI of the LAD was avoided. The patient did well after 4 years of follow-up.*

Diffuse epicardial disease. Ischemia in a myocardial territory can be the result of a focal stenosis, and in this case it makes sense to perform PCI. On the other hand, myocardial ischemia can also be the result of a diffusely atherosclerotic coronary artery without a demonstrable focal lesion. In the case of a diffusely diseased vessel, stenting certain segments or spots will not be beneficial to the patient, unless focal obstruction to flow exists. The pressure pull-back curve is a helpful instrument for assessing the presence and the extent of such diffuse disease. As can be seen in figure 5, the FFR measured distally in the LAD is 0.71, which means that myocardial ischemia is certainly inducible in this region. When making the hyperemic pull-back curve, it can be clearly seen that the pressure decline in the artery is gradual, and there is no sudden pressure drop corrsponding to a focal stenosis. This means that this patient cannot be helped with PCI and should be managed medically. On the other hand, in other patients with similar diffuse disease, coronary pressure measurement may indicate a particular location where a pressure drop occurs. In such cases, stenting the respective spot or segment is recommended.

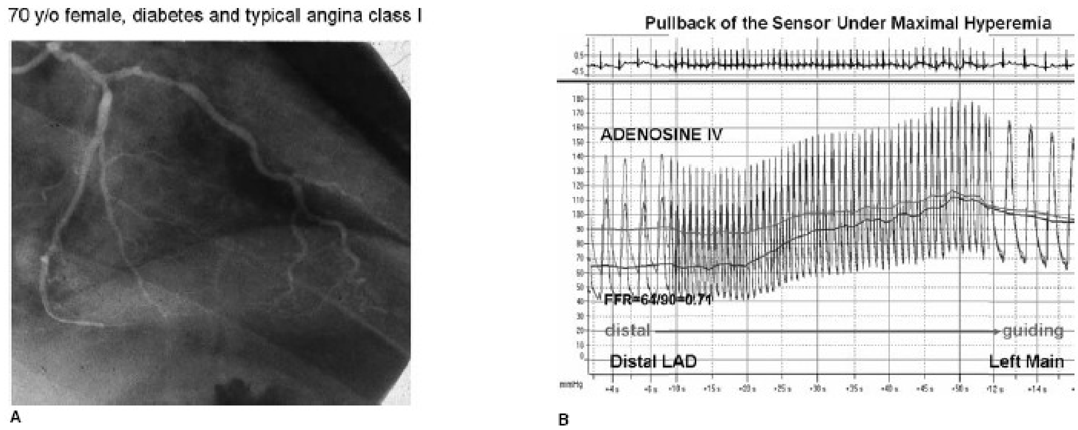


Figure 5. *Example of the use of FFR and the pressure pull-back curve to demonstrate diffuse disease. On the angiogram, severe and diffuse atherosclerosis LAD, the pressure wire was placed distally in the vessel and was manually pulled back towards the guiding catheter under fluoroscopy and steady-state maximum hyperemia. As can be clearly seen from the pressure*

tracings, FFR is below 0.75, indicating that inducible ischemia is present, and the patient will be likely to have ischemic complaints. However, no local pressure drop exists, but a gradual increase in distal coronary pressure is seen across the full length of the is present. To fully investigate the vessel. This implies that a PCI in any segment of the vessel will not be benificial, and conservative treatment is indicated.

Bypass grafts. Until recently, only few data have been available for FFR in bypass grafts. It has been suggested that resistance in an internal thoracic artery would be higher than in a venous graft. In earlier studies, it has even been suggested that resistance in an internal thoracic artery would be so high that myocardial ischemia could result, especially shortly after the operation in the case of a large myocardial territory depending upon the graft.

Glineur et al. showed that a normal venous bypass has a resistance which is almost negligible and therefore is comparable in this respect to a normal coronary artery. In the internal thoracic artery the resistance is higher but amply above the treshold at which myocardial ischemia might occur (40).

Important considerations. For adequate assessment of the hemodynamic significance of an epicardial stenosis, the induction of true maximum hyperemia is of paramount importance. If submaximal hyperemia is induced, the FFR will be overestimated, and thus the severity of the lesion underestimated, leading to erroneous conclusions and possibly wrong decision making. Several agents can be used to ensure maximum hyperemia, of which adenosine, administered through a central vein, is in our view the most convenient and reliable. As De Bruyne et al. demonstrated (43), the adequate dose to ensure maximum hyperemia is 140 ug/kg/min of adenosine or adenosine triphosphate (ATP) in a central (femoral) vein. As an alternative, 20 mg of intracoronary papaverine bolus can be administered to achieve sustained maximum hyperemia, however this rarely results in ventricular arrhytmias. If no sustained hyperemia is needed (ie if a pullback recording is not necessary), 40 microg or higher doses of intracoronary adenosine can also be used. The operator should be well aware of the fact that the hyperemic effect of this intracoronary adenosine is very short, and no steady state hyperemia will occur. Intracoronary adenosine 15-20 microg, used in many patients, was possibly inadequate in a number of them to achieve maximum hyperemia. Such low dosages should be discouraged. For all the studies described in this thesis, intravenous adenosine at a dosage of 140 ug/kg/min was used.

Conclusion. Fractional flow reserve is a simple, straightforward and efficient way to guide decision-making and solve clinical dilemmas in coronary artery disease. Moreover, in certain situations (eg. multivessel disease, sequential stenoses), it is an essential tool to determine optimum patient treatment. For all studies described in this thesis, FFR was used as gold standard to conclude if a particular stenosis was significant or not.

References

1 . Sones FM, Shirey EK. Cine coronary arteriography. Med Concepts Cardiovasc Dis 1962;31:735-738

2. Seldinger SI. Catheter replacement of the needle in percutaneous angiography; a new technique. Acta Radiol.1953;39:368-73.

3. Amplatz K, Formanek G, Stranger P et al. Mechanics of selective coronary artery catheterisation via femoral approach. Radiology. 1967;89:1040-47.

4. Judkins MP. Selective coronary arteriography. I. A percutaneous transfemoral approach. Radiology 1967;89:815-824

5. Campeau. Percutaneous radial artery approach for coronary angiography. Catheter Cardiovasc Diagn 1989;16:3-7

6. Schwartz JN, King Y, Hackel DB, et al. Comparison of angiographic and postmortem findings in patients with coronary artery disease. Am J Cardiol 1975;36:174-8

7. Roberts CS, Roberts WC. Cross-sectional area of the proximal portions of the tree major coronary arteries in 98 patients with different coronary events: Relationship to heart, weight, age, and sex. Circulation 1980;62:953-59

8. Davis K, Kennedy JW, Kemp HG, et al. Complications of coronary arteriography from the Collaborative Study of Coronary Artery Surgery (CASS).Circulation 1979;59:1105-12

9. Galbraith JE, Murphy ML, Desoya N. Coronary angiogram interpretation : Interobserver variability. JAMA 1981 ;240 :2053-59

10. Vladover Z, Frech R, van Tassel RA, et al. Correlation of the antemortem angiogram and the postmortem specimen. Circulation 1973;47:162-8

11. Nissen SE, DeFranco A, Tuzcu EM. Detection and quantifcation of artherosclerosis : The emerging role for intra-vascular ultrasound. In: Furster V ed. Syndromes of Atherosclerosis: Correlations of Clinical Imaging and Pathology. Armonk, NY: Futura; 1996:291

12. Nissen SE, Gurley JC. Application of inravascular ultrasound and quantitation of coronary atherosclerosis. Int J Cardiac Imaging 1991;6:165-77

13. TenHoff H, Korbijn A, Smi ThH, et al. Image artifarcts in mechanically drive ultrasound catheters. Int J Cardiac Imaging 1989;4:195-9

14.Di Mario C, Madretsma S, Linker D, et al. The angle of the incidence of the ultrasonic beam: A critical factor for the quality in intravascular ultrasonography. Am Heart J 1993;125:442-8

15. Hausmann D, Erbel R, Alibelli-Chemarin MJ, et al. The safety of intracoronary ultrasound: A multicentre survey of 2207 examinations. Circulation 1995;91:623-30

16. Batkoff BW, Linker DT. Safety of intracoronary ultrasound: Data from a multicentre European registry. Cathet Cardiovasc Diagn 1996; 38:238-41

17. Pinto FJ, St Goar FG, Gao SZ, et al. Immediate and one-year safety of intracoronary ultra-sound imaging: Evaluation with serial quantitative angiography. Circulation 1993;88:1709-14

18. Bunce NH, Lorenz CH, Pennell DJ. MR coronary angiography: 2001 update. Rays 2001;26(1):61-9

19. Regenfus M, Ropers D, Achenbach S, et al. Diagnostic value of maximum intension projections versus source images for assessment of contract-enhanced three-dimensional breath-hold magnetic resonance coronary angiography. Invest Radiol 2003;38(4):200-6

20. Plein S, Jones TR Ridgway JP, et al. Tree-dimentional coronary MR angiography performed with subject-specific cardiac acquisition windows and motion-adapted respiratory gating. AJR 2003;180(2):505-12

21. Watanabe Y, Nagayama M, Amoh Y, et al. High-resolution selective three-dimentionalmagnetic resonance coronary angiography with navigator technique: Segment-by-segment evaluation of coronary stenosis. J Magn Reson Imaging 2002;16(3):238-45

22. Vetter HO, DrieverR, Mertens H, et al. Contrast-enhanced magnetic resonance angiography of mammary artery grafts after minimally invasive coronary bypass surgery. Ann Thorac Surg 2001;71(4):1229-32

23. Engelman MG, Knez A, von Smekal A, et al. Non-invasive coronary bypass graft imaging after multivessel revascularisation. Int J Cardiol 2000;76(1):65-74

24. Molinari G, Sardanelli F, Zandrino F, et al. Value of navigator echo magnetic resonance angiography in detecting occlusion/patency of arterial and venous, single and sequential coronary bypass grafts. Int J Cardiovasc Imaging 2000;16(1)149-60

25. Nieman K, Cademartiri F, Lemos P, et al. Reliable non-invasive coronary angiography with fast submillimeter multislice spiral computed tomography. Circulaton 2002;106:2051-54.

26. Ropers D, Ulzheimer S, Wenkel E, et al. Investigation of aortocoronary artery bypass grafts by multislice computed tomography with electrocardiographic image reconstruction. Am J Cardiol 2001;23(3):792-95

29. Topol EJ, Nissen SE. Our preoccupation with coronary lumenology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995;92:2333-2342

30. Reiber JHC, Serruys PW, Kooijman CJ, et al. Assessment of short- medium- and longterm variations in arterial dimension from computer assisted quantification of coronary cine angiograms. Circulation 1985;71:280-288

31. Pavin D, Delonca J, Siegenthaler M, et al. Long-term (10 years) prognostic value of a normal thallium-201 myocardial exercise scintigraphy in patients with coronary artery disease documented by angiography. Eur Heart J 1997;18:69-77

32. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation 2000;101:1465-78

33. Kirkeeide RL, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial perfusion during pharmacologic coronary vasodilation: VIII. Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. J Am Coll Cardiol 1986;7:103-113

34. Gould KL, Kirkeeide RL, Buchi M: Coronary flow reserve as a physiologic measure of stenosis severity. J Am Coll Cardiol 1990;15:459-474

35. Pijls NHJ, Van Son JAM, Kirkeeide RL, et al. Experimental basis of determining maximum coronary, myocardial and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993; 87: 1354-1367

36. Pijls NHJ, Van Gelder B, Van der Voort P, et al. Fractional Flow Reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation 1995; 92: 3183-3193

37. Pijls NHJ, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. N Engl J Med 1996; 334: 1703-1708

38. Bech GJW, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve to decide upon the appropriateness of angioplasty: a prospective randomized trial. Circulation 2001; 103: 2928-2934

39. De Bruyne B, Pijls NHJ, Bartunek J, et al. Fractional flow reserve in patients with prior myocardial infarction. Circulation 2001; 104: 157-162

40. Glineur D, Pocelet A, El Khoury G, et al. Fractional flow reserve of pedicled internal thoracic artery and saphenous vein grafts 6 months after bypass surgery. Eur J Cardiothorac Surg. 2007 ;31(3) :376-81.

41. Fearon WF, Yeung AC, Lee DP, et al. Cost-effectiveness of measuring fractional flow reserve to guide coronary interventions. Am Heart J 2003; 5: 882-887

42. Leesar MA, Abdul-Baki T, Akkus NI, et al. Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina. J Am Coll Cardiol 2003;41:1115-1121

43. De Bruyne B, Pijls NHJ, Barbato E, et al. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. Circulation 2003; 107: 1877-1881

44. McGinn AL, White CW, Wilson RF. Interstudy variability of coronary flow reserve: Influence of heart rate, arterial pressure, and ventricular preload. Circulation 1990;81:1319-30

45. Czernin J,Muller P, Chan S et al. Influence of age and hemodynamics on myocardial blood flow and reserve. Circulation 1993;88:62-9

46. Gould KL, Libscomb K, Hamiltom GW. Physiologic basis for assessing critical coronary stenosis: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol 1974;33:

Chapter 3

Relation between coronary stenosis severity and bypass graft flow assessed by fractional flow reserve measurements: Mathematical and in vitro analysis

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Abstract

For both arterial and venous conduits, early graft dysfunction is a well known problem after coronary bypass surgery. Although this phenomenon is not completely understood, it has been suggested that grafting non-significantly stenosed coronary arteries promotes this condition. Fractional flow reserve measurement is the gold standard for physiological analysis of the severity of a stenosis in a coronary artery.

A mathematical and in vitro model were used to establish the influence of the severity of a stenosis in a coronary artery measured by fractional flow reserve on the flow in an arterial or venous bypass graft.

Both models showed that the flow through arterial conduits is more influenced by the severity of the stenosis in a native coronary artery than flow in venous conduits due to the difference in intrinsic resistance. The flow through an arterial conduit decreases more rapidly with less severe stenosis in a coronary artery than with the flow trough a venous conduit. Moreover, in both models myocardial blood flow never reaches its normal value when using an arterial conduit. When using a venous conduit, the normal myocardial blood flow could be achieved.

In conclusion, decrease of flow in an arterial or venous conduit anastomosed on a coronary artery with a mild stenosis can induce early dysfunction of such graft.

Arterial conduits are more susceptible to this phenomenon than venous conduits

Introduction

Coronary artery bypass grafting is a well established treatment for patients with obstructive coronary artery disease. However, occlusion or obstruction of these bypass grafts may occur over time. During the first year after surgery, thrombosis and/or fibro-intimal proliferation of the graft predominate, while later on athero-sclerosis occurs, especially in venous bypass grafts(1). Little is known about factors that may contribute to these adverse events, though anti-platelet therapy and correction of cardiovascular risk factors have been shown of value. It has been suggested in retrospective, angiography-based studies that grafting of less critical stenosis (which may imply lower flow rates through the bypass graft) may be a risk factor of early dysfunction of the graft(2). This hypothesis, although important , has never been elaborated in a mathematical model, neither been tested by functional assessment of the severity of a stenosis in a coronary artery in the setting of an in vitro model.

Using fractional flow reserve (FFR), the functional severity of a stenosis can be assessed by the ratio Pd/Pa, where Pd represents the perfusion pressure distal of a stenosis and Pa the perfusion pressure proximal of a stenosis at maximum hyperemia. This ratio of perfusion pressures is representative for the ratio of maximum blood flow in a stenotic coronary artery to maximum blood flow in the normal coronary artery. FFR is the gold standard for physiologic stenosis severity and a value below 0.75 indicates a functionally significant stenosis(3).

The aim of this study was to establish the flow through a bypass graft in relation to functional stenosis severity in the native vessel. Therefore, we first used a mathematical resistance model to predict flow through bypass grafts of different length and diameter in relation to stenosis severity in a coronary artery and next we tested these predictions in a sophisticated, physiologically representative in vitro model mimicking the epicardial coronary arteries, bypass grafts and microcirculation.

Materials and methods

Mathematical model. A mathematical resistance model was developed, using Ohm's law, to predict the flow through a arterial bypass graft (length 25 cm, diameter 2 mm) mimicking the left internal thoracic artery and a venous bypass graft (length 15 cm, diameter 4 mm) in relation to the stenosis severity of a coronary artery (diameter 3mm). Figure 1

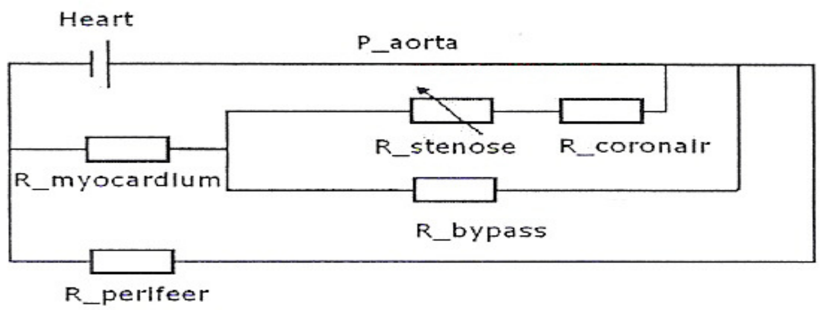

***Figure 1.** Mathematical resistance model to predict the flow through a bypass graft in relation to the stenosis severity of a coronary artery.*

In Vitro Model. The in vitro model we developed, consists of a pump providing pulsatile flow at room temperature and a systematic and a coronary circulation (figure 2).

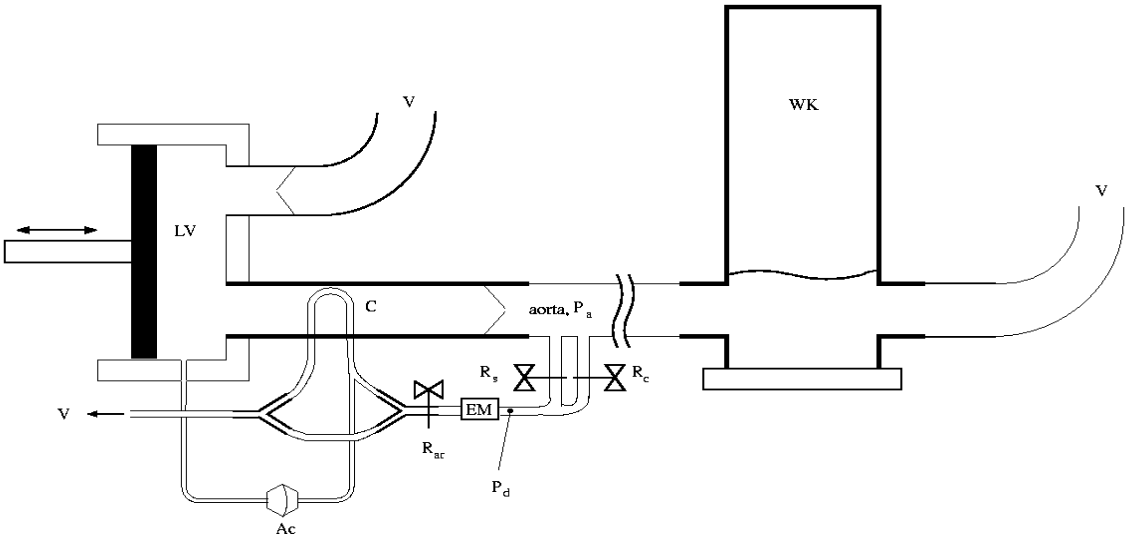

Figure 2. *In vitromodel of the circulation used in this study: LV, left ventricle; V, venous outlet; Ac, accumulator; C, collapsible tube; Rar, arteriolar resistance clamp; EM, electromagnetic flow sensor in the coronary artery; Rc, coronary stenosis clamp; Rg, graft clamp; Pa, pressure sensor in the aorta; Pd, pressure sensor in the coronary artery; WK, Windkessel. For further explanation: see text.*

The in vitro heart includes a rigid chamber with a piston inside it, driven by a computer-controlled linear motor and two artificial valves. The aorta is modelled as a tube made out of polyurethane and is connected to a Windkessel, modelling the distal systemic compliance. Two external occluders provide the aortic resistance and the peripheral resistance.

The coronary circulation consists of an epicardial coronary artery, a dual-tubed myocardium, and a venous outlet. The coronary artery is modelled with physiological dimensions and capacitance; the myocardium is modelled as a resistive circuit without significant capacitance but with a variable volume. Also the tubes mimicking an arterial graft and a venous graft are modelled with physiological dimensions and capacitance. This varying volume is modelled by a collapsible myocardial tube through the LV chamber. In addition, an accumulator is used, connecting the LV with the proximal side of the collapsible tube and containing a membrane, allowing the transmittance of LV pressure to the collapsible tube, but not enabling flow between LV and myocardium. Thus, the extravascular compression on the microcirculation by the contraction of the heart is realistically mimicked. Before that, we have validated physiologic coronary flow and pressure are present througout the complete heart cycle with flow predominantly during diastole in this model.

A single tube connects the coronary venous outlet to the venous reservoir and has no additional resistance. The arteriolar sphincter resistance (R_{ar}), crucial for the modelling of autoregulation, is present as a clamp and is placed at the entrance of the myocardial circulation. A coronary stenosis can be mimicked by an adjustable external occluder on the coronary artery, allowing a wide range of stenosis severity simulation.

In this model, the only driving force for blood flow is the aortic pressure. The variations in myocardial blood flow in the absence of an epicardial stenosis are merely generated by changes in resistance of arteriolar and myocardial vasculature, and by the variable and adjustable extravascular compression in part of the myocardium, as is the case in true human physiology (4-6).

In the totally vasolidated state (arteriolar resistance is minimal; no epicardial stenosis), myocardial flow equals 200 ml/min; in the resting state, 60 ml/min. By inducing a variable stenosis in the epicardial artery, hyperaemic myocardial blood flow can range from 0 to 200 ml/min.

Systemic and coronary phasic and mean flow are measured by electromagnetic flow sensors (Transflow 1401, Skalar) directly proximal to the aortic valve (systemic flow), and in the coronary artery distal to the stenosis (coronary flow). Pressure is measured in the left ventricular cavity, the ascending aorta, and in the coronary circulation by sensor-tipper pressure wires. Extensive validation studies with this in vitro setup have shown that it is possible to mimic coronary pressure and flow at both baseline and hyperemia in physiological and pathological conditions (7).

In this model, bypass grafts were implemented by connecting polyurethane tubes with a length of 15 and 25cm and a diameter of 4 and 2mm respectively between the ascending aorta and the distal coronary artery. These tubes were representing respectively a venous and an internal thoracic artery bypass. In these bypasses, a variable degree of stenosis could be induced by clamps, identical to the situation of the native coronary artery.

Pressure measurements. For measurement of distal coronary pressure, a commercially available 0.014"floppy pressure guidewire (PressureWire 4, Radi Medical Systems, Uppsala, Sweden) was used with modified software. This wire has a microsensor at 3 cm from the floppy tip, which enables recording of high-fidelity coronary pressure measurement with an accuracy of 2mmHg. All signals can be displayed on the regular catheter laboratory recording system or at a suitable interface (Radi-Analyzer) enabling online analysis as described below. Pressure is sampled with a frequency of 500Hz. The fractional flow reserve (FFR) is the ratio between the pressure distal of a stenosis and proximal of the same stenosis. The normal value of the FFR in absence of a stenosis is 1.0, the cut off point for inducible ischemia is 0.75.

The sensor of the pressure wire was placed in the coronary artery distal to the anastomosis with the arterial conduit or venous bypass graft. Simultaneously, aortic pressure (equal to proximal coronary pressure) was measured by a similar sensor located in the aorta as described above.

Sequence of different degrees of stenosis severity. At first, blood flow was measured in the native artery and the bypass graft in the absence of any stenosis. FFR of the native coronary artery equaled 1.0 in that situation. Next, different degrees of stenosis in the native coronary artery were created by constricting the coronary clamp, guided by decrease of FFR. FFR was decreased in this way from 1.0 to 0.4 in steps of 0.1.

At every degree of stenosis and for both types of conduits, flow was recorded in the native artery and the graft and plotted versus the FFR value of the native artery. All measurements were performed 3 times for every degree of stenosis.

Results

Mathematical model. With increasing FFR value of the coronary artery, the flow through the arterial conduit is decreasing rapidly making the arterial conduit more susceptible for competitive flow as a result of the intrinsic resistance of the arterial conduit (figure 3). Moreover, at comparable perfusion pressure, maximum achievable blood flow in the arterial graft only reached a value of 87% of normal myocardial blood flow as provided by a normal coronary artery.

The flow through the venous bypass is preserved also at higher FFR values, making the venous bypass less susceptible to competitive flow, (figure 4), and maximum achievable flow in the venous grafts equals 100% for maximal flow achievable by a normal native coronary artery.

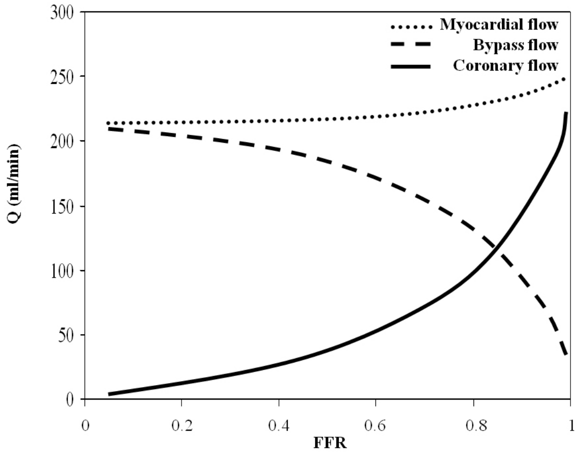

Figure 3. *Flow through the arterial conduit is rapidly deceasing with increasing FFR. Normal flow is only reached in absence of a stenosis in the native coronary artery*

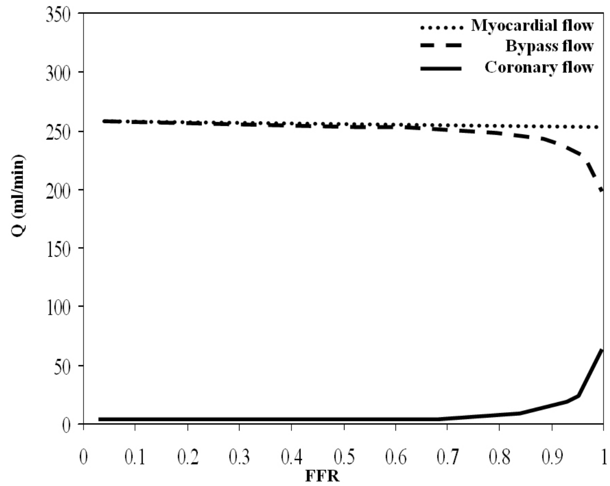

Figure 4. *Flow through a venous conduit is preserved almost independent of the stenosis severity of the coronary artery. The total maximum blood flow is reached independent of the FFR.*

In vitro model. Flow measurements in the in vitro model show the same phenomenon for the arterial conduit and the venous graft as was observed in the mathematical model. The result of this phenomenon is that the FFR measured distal of the anastomosis of the arterial conduit on the coronary artery will never reach the completely normal value of 1.0. Normal myocardial blood flow will not be achieved although the maximum value of 85% is sufficiently above the ischemic threshold of 0.75 to quarantee sufficient perfusion, even during maximum exercise. This in contrary to a venous bypass graft. The FFR measured distal of the anastomosis of a venous bypass graft will reach 1.0, providing normal maximum myocardial blood flow. (figure 5 and 6)

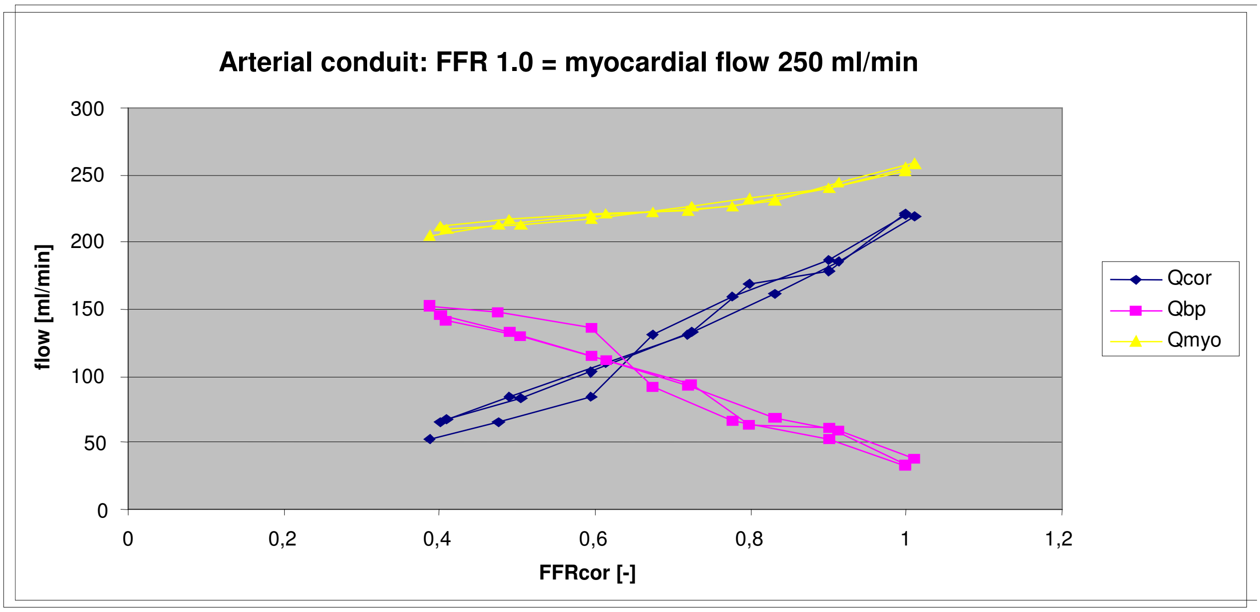

Figure 5. *Qcor, flow through the coronary artery; Qbp, flow through the bypass graft; Qmyo, total myocardial blood flow.*

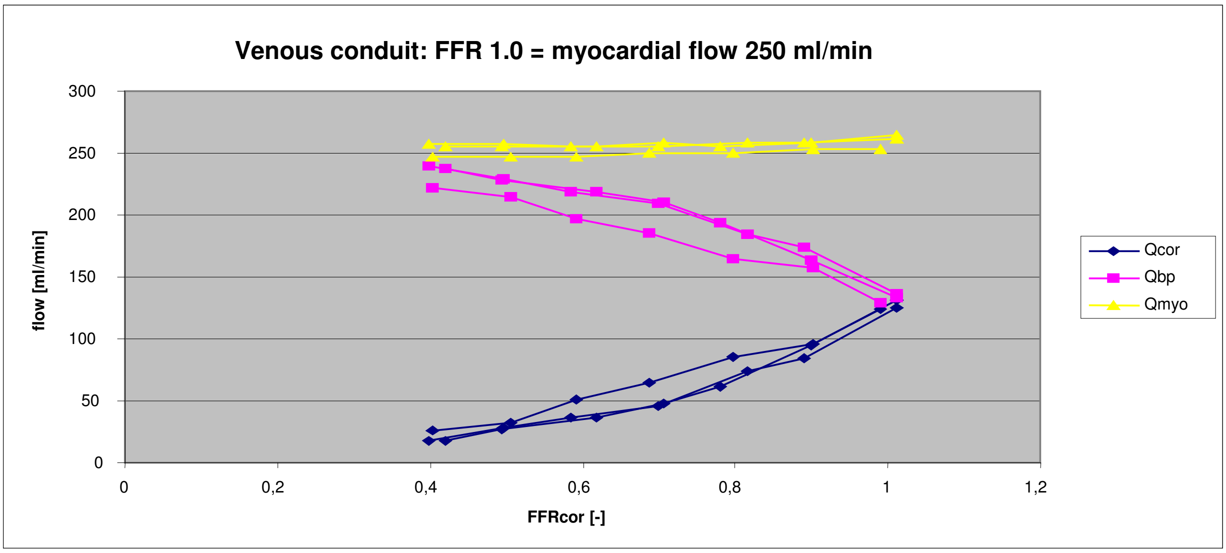

Figure 6. *Qcor, flow through the coronary artery; Qbp, flow through the bypass graft; Qmyo, total myocardial bllod flow*

Discussion

Cardiologists and cardio-thoracic surgeons have often suggested that grafting less critical stenosis is a risk factor of early graft dysfunction. Only recently, this hypothesis was studied in a prospective angiographic study showing a significant higher graft dysfunction of bypass grafts on coronary arteries with non significant lesions(8). Most data concerning patency of bypass grafts were retrospective and only a part of the patients underwent repeat angiography(9-11). More specifically, it has been suggested that competitive flow has a detrimental effect on the patency of arterial grafts and that arterial grafts should be used only for target vessels with sub-occlusive stenosis(12, 13). It has also been shown that venous bypass grafts have a better patency than arterial bypass grafts (both left internal thoracic artery and radial artery) in the first year after coronary surgery before artero-sclerosis occurs in venous bypass grafts. In this context, the string sign of a mammarian graft should be considered as a functional occlusion of the bypass (8, 14). To our knowledge, this phenomenon of early graft occlusion in relation to the severity of the stenosis in the grafted native coronary artery has never been studied in a mathematical or in vitro model.

In the mathematical model we used, it was shown that the flow through the arterial conduit decreases rapidly when the FFR is > 0.75, which is considered as the threshold for a hemodynamically significant stenosis. The flow through the venous bypass was only slightly influenced by the flow through the coronary artery and did not decrease significantly, not even when it was placed on an almost normal native artery. Further on it was observed that the FFR measured distal of the anastomosis with the arterial conduit never reaches the value of 1.0 meaning that normal maximum myocardial flow was never achieved. In contrast, in the case of a venous bypass graft, normal maximum myocardial blood flow can always be achieved irrespective of the severity of the stenosis in the coronary artery.

Measurements in the in vitro model showed identical findings: The flow trough the arterial conduit was more influenced by the stenosis severity of the coronary artery than the venous bypass graft, never reaching a normal maximum myocardial blood flow.

In the clinical setting we also have observed this phenomenon. The FFR measured distal of the anastomosis with an arterial conduit is between 0.85 and 0.90 but never reaches the normal value of 1.0 as is seen with venous bypass grafts.

It is interesting to note that in a rather large clinical study performed by Glineur et al, almost identical observations were made in patients undergoing repeated coronary angiography and FFR measurements 6 months after bypass surgery.(15)

In that study in 23 asympomatic patients, 12 left internal mammarial arteries, 10 right mammarial arteries and 21 venous grafts were investigated. All these grafts were angiographically normal. FFR equaled 0.90 ±0.04, 0.95 ± 0.03 and 0.96 ± 0.03 respectively for the left internal mammarial arteries, right mammarial arteries and venous grafts, thus confirming our predictions in clinical practice in true humans.

The origin of this observation is caused by a higher intrinsic resistance in arterial conduits due to their smaller diameter and greater length than venous conduits.

The clinical relevance is not easy to estimate but the fact that arterial conduits are more susceptible to high flow through the native coronary artery than venous conduits could implicate a higher incidence of early graft failure when arterial conduits are placed on coronary arteries with mild or intermediate stenosis.

Study limitations

Extrapolation of our findings to the human laboratory should be done with caution. Although the in vitro model of the coronary and myocardial circulation used in this study mimics true coronary circulation, unexpected confounding factors like the dynamic response of graft diameter might be present in the human catheterisation laboratory and not accounted for in our model.

Our model merely represents the situation of maximum flow (corresponding with maximum exercise in true life) because a situation like that is most important and angina pectoris occurs when maximum flow is insufficient to match myocardial oxygen demand. Under resting conditions, when mycardial flow is only 25-30% of maximum flow, mutual distribution of flow between native artery and bypass graft can be different and was not studied in our model.

Under resting conditions, flow in a mammarian graft placed on a non-significantly stenotic artery can even be lower. However, it can be presumed that for maintenance of graft patency, it is a minimum prerequisite that at least intermittantly flow should be present through the graft , as is the case during exercise, corresponding with maximum or near-maximum myocardial oxygen demanded perfusion.

Despite this limitation, this study shows a clear relation between the flow through the coronary artery and the flow through an arterial and venous conduit in which the latter is less susceptible to the flow in the coronary artery and could be an explanation for a better patency before arterio-sclerosis influences the patency of a venous bypass graft.

Conclusion

In this study, in a mathematical and in-vitro model of the coronary circulation, we demonstrated how maximum flow in a coronary bypass graft is influenced by the stenosis in the native coronary artery.

Effects were most pronounced for arterial grafts and our observations closely resembled data recently achieved in humans.

References

1. Motwani JG, Topol EJ. Aorta coronary saphenous vein graft disease: pathogenesis, predisposition and prevention. Circulation 1998;97:916-31.
2. Wilson RF, Marcus ML, White CW. Effects of coronary bypass surgery and angioplasty on coronary blood flow and flow reserve. Prog Cardiovasc Dis 1988;31:95-114.
3. Pijls NHJ, de Bruyne B, Peels K, et al. Measurements of fractional flow reserve to assess the functional severity of coronary stenosis. New Engl J Med 1996;334:1703-8.
4. Bassenge E, Heusch G. Endothelial and neuro-humoral control of coronary blood flow in health and disease. Rev Physiol Biochem Pharmacol 1990;117:77-165
5. Dole WP. Autoregulation of the coronary circulation. Prog Cardiovasc Dis. 1987;29: 293-323.
6. Spaan JAE. Basic coronary physiology. In: Spaan JAE, editor. Coronary blood flow: mechanics, distribution and control. Dordrecht: Kluwer Academic Publishers; 1991. p 1-36.
7. Geven MC, Bothe VN, Aarnoudse WH, et al. A physiologically representative in vitro model of the coronary circulation. Physiol Meas.2004;25:891-904
8. Botman CJ, Schonberger J, Koolen D, et al. Does stenosis severity of native vessels influence graft patency? A prospective fractional flow reserve guided study. Ann Thorac Surg 2007;83(6):2093-7.
9. Sabic JF, Lytle BW, Blackstone EH, et al. Does competitive flow reduce internal thoracic artery graft patency? Ann Thorac Surg 2003;76(5):1460-6

10. Berger A, MacCarthy PA, Siebert U, et al. Long-term patency of internal mammary artery byass grafts :relationship with preoperative severity of the native coronary artery stenosis. Circulation 2004;110(11 supl 1):II36-40.

11. Gansera B, Schiller M, Kiask T, et al. Internal thoracic artery vs. vein grafts postoperative angiographic findings in symptomatic patients after 1000 days. Thorac Cardiovasc Surg 2003;51:239-43.

12. Gaudino M, Alessandini F, Pragliola C, et al. Effect of target artery location and severity of stenosis on mid-term patency of aorta-anastomosed vs. internal thoracic artery-anastomosed radial artery grafts. Eur J Cardiothorac Surg 2004 ;25(3) :424-8

13. Sajja LR, Mannam G, Pantula NR, et al. Role of radial artery graft in coronary artery bypass grafting. Ann Thorac Surg 2005;79(6):2180-8

14. Dersai ND, Cohen EA, Naylor CD, et al. A randomised comparison of radial artery and saphenous-vein coronary bypass grafts. N Engl J Med 2004;351(22):2302-9.

15. Glineur D, Pocelet A, El Khoury G, et al. Fractional flow reserve of pedicled internal thoracic artery and saphenous vein grafts 6 months after bypass surgery. Eur J Cardiothorac Surg. 2007 ;31(3) :376-81.

Chapter 4

Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve guided study.

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Abstract

Background. After coronary bypass surgery occlusion or narrowing of bypass grafts may occur over time. It has been suggested that grafting of less critical stenosis may be a risk factor for early dysfunction of the graft. This hypothesis, although important, has never been tested prospectively.

Methods. In 164 patients eligible for coronary bypass surgery, not suitable for percutaneous intervention and with at least one intermediate lesion, fractional flow reserve was measured in al lesions to be grafted to establish if a lesion was functionally significant or not. The surgeon was blinded to the results of these measurements. One year after surgery coronary angiography was performed to establish bypass graft patency.

Results. At coronary angiography after one year 8.9% of the bypass grafts on functionally significant lesions were occluded and 21.4% of the bypass grafts on functionally non-significant lesions were occluded. There was no difference in angina class or repeat interventions between patients with or without occluded bypass grafts.

Conclusion. The patency of bypass grafts on functionally significant lesions is significantly higher than the patency of bypass grafts on non-significant lesions, however this finding has no clinical relevance as patients with patent or occluded bypass grafts on non-significant lesions did not suffer from an excess of angina or repeat interventions.

Introduction

Coronary artery bypass grafting (CABG) is a well established treatment for patients with obstructive coronary artery disease. However, occlusion or narrowing of these bypass grafts may occur over time. During the first year after intervention thrombosis and/or fibro-intimal proliferation of the graft predominate, while later on atherosclerosis appears(1). Little is known about factors that may contribute to these adverse events, though anti-platelet therapy and correction of cardiovascular risk factors have been shown of value. It has been suggested that grafting of less critical stenosis (which may imply lower flow rates through the bypass graft) may be a risk factor of early dysfunction of the graft(2). This hypothesis, although important , has never been tested prospectively.

In normal clinical practice, coronary arteries eligible for surgical re-vascularisation are selected on a subjective basis: visual estimation of stenosis severity, morphological appearance of the lesion which may be judged as unfavourable for percutaneous coronary intervention (PCI) and the physicians personal preference.

Fractional flow reserve (FFR) calculated from coronary pressure measurements permits reliable assessment of the functional severity of a stenosis in a coronary artery.

FFR of the coronary artery equals the ratio Pd/Pa at maximal hyperemia where Pa represents mean aortic pressure , measured by the guiding catheter, and Pd represents the distal coronary pressure , measured by a pressure wire. FFR is the gold standard for physiologic stenosis severity and a value below 0.75 indicate a functionally significant stenosis(3).

The purpose of the present study is to evaluate prospectively the angiographic patency of bypass grafts after one year in relation to the pre-operative angiographic and functionally severity of the coronary lesion assessed by FFR measurement in patients who underwent CABG.

Patients and methods

Between September 2003 and September 2004, 164 patients who were eligible for CABG were included in the present study.

The patients were selected for the surgical procedure on the basis of coronary artery disease not suitable for PCI and at least one intermediate lesion (stenosis severity 50-70% on visual estimation). Prior to bypass surgery FFR was measured in all vessels intended to be grafted and the surgeon was blinded to these measurements.

These patients were followed clinically over a period of one year and at the end of that period graft patency was evaluated by coronary angiography. A flow chart of the study design is presented in figure 1.

The study was approved by the institutional review board and written informed consent was obtained from all patients before inclusion in this study.

Figure 1:

Study Flow Chart:

Angiogram eligible for surgery

↓

Informed consent

↓

FFR measurement for every lesion
the surgeon intends to bypass

↓

CABG according to common
standard practice

↓

6 months clinical follow-up

↓

12 months follow-up
clinical and angiography

Figure 1*: A flow chart shows the study design. (CABG= coronary artery bypass grafting; FFR= fractional flow reserve).*

Coronary angiography and FFR measurements

After administration of 5000 units of heparin, a left or right coronary guiding catheter was advanced in the left or right coronary ostium, 200 micrograms of nitroglycerin was administered intra-coronary and angiograms were performed of the left and right coronary arteries in at least two orthogonal views. Thereafter a 0.014" sensor-tipped pressure guide wire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden) was advanced to the tip of the guiding catheter and after equal pressures were confirmed at that location , the wire was advanced into a coronary artery. Intravenous adenosin 140 micrgr/kg/min was administered by the femoral vein to induce maximum coronary hyperemia. FFR was calculated by the ratio Pd/Pa at steady-state maximum hyperemia, where Pd equals mean coronary pressure distal in the coronary artery (recorded by the pressure wire) and Pa equals mean aortic pressure (recorded by the guiding catheter) as described before(4). All measurements were performed twice. After the second measurement a pullback curve was performed at sustained hyperemia for precise localisation of a pressure gradient and precise determination of the functional severity of a localized stenosis. At present FFR is considered as the gold standard for physiologic assessment of the coronary artery(3).

Surgical technique.

The surgical technique used was decided by the personal preference of the surgeon. The internal mammary artery, the radial artery and the saphenous vein were used as bypass graft. The surgeon was blinded to the results of the FFR measurements and those vessels were grafted as judged relevant by the surgeon an he cardiologist based on classical angiographic assessment when the patient was accepted for CABG. In this way all patients received optimal clinical treatment according to the present standard for CABG, based on angiographic stenosis assessment. The stenosis severity was classified into 5 groups: total occlusion (100% stenosis), subtotal (>90%

stenosis), significant (70-90% stenosis), intermediate (50-70% stenosis) and non-significant (<50% stenosis).

Follow-up

All patients were followed at the out-patients clinic 3 months, 6 months and 1 year. After 1 year coronary angiography was performed

Analysis of data

All FFR measurements were stored digitally and analysed off-line. FFR is expressed as usual by a number between 0 and 1, expressing the achieved maximum blood flow as a fraction of the normal blood flow if no coronary artery disease would be present at all.

All data are reported as mean +/- standard deviation.

Differences between proportional (discrete or categorical) data were tested by Fisher's exact test and ANOVA. P<0.05 was considered significant.

Results

Procedural results

A total of 164 patients were included in this study, 128 patients were male, 36 were female and the mean age was 62, with a range from 33 to 84 years. Of these 164 patients who were scheduled for CABG, 2 patients refused operation and one patient died the day before operation. An other patient died post-operative due to left ventricular failure. The baseline characteristics of these patients are mentioned in table 1.

Table 1:

Baseline characteristics (164 pat.)	
Male/Female	78% / 22%
Age	33-84 (mean 62.4)
Hypertension	50%
Diabetes	16.4%
Hypercholesterolemia.	87.1%
Smoking	37.8%
Family history	53%
1 vessel disease	1 pat.
2 vessel disease	46 pat.
3 vessel disease	107 pat.
Stenosed vessels:	
LDA	153
RCX	152
RCA	108
EF	63 ±7
Angina class (CCS):	
AP I	5.5%
AP II	23.8%
AP III	46.3%
AP IV	24.4%
Patient history:	
PCI	26.2%
MI	19.5%
CABG	0%
Current medication:	
Asperin	95.1%
ß-blocker	86.6%
Statin	78.7%
ACE inhibitor/AIIA	34.1%

ACE = angiotensin converting enzyme inhibitor; AIIA = angiotensin 2 antagonist; AP = angina pectoris; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; LDA = left descending artery; RCX = circumflex artery; RCA = right coronary artery.

Clinical follow-up

During a follow-up of one year none of the remaining 160 patients died. Of these patients 138 were in class I according to the Canadian cardiovascular society (CCS), 12 in class II and 2 in class III. Additional PCI was necessary in 7 patients and one patient underwent repeat CABG.

Graft patency in relation to angiographic and functional stenosis severity

In 153 of the 164 patients included in this study (all of these 164 patients underwent FFR measurements) repeat angiography was performed after one year follow-up to establish patency of the bypass grafts. Two patients refused operation, 2 patients died and 7 patients refused repeat angiography.

In these 153 patients a total of 525 lesions were analysed by FFR and all these lesions were grafted. With FFR measurements 357 lesions were considered as significant (FFR<0.75) and 168 as non-significant (FFR>0.75).

At catheterisation after one year of follow-up 8.9% of the bypass grafts on functionally significant lesions were occluded and 21.4% of the bypass grafts on functionally non-significant lesions were occluded.

There was no difference in angina class between patients with or without occluded bypass grafts after one year follow-up.

In functionally significant lesions 13.7% of the arterial and 5.9% of the venous conduits were occluded after one year, in functionally non-significant lesions respectively 21.9% and 20.0%. The patency of the LIMA grafts was 93.8% and the patency of the Radial conduits was 71%.
In the group of visual intermediate lesions, graft occlusion occurred in 9.8% of the functional significant lesions and in 20.2% of the functionally non-significant lesions.
When the vessel diameter was taken in consideration, with a vessel diameter < 2.0 mm the graft patency was 79% and with a vessel diameter > 2.0 mm 96.1%. The results are presented in table 2.

Table 2: Influence of fractional flow reserve, vessel diameter and type of graft on graft patency.

Total no.of vessels	FFR < 0.75	FFR > 0.75	P-value
Patent	325	132	
Occluded	32	36	
Total	357	168	< 0.0001

FFR < 0.75	Patent	Occluded	P-value
Arterial	120	19	
Venous	205	13	
			<0.02

FFR < 0.75	Patent	Occluded	P-value
LIMA	96	9	
RA	34	10	
			<0.03

FFR > 0.75	patent	occluded	P-value
Arterial	57	16	
Venous	75	20	
			1.000

Vessel diameter	<2.0	?2.0	P-value
No. of vessels	339	186	
Occluded	59	7	
			<0.0001

Intermediate lesions	FFR <0.75	FFR >0.75	P-value
Patent	120	95	
Occluded	13	24	
			<0.02

FFR = Fractional Flow Reserve
LIMA = Left Internal Mamarial Artery
RA = Radial Artery

Visual estimation of stenosis severity (total occlusion, subtotal stenosis, significant stenosis, intermediate stenosis and insignificant stenosis) shows a trend to a higher occlusion rate of the bypass graft related to less severe stenosis rate. The relation between visual stenosis severity and graft occlusion is shown in figure 2.

Figure 2

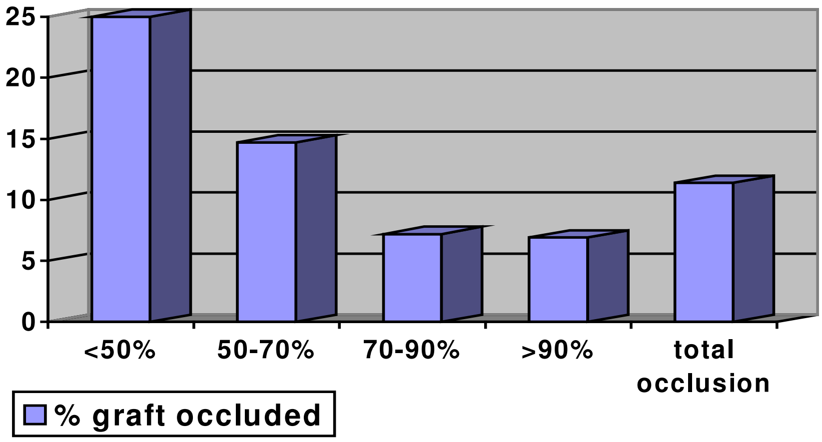

Figure 2: *The relation between the angiographic stenosis severity (horizontal axis) and the rate of graft failure after angiographic follow-up at 1 year.*

Functional severity of the lesions divided in 5 groups (FFR 0.40-50, FFR 0.50-0.60, FFR 0.60-0.70, FFR0.70-0.80, FFR 0.80-0.90 and FFR 0.90-1.00) also show a higher occlusion rate of the bypass grafts in functionally less severe stenosis. The relation between FFR and graft occlusion is shown in figure 3.

Figure 3:

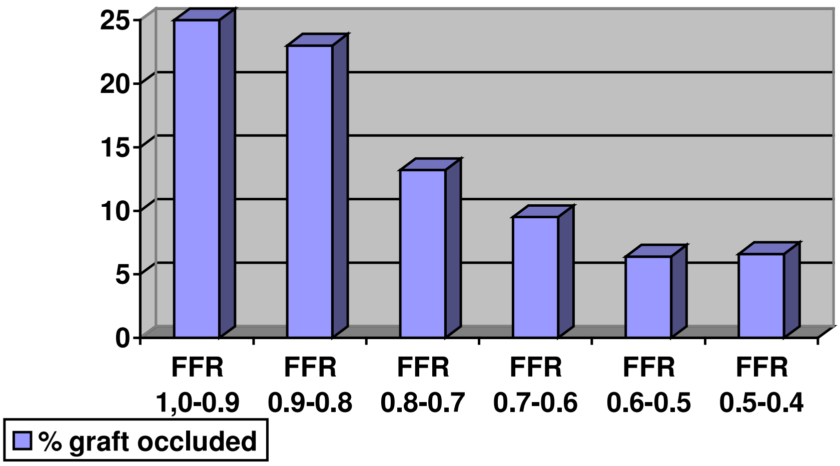

Figure 3*: The relation between functional stenosis severity established by fractional flow reserve (FFR) measurements and the rate of graft failure at angiographic follow-up after 1 year.*

Comment

Till the present time the hypothesis of cardiac surgeons and cardiologists suggests that grafting of less critical stenosis may be a risk of early dysfunction of the bypass graft and more over that competitive flow may cause symptoms of angina and early graft dysfunction. The clinical relevance of this finding has never been studied (2).

The data known about bypass graft dysfunction after CABG is mostly retrospective (5). IMA patency would decrease as coronary competitive flow increases due to less severe stenosis rate. However this was concluded retrospectively and only a part of he study population underwent repeated coronary angiography (6,7). Competitive flow has also a detrimental effect on the patency of IMA anastomosed radial grafts (RA) and this technique should be used only for target vessels with sub-occlusive stenosis (8). Vessel diameter also has an important impact on graft patency, with smaller vessel diameters lower graft patency was shown, also retrospectively, in saphenous vein grafts (9). This phenomenon has also been described for arterial conduits, with stenosis < 60% patency was 65%, and stenosis > 60% patency was 90.9%. However angiography was only performed if a patient was symptomatic (10). Several studies report that saphenous vein grafts have a higher occlusion rate than arterial conduits, but the superiority of arterial conduits was documented in a negative selected symptomatic population (10,11,12,13). Other factors have been evaluated in relation to graft patency. The patency rates of sequential saphenous vein grafts are generally superior than individual saphenous vein grafts (86.6% versus 69.6%), especially for poor runoff coronary vessels, provided that the most distal located anastomosis is performed on a coronary vessel with a good diameter (14). Diabetes did not made any difference in graft patency as was concluded in the BARI trial, however angiography was not performed on a regular base, but symptom guided (15).

The outcome of graft patency after off-pump surgery is not conclusive yet. A lower patency rate has been reported but also equal patency rates compared to conventional on-pump surgery (16,17,18). Also harvesting techniques of conduits may influence the outcome because of mechanical damage inflicted during harvesting (19).

To our best knowledge no prospective study has been conducted to show the relation between functionally stenosis severity and angiographic assessment of graft occlusion after one year of follow-up.

In this cohort 525 lesions in 153 patients were analysed pre-operatively with FFR and after one year the patency of the bypass graft was evaluated by coronary angiography. The primary end-point of the present study (graft patency in relation to functional stenosis severity) showed a patency rate of 91.1% of grafts on functionally significant lesions and 78.6% of grafts on non-significant lesions (p-value < 0.0001). Although the finding of a significant difference between patency rates of bypass grafts on functionally significant and functionally non-significant lesions was to be expected, the patency rate of bypass grafts on non-significant lesions is higher than mentioned in the literature (10). An explanation for this finding can be the negative selection of patients in whom angiography was done guided by coronary incidents and/or angina (10).

Also consistent with what was to be expected was the fact that a smaller diameter of the coronary artery gave a significant lower patency rate of 79% in vessels with a diameter < 2.0mm, and 96.1% on vessels with a diameter > 2.0mm (p-value < 0.0001).

Bypass grafts on functionally significant lesions showed a patency rate of 86.3% of arterial conduits and a patency rate of 94.1% of saphenous vein grafts (p-value 0.02). This finding seems surprising, but the usual smaller diameter and bigger length of arterial conduits than that of venous conduits may lead to an initial higher resistance and lower flow through these conduits accompanied by lower patency rate after one year of these arterial conduits (our own experimental, non-published data). The disappointing results of arterial re-vascularisation are attributed to the low patency rates of the RA conduits (71%) The patency rate of the LIMA conduits were 93.8%. This is concordant with the literature (20,21).

Bypass grafts on functionally non-significant lesions showed no difference in patency rate between arterial and saphenous vein conduits after 1 year, respectively 78.1% and 80% (p-value 1.000). These are higher patency rates of bypass grafts on functionally non-significant lesions than reported in previous studies, these studies were not prospective and the performed follow-up catheterisations were symptom guided.

A common controversy between cardiothoracic surgeons and interventional cardiologists is how to treat intermediate lesions (stenosis severity >50% and <70%). It has already been shown that FFR measurements is the tool of choice to divide this group of stenosis in functionally significant or non-significant, so that patients with multi-vessel disease with one or two intermediate lesions can be divided into two groups, one with functional 3 vessel disease who underwent CABG and one with functional 1 or 2 vessel disease who underwent PCI. After 2 year follow-up there was no difference in outcome in these groups (22). In this cohort 252 intermediate lesions were analysed, 133 lesions were functionally significant and 119 lesions were functionally non-significant. The patency rates were respectively 91.2% and 79.8%. This difference is significant, but there was no difference in angina class between patients with occluded or patent grafts. The 8 patients who were subjected to repeat intervention suffered from occlusion of a bypass graft on a functionally significant stenosis.

With increasing visual stenosis severity the graft patency rate increases, the same phenomenon is seen with assessment of functional stenosis severity. As described above this finding has no clinical relevance.

Conclusion

In this prospective blinded study patency of bypass grafts on functional significant lesions is significantly higher than the patency rate of bypass grafts on non-significant lesions, however this finding has no clinical relevance as patients with patent or occluded bypass graft on non-significant lesions did not suffer from a excess of angina or coronary repeat interventions.

Limitations

The size of the cohort in relation to the number of occluded bypass grafts, which is an outcome variable, and the follow-up of one year are recognized as limitations of this study.

It may also not be safe to extrapolate our findings to a longer period of follow-up.

References:

1) Motwani JG, Topol EJ. Aorta coronary saphenous vein graft disease: pathogenesis, predisposition and prevention. Circulation 1998;97:916-31.
2) Wilson RF, Marcus ML, White CW. Effects of coronary bypass surgery and angioplasty on coronary blood flow and flow reserve.
Prog Cardiovasc Dis 1988;31:95-114.
3) Pijls NHJ, de Bruyne B, Peels K, et al. Measurements of fractional flow reserve to assess the funcional severity of coronary artery stenoses.
New Engl J Med 1996;334:1703-8.
4) Pijls NHJ, van Gelder B, Van der Voort P, et al. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow.
Circulation 1995;92:3183-93
5) Gansera B, Schiller M, Kiask T, et al. Internal thoracic artery vs. vein grafts—postoperative angiographic findings in symptomatic patients after 1000 days.
Thorac Cardiovasc Surg 2003;51(5):239-43.
6) Sabik JF 3rd, Lytle BW, Blackstone EH, et al. Does competitive flow reduce internal thoracic artery graft patency? Ann Thorac Surg 2003;76(5):1460-6.
7) Berger A, MacCarthy PA, Siebert U, et al. Long-term patency of internal mammary artery bypass grafts: relationship with preoperative severity of the native coronary artery stenosis. Circulation 2004;110 (11supl 1):II36-40.
8) Gaudino M, Alessandrini F, Pragliola C, et al. Effect of target artery location and severity of stenosis on mid-term patency of aorta-anastomosed vs. internal thoractic artery-anastomosed radial artery grafts. Eur J Cardiothorac Surg 2004;25(3):424-8.

9) Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study.
J Am Coll Cardiol 2004;44(11):2149-56

10) Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. Ann Thorac Surg 2004;77(1):93-101.

11) Raja SG, Haider Z, Ahmad M, Zaman H. Saphenous vein grafts: to use or not to use? Heart Lung Circ 2004;13(4):403-9.

12) Shah PJ, Bui K, Blackmore S, et al. Has the in situ right internal thoracic artery been overlooked? An angiographic study of the radial artery, internal thoracic arteries and saphenous vein graft patencies in symptomatic patients.
Eur J Cardiothorac Surg 2005;27(5) :870-05.

13) Gaudino M, Cellini C, Pragliola C, et al. Arterial versus venous bypass grafts in patients with in-stent restenosis. Circulation 2005;112(9suppl):I265-9.

14) Farsak B, Tokmakoglu H, Kandemir O, et al. Angiographic assessment of sequential and individual coronary artery bypass grafting. J Card Surg 2003;18(6):524-9;
discussion 530-1.

15) Schwartz L, Kip KE, Frye RL, et al. Coronary bypass graft patency in patients with diabetes in the Bypass Angioplasty Revascularization Investigation (BARI).
Circulation 2002;106(21):2652-8.

16) Khan NE, De Souza A, Mister R, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass sugery. N engl J Med 2004;350(1):21-8.

17) Lingaas PS, Hol PK, Lundblad R, et al. Clinical and radiologic outcome of off-pump coronary surgery at 12 months follow-up: a prospective randomized trial.

Ann Thorac Surg 2006;81(6):2089-95.

18) Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. Nat Clin Pract Cardiovasc Med 2005;2(4):182-3.

19) Ahmed SR, Johansson BL, Karlsson MG, et al. Human saphenous vein and coronary bypass surgery: ultrastructural aspects of conventional and "no-touch"vein graft preparations. Histol Histopathol 2004;19(2):421-33.

20) Desai ND, Cohen EA, Naylor CD, et al. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. N Engl J Med 2004;351(22):2302-9.

21) Khot UN, Friedman DT, Pettersson G, et al. Radial artery bypass grafts have an increased occurrence of angiographically severe stenosis and occlusion compared with left internal mammary arteries and saphenous vein grafts. Circulation 2004;109(17):2086-91.

22) Botman CJ, Pijls NHJ, Bech JW, et al. Percutaneous Coronary Intervention or Bypass Surgery in Multivessel Disease? A Tailored approach Based on Coronary Pressure Measurement. CCI 2004;63(2):184-191.

Chapter 5

Long-term outcome after surgical left main coronairy angioplasty

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Abstract

Background. Direct surgical angioplasty of the left main coronary artery is aimed to restore a more physiological flow of the left coronary artery compared to conventional bypass surgery and allows subsequent percutaneous coronary interventions of more distal coronary lesions if necessary. Only few data are known on long-term outcome in these patients.

Methods. In 1996 and 1997, in 31 patients in our hospital, surgical angioplasty of the left main coronary artery was attempted. The left main coronary artery was approached in the anterior way. Follow-up was performed during 8 years and concluded by invasive anatomic and functional evaluation of the left main coronary artery.

Results. In 4 of these patients the procedure was converted to conventional bypass surgery due to calcification of the left main coronary artery. Of the remaining 27 patients, 3 patients died in the peri-operative period and 4 other patients died during follow-up. In 18 of the 20 survivors, coronary angiography was performed after 8 years and the left main coronary artery was also evaluated by intravascular ultrasound (IVUS) and coronary pressure based fractional flow reserve measurement (FFR). At angiography and IVUS, a dilated funnel shaped left main coronary artery was seen in all of these patients. In 1 patient, a hemodynamical significant left main coronary artery stenosis was present (FFR < 0.75) and in this patient coronary-artery bypass surgery was performed.

Conclusion. Although the majority of the survivors had a satisfactory anatomic and physiologic result after direct surgical angioplasty of the left main coronary artery, the total mortality of 23% was disappointing and we do not recommend this procedure as a first choice treatment for left main coronary artery disease.

Introduction

Direct surgical angioplasty of the left main coronary artery (LMDSA) has been advocated over years with the perspective to restore physiologic flow in the left main coronary artery (LMCA) (1). Endarterectomy of proximal coronairy arteries was first reported by Baily and Lemmon in 1957 (2). The first cases of LMCA reconstruction were described by Effer and Sabiston and coworkers in 1965 (3). Both approaches were abandoned because the operative mortality was unacceptably high compared with that of conventional bypass grafting (3,5) and exceeded 45%. With the introduction of better myocardial protection techniques and new surgical techniques to enlarge the LMCA, renewed interest for LMDSA arose. Using venous graft material or pericardial patches for interposition or reconstruction of the LMCA, the technique was advocated as an alternative for classic bypass surgery in patients with isolated LMCA disease, without contraindications as calcifications, involvement of the distal bifurcation or older age (6). Although venous material was normally used in performing LMCA angioplasty, an alternative method used a segment of the proximal right internal mammary artery as an onlay patch for surgical angioplasty (7).

Follow-up of LMDSA is limited to a number of small studies evaluating the short-term results by coronary angiography, magnetic resonance imaging(MRI), intra vascular ultrasound (IVUS), spiral computed tomography or trans-esophageal echo cardiography (8,9,10,11).

In the present study we report the long-term outcome (8 years) of 31 patients who underwent LMDSA in our hospital between 1996 and 1997, and in whom coronary angiography, intravascular ultrasound (IVUS) and fractional flow reserve (FFR) measurements of the LMCA were performed to obtain the best possible anatomic and physiologic information about the LMCA 8 years after surgery.

Patients and methods.

Between January 1996 and december1997, 31 patients underwent LMDSA and all of them were included in the present study.

The patients were selected for the surgical procedure on the basis of isolated LMCA stenosis, isolated LMCA stenosis and valvular disease, or LMCA stenosis and right coronary artery stenosis. Visible calcification of the LMCA on the coronary angiogram and extension of the disease including the LMCA bifurcation were exclusion criteria for LMDSA.

These patients were followed clinically over a period of 8 years and at the end of that period , the LMCA was evaluated by coronary angiography , IVUS and FFR.

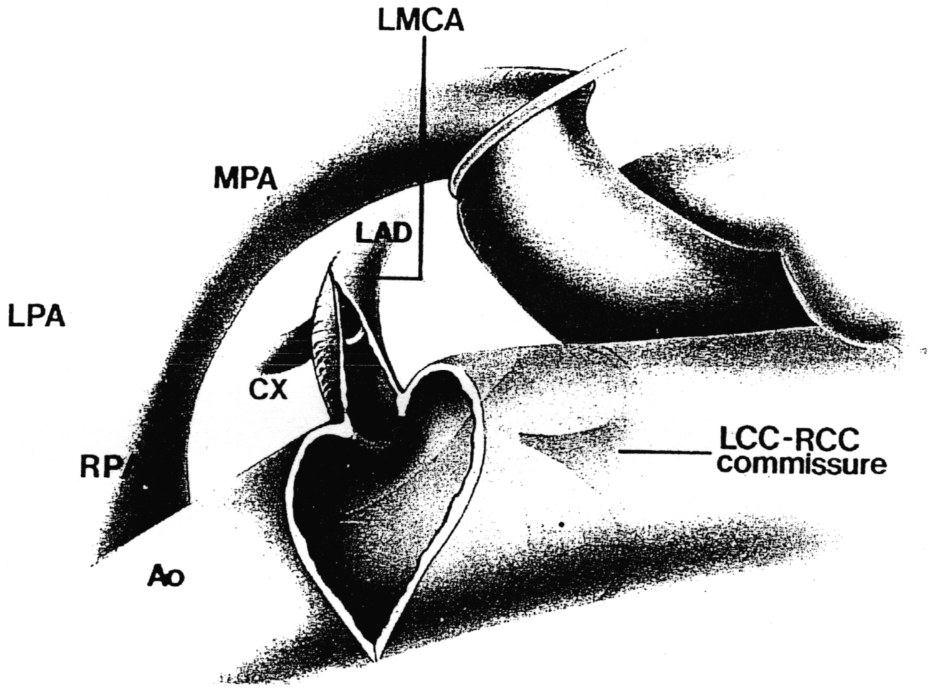
The study was approved by the institutional review board and written informed consent was obtained from all patients prior to the follow-up investigations. The baseline characteristics of the study population are mentioned in table 1.

Table1. Patients' characteristics and risk factors (n=31)

	No.	%
Male	23	74
Female	8	26
Age	44-79 (mean 62)	
Previous infarction	4	13
Previous CABG	0	0
Previous PCI	2	6
Smoking	8	26
Diabetes	6	19
Hyperchol.	20	65
Hypertension	15	48
Fam. History	12	39
Angina class		
I	0	0
II	0	0
III	13	42
IV	18	58
Ejection fraction		61 ±8

Surgical technique

The LMCA was approached anteriorly. The incision was started on the anterior aspect of the aortic root and was extended across the left lateral wall toward the LMCA. The main pulmonary artery was usually retracted to the left to facilitate exposure. The anterior aspect of the LMCA was incised across the stenosis. A venous onlay patch was used to enlarge not only the LMCA but also the adjacent 2 cm of the aortic incision to give the LMCA ostium a funnel shape, which was assumed to favor laminar blood flow (1). Using a venous patch was the preference of the performing surgeon.(Figure 1)


LMCA
MPA
LAD
LPA
CX
RP
Ao
LCC-RCC
commissure

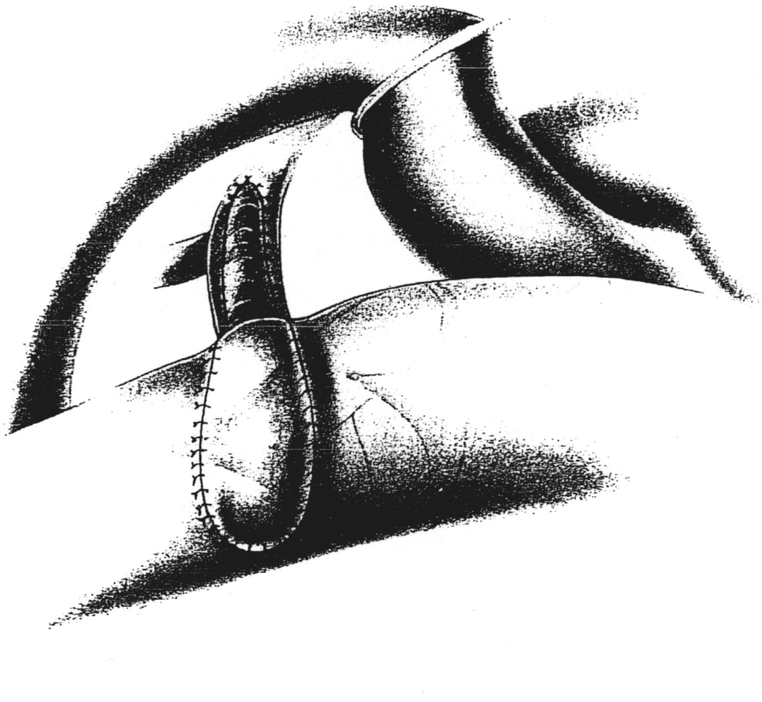


Figure 1. *Anterior approach to LMCA surgical view. The main pulmonary artery (MPA) is retracted away from the aorta (Ao). A generous exposure of LMCA and of its distal bifurcation between circumflex artery (CX) and left anterior descending artery (LAD) is obtained. The transverse aortotomy should stay away from the commissure between the left coronary cusp (LCC) and the right coronary cusp (RCC)*

The onlay patch is enlarging not only the LMCA but also a part of the aortotomy so as to obtain a funnel shape.

Invasive follow-up: Coronary angiography, FFR measurements and IVUS

Patients were seen at the outpatient clinic on a one-year basis. In those patients alive after 8 years, invasive anatomic and physiologic evaluation of the LMDSA was performed and documented hereafter: After administration of 5000 units of heparin, a left coronary guiding catheter was advanced in the left coronary ostium, 200 micrograms of intra-coronary nitroglycerin was administered and angiograms were performed in at least two orthogonal views for off-line quantitative coronary analysis (QCA). Thereafter, a 0.014" sensor-tipped pressure guidewire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden) was advanced to the tip of the guiding catheter and after equal pressures were confirmed at that location, the wire was advanced across the LMCA . Intravenous adenosine 140 microg/kg/min was administered via the femoral vein to induce maximum coronary hyperemia (12). FFR was calculated by the ratio Pd/Pa at steady-state maximum hyperemia, where Pd equals mean coronary pressure distal of the LMCA (recorded by the pressure wire) and Pa mean aortic pressure (recorded by the guiding catheter) as described before (12,13). All measurements where performed twice with the pressure wire once in the left anterior descending artery and once in the left circumflex artery. After the second measurement a pullback curve was performed at sustained hyperemia for precise localization of pressure gradient, if present. FFR is considered as the gold standard for physiologic assessment of the coronary artery (13).

Thereafter, IVUS was performed (Galaxy IVUS imaging system, Boston Scientific, United States of America) using the pressure wire as guide wire for advancing the IVUS catheter across the LMCA and a automatic pullback of the IVUS catheter was performed at 0.5 mm/s. IVUS is considered as the gold standard for anatomic assessment of a coronary artery.

Analysis of data

All QCA data, FFR and IVUS measurements were stored digitally, on paper and on videotape and analyzed off-line by an independent experienced reviewer. Because of the funnel shape of the LMCA after LMDSA, as a matter of fact no reference diameter for QCA and IVUS were available and therefore the results of these methods are expressed as minimal lumen diameter and minimal square area. FFR is expressed as usual by a number between 0 and 1, expressing the achieved maximum blood flow as a fraction of the normal maximum blood flow if no LMCA disease would be present at all. All data are expressed as mean +/- standard deviation and the range is added between brackets.

Results.

Procedural results

A total of 31 patients were scheduled for MLDSA, 23 patients were male, 8 female and the mean age was 62 with a range form 44 to 79 years. Twenty-two patients were planned for isolated surgical angioplasty without concomitant surgery, 4 patients for additional grafting of the right coronary artery and 5 patients for additional mitral valve surgery.

In 4 patients the primary operation was converted to conventional coronary artery bypass surgery because of severe calcification of the LMCA. The patients who underwent LMDSA with or without concomitant grafting of the RCA were treated with aspirin; patients with concomitant valve surgery were treated with coumadin

Three patients died shortly after surgery. One patient with previous myocardial infarction and severe mitral valve regurgitation died as the result of left ventricular failure after 1 day. A second patient died due to extensive myocardial infarction after acute closure of the LMCA 2 days after surgery. The myocardial infarction occurred after a period of hypotension in the intensive care unit. The third patient died after 14 days as a result of mediastinitis (table 2).

Table 2. Adverse events related to LMDSA during hospital stay and follow-up

Patient	Type of surgery	Event	Time interval to event
1	LMDSA	Myocardial infarction †	2 days
2	LMDSA	Conversion	Same day
3	LMDSA	Conversion	Same day
4	LMDSA	Myocardial infarction †	6 years
5	LMDSA	Myocardial infarction †	7 years
6	LMDSA	None	
7	LMDSA	None	
8	LMDSA	None	
9	LMDSA	None	
10	LMDSA	None	

11	LMDSA	None	
12	LMDSA	None	
13	LMDSA	None	
14	LMDSA	None	
15	LMDSA	None	
16	LMDSA	None	
17	LMDSA	None	
18	LMDSA	None	
19	LMDSA	None	
20	LMDSA	None	
21	LMDSA	None	
22	LMDSA	None	
23	LMDSA + venous graft RCA	Conversion	Same day
24	LMDSA + venous graft RCA	Pneumonia †	5 years
25	LMDSA + venous graft RCA	None	
26	LMDSA + venous graft RCA	None	
27	LMDSA + valve surgery	Left ventricular failure †	1 day
28	LMDSA + valve surgery	Mediastinitis †	14 days
29	LMDSA + valve surgery	Conversion	Same day
30	LMDSA + valve surgery	Myocardial infarction †	6 years
31	LMDSA + valve surgery	None	

†: patient died

LMDSA=left main direct surgical angioplasty; RCA=right coronary artery.

Clinical follow-up

During a follow-up of 8 years in the remaining 24 patients, another 4 patients died, of whom 3 as a result of progression of coronary artery disease, and 1 due to pulmonary disease.

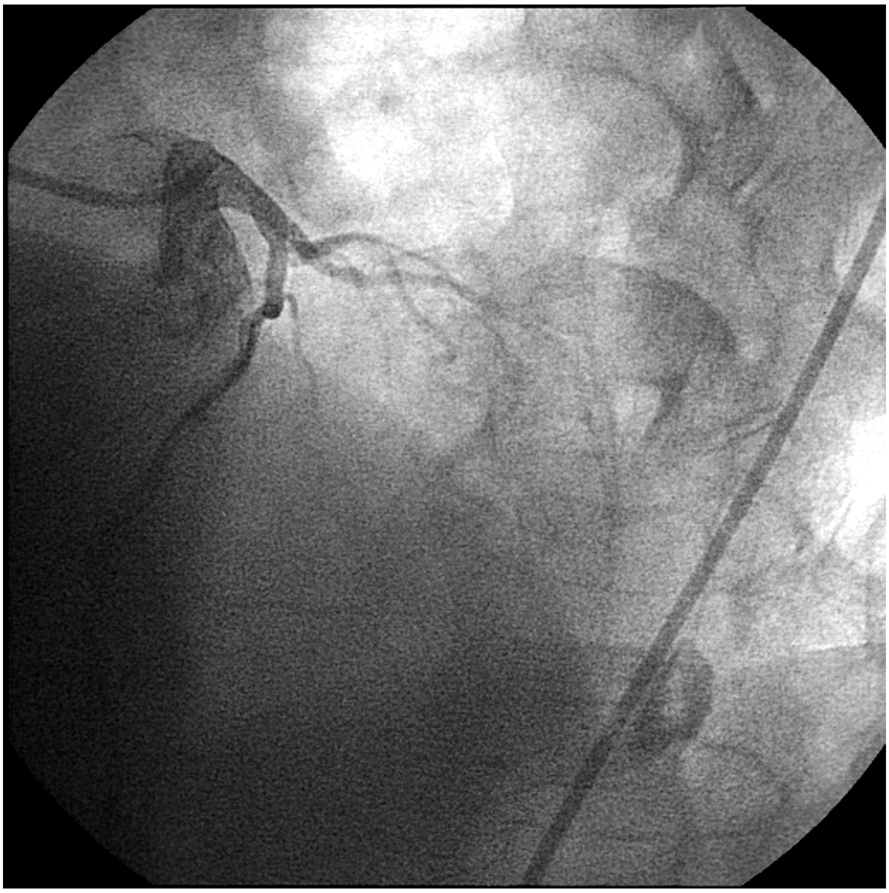
Of the remaining 20 patients alive at the end of the 8 year follow-up period, 18 were in class I according to the Canadian cardiovascular society (CCS) and 2 in class II. No additional percutaneous interventions or repeated surgery had been necessary in any of the surviving patients up to the moment of the follow-up invasive investigations.

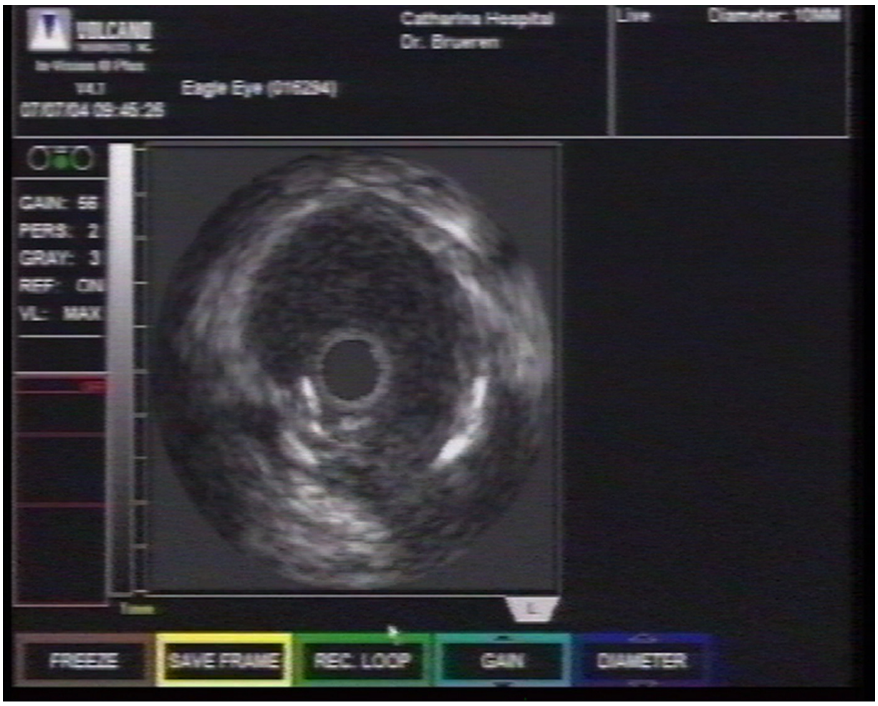
Invasive follow-up: coronary angiography, FFR and IVUS

In 18 of the 20 patients, alive after 8 years of follow-up, invasive evaluation of the LMCA was performed. Also, IVUS and FFR measurements were successfully performed in all these patients. Two patients refused the invasive follow-up.

At angiography, a wide open funnel shaped LMCA was seen in all 18 patients. At QCA, the minimal lumen diameter was 3.1 ± 0.77mm. In one patient, an intermediate stenosis in the LMCA bifurcation was present (Figure 2), and in another patient a severe stenosis in the left anterior descending artery distal to the first diagonal branch was noted (Figure 3).

The angiographic findings corresponded well with the IVUS measurements. The LMCA was wide open in all patients; one patient had plaque and calcification on the LMCA bifurcation, and in another patient the left descending artery was diffusely diseased with a severe stenosis as described before (Figure 2 and 3). The cross sectional area was 12.1 ± 1.3mm².





VOLCANO
Catharina Hospital
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REC. LOOP
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DIAMETER

Figure 2. *An insignificant lesion of the distal left main coronary artery is shown both with angiography and intravascular ultrasound. Although this lesion was anatomically not significant, it proved to be significant with fractional flow reserve measurement. This patient underwent reoperation.*

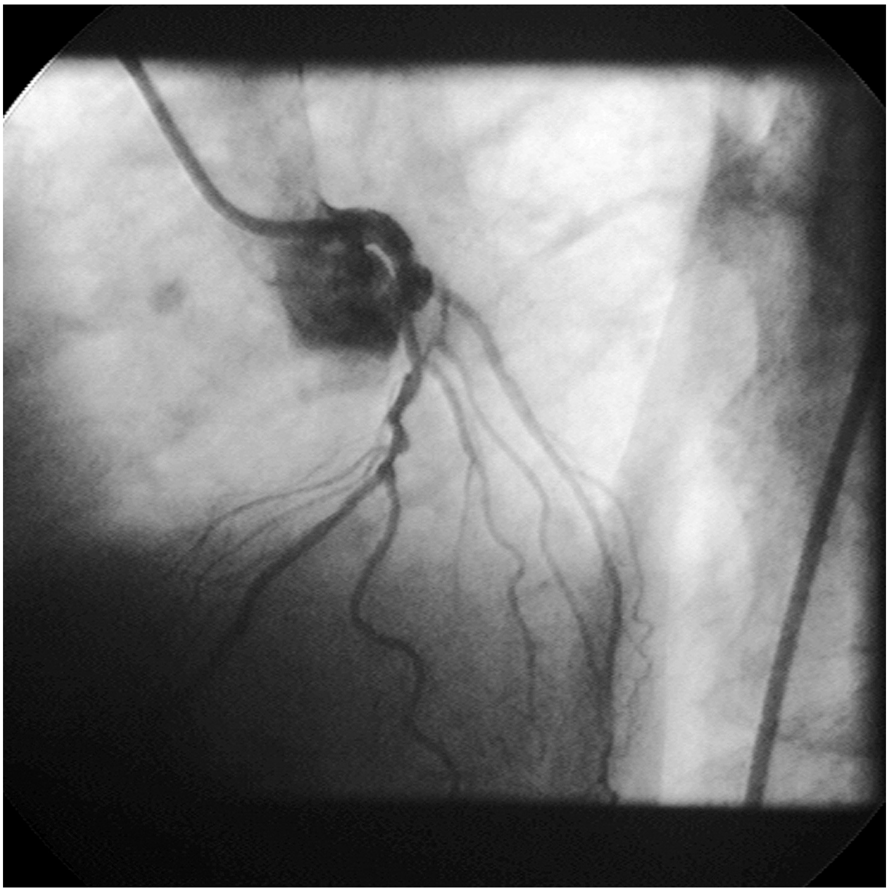

Figure 3. *A significant lesion is shown in the mid part of the left anterior descending artery with angiography and intravascular untrasound. It also proved to be significant with fractional flow reserve measurement. This patient underwent a percutaneous intervention of this lesion.*

At coronary pressure measurement, FFR was 0.93 ± 0,09 (range 0.66 to 1.00). In 2 patients FFR was below 0.75, considered as the threshold for a significant stenosis(14,15), and in these 2 patients repeated coronary bypass surgery or percutaneous coronary intervention was performed. The clinical follow-up, anatomic and physiologic data are presented in table 3.

Table 3. Clinic graphic, IVUS and physiologic data 8 years after LMDSA (n=18)

Patient	Angina class	QCA (mld)	IVUS (csa)	FFR	Repeat intervention
1	I	4.4	23.9	1.00	None
2	I	3.5	14.7	0.93	None
3	II	2.0	3.6	0.66	CABG
4	I	2.3	4.5	0.96	None
5	I	3.1	9.6	0.93	None
6	I	4.9	21.7	0.98	None
7	I	3.8	17.3	0.95	None
8	I	3.0	10.3	0.98	None
9	I	2.6	8.2	0.96	None
10	II	2.9	11.3	0.73	PCI
11	I	3.2	14.2	0.96	None
12	I	2.6	9.6	0.98	None
13	I	2.4	8.3	0.95	None
14	I	2.1	15.7	0.93	None
15	I	3.6	12.4	0.96	None
16	I	2.8	9.1	1.00	None
17	I	2.5	8.3	0.98	None
18	I	4.1	15.6	0.96	None
19	I	NA	NA	NA	None
20	I	NA	NA	NA	None

Mld= minimal lumen diameter (mm); csa=cross sectional area (mm^2)

Comment

Long-term outcome after surgical angioplasty of the LMCA in our clinic resulted in a mortality of 23% after 8 years, which seems somewhat disappointing, if compared to mortality after conventional bypass surgery or even to PCI of the LMCA after long-term follow-up(16). However in those patients alive after 8 years, invasive evaluation by coronary angiography, IVUS and FFR measurements, showed good results of LMDSA in all but 2 patients. Also the functional class in these survivors was excellent.

The most common etiology of LMCA stenosis is arteriosclerosis and accounts for the majority of the LMCA stenosis affecting particularly the mid-part and distal bifurcation, often associated with two or three vessel disease. LMCA stenosis is present in 9% of the patients undergoing bypass surgery (17). Isolated stenosis of the ostium and first third of the LMCA has a prevalence of 1% only(18). Coronary artery bypass surgery is an excellent treatment of LMCA stenosis but with some potential limitations, such as complete graft- dependent perfusion because of progressive occlusion of the LMCA and the risk of arteriosclerotic changes of the bypass graft or occlusion of the grafts (19,20). It has also been suggested that perfusion of a large area of the myocardium retrograde would be suboptimal (6).

Direct surgical angioplasty of the LMCA was suggested as a good alternative by restoring native antegrade flow and allowing PCI of peripheral lesions as coronary artery disease progresses (6,20). The patients in the present study were selected because of isolated LMCA disease not including the bifurcation and without visual calcification on coronary angiography. Concomitant right coronary artery disease and valve surgery were not exclusion criteria. There was no specific lack of conduits. In our opinion LMDSA can be used in the case of reoperation for aortic stenosis with other conduits intact. Also this technique can be used for isolated LMCA stenosis or as a hybrid procedure when concomitant right coronary artery disease is present, LMDSA followed by percutaneous intervention of the right coronary artery when there is lack of conduits. Technically, two principal methods have been described on how to get access to the LMCA, the posterior and the anterior approach (1,6,21,22). Post-operative angiography shows a slight difference in angiographic appearance between both techniques, with a larger neo-ostium when using the posterior approach. The significance of this finding is not known (7). Restenosis of the LMCA is reported in both approaches (1,3,11). In the present study the anterior approach was used.

In most studies either a pericardial or saphenous vein onlay patch was used. However it is well documented that the internal mammary artery(IMA) has a higher patency compared to venous material when used in bypass surgery (23,24,25,26). The IMA resembles coronary arteries with respect to histological properties more closely than autologous pericardium or the saphenous vein. To reduce restenosis and acute thrombosis, also the IMA was used as an onlay patch and excellent results with this technique have been reported (7). A disadvantage in using the IMA as an onlay patch is that it cannot be used anymore as a bypass graft when re-operation is necessary.

To evaluate the results of surgical angioplasty of the LMCA different methods have been used, but not on a regular basis or systematically in follow-up studies. Most reports concern one or just a few patients (8,10,11,27). Dion and colleagues (1) reported a larger series of 47 patients treated by LMDSA with a mortality of 19% after a mean clinical follow-up of 6 years, but all other studies are too small or have a very short follow-up so that no conclusions can be drawn (26-28).

The techniques used for invasive evaluation of LMDSA in our present study were coronary angiography, IVUS and FFR measurements, in order to obtain complete anatomic and physiologic information. To our best knowledge, such combined morphologic and physiologic assessments has not been reported.

Feasibility of IVUS alone was already shown in previous reports (2). Also with MRA and angiography, the typical funnel shaped LMCA was shown after surgical angioplasty, as we saw in this present study (1,10,18). In our opinion, IVUS is suboptimal for evaluating the LMCA after surgical angioplasty due to the wide funnel shape because often the IVUS catheter cannot be positioned central in the LMCA, and no reference diameter is present.

So far no information was available about the hemodynamic properties of the LMCA after surgical angioplasty. An average FFR of 0.93 ± 0.06, indicates that also in this respect, a good functional operative result was present in the majority of the patients alive after 8 years. Only in one patient a significant pressure drop was present in the distal LMCA and that patient underwent repeat bypass surgery. An other patient had a significant stenosis in the mid RDA and was treated with PCI. These 2 patients had a FFR well under 0.75. All the 16 remaining patients showed a FFR >0.90 indicating that there was no significant hyperemic pressure drop in the LMCA after surgical angioplasty even after 8 years, ruling out any flow obstruction in the LMCA regardless of its funnel shaped morphology.

Although the invasive follow-up showed favorable results in the survivors, the present study also shows a relatively high mortality after long-term follow-up, especially when taking in to account the relative young age and preserved left ventricular function of the patients at the time of the initial procedure. On the other hand 5 patients had concomitant valve surgery of which two patients died in the post operative period; these deaths had no direct relation with LMDSA. Furthermore, the amount of calcification in the LMCA was not evaluated preoperatively, accounting for the 4 conversions to classic bypass surgery. To rule out abundant calcification of the LMCA, IVUS or other imaging techniques could play a role in pre-operative assessment of the feasibility of LMDSA (29,30,31).

Conclusion

Although the total mortality of 23% was disappointing, in the majority of the survivors an excellent anatomic and physiologic result of LMDSA was observed after 8 years of follow-up. Provided thee is a good preoperative assessment of the LMCA with respect to calcification and other contraindications such as involvement of the LMCA bifurcation and older age are ruled out, LMDSA deserves a place in the array of surgical techniques.

References

1. Dion R, Verhelst R, Matta A, et al. Surgical angioplasty of the left main coronary artery. J Thorac Cardiovasc Surg 1990;99:241-250.
2. Bailey CP, Lemmon WN. Survival after coronary endarterectomy.JAMA 1957;164:641-6.
3. Effer DB, Sones FM, Favaloro R, et al. Endarterectomy with patch graft reconstruction: clinical experience with 34 cases. Ann Surg 1965;162:590-601.
4. Bortototti U, Milano A, Balbarini A, et al. Surgical angioplasty for isolated coronary ostial stenosis. Tex Heart Inst J. 1997;24:366-71.
5. Favaloro RG, Effler DB, Groves LK, et al. Severe segmental obstruction of the left main coronary and its division: surgical treatment by the saphenous vein graft technique. J Thorac Cardiovasc Surg; 1970; 60:469-82.
6. Hitchcock JF, Robles de Medina EO, Jambroes G. Angioplasty of the left main coronary artery for isolated left main coronary artery disease. J Thorac Cardiovasc Surg 1983;85:880-4.

7. Liska J, Jonsson A, Lockowandt U, et al. Arterial patch angioplasty for reconstruction of proximal coronary artery stenosis. Ann Thorac Surg 1999; 68:2185-90.
8. Sharoni E, Erez E, Shapira Y, et al. Transesophagal echocardiography evaluation and follow-up left main coronary artery patch angioplasty. Eur J Cardiothorac Surg. 2003;23 :585-8.
9. Spencker S, Hetzer R, Kreps P, et al. Surgical angioplasty of the left main coronary artery. Evaluation and postoperative follow-up with intravascular ultrasound. Z Kardiol, 2002;91:846-52.
10. Briffa NP,Clarke S, Kugan G, et al. Surgical angioplasty of the left main coronary artery: follow-up with magnetic resonance imaging. Ann Thorac Surg 1996;62:550-2.
11. Meseguer J, Hurle A, Fernandez-Latorre F, et al. Left main coronary artery angioplasty: mid term experience and follow-up with spiral computed tomography. Ann Thorac Surg 1998;65:1594-8.
12. Pijls NHJ, Van Gelder B, Van Der Voort P, et al. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation 1995;92: 3183-93.
13. Pijls NHJ, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenosis. N Engl J Med 1996;334:1703-08.
14. Leesar MA, Masden R, Jasti V. Physiological and intravascular ultrasound assessment of an ambiguous left main coronary artery stenosis. Catheter Cardiovasc Interv 2004;62:349-57.
15. Jasti V, Ivan E, Yalamanchili V, et al. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. Circulation 2004;110:2831-36.

16. Brener SJ, Lytle BW, Casserly IP, et al. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. Circulation 2004;109:2290-5.
17. Edwards FH, Clark RE, Schwatz M. Coronary artery bypass grafting: the society of thoracic surgeons national database experiency. Ann Thorac Surg 1994;57:12-9.
18. Dion R, Elias B, El Khoury G, et al. Surgical angioplasty of the left main coronary artery. Eur J Cardiothorac Surg 1997;11 :857-64.
19. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Circulation 1995;91:2325-34.
20. Gomberg J, Klein LW, Seelaus P, et al. Surgical revascularisation of left main coronary artery stenosis: determents of preoperative and longterm-outcome in the 1980s. Am Heart J 1988;116:440-6.
21. Ridley PD, Wisheart JD. Coronary ostial reconstruction. Ann Thorac Surg 1996;62:293-5.
22. Sullivan JA, Murphy DA. Surgical repair of stenotic ostial lesions of the left main coronary artery. J Thorac Cardiovasc Surg 1989;98:33-36.
23. Lytle BW, Loop FD, Cosgrove DM, et al. Long-term (5 to 12 years) serial studies of internal mammary artery and sapnenous vein coronary bypass grafts. J Thorac Cardiovasc Surg 1985;89:248-258.
24. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1-5.
25. Lytle BW, Blackstone EH, Loop FD, et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855-872.
26. Buxton BF, Komeda M, Fuller JA, et al. Bilateral internal thoracic artery grafting may improve outcome of coronary artery surgery. Circulation 1998;98:II1-6.

27. Shimakura T, Morishita A, Miyagishima M, et al. Surgical angioplasty of isolated left coronary ostial stenosis. Kyuba Geka, 2002;55:395-400.

28. Malyshev M, Gladyshev I, Safuanov A, et al. Surgical angioplasty of the left main coronary artery and/or proximal segment of the right coronary artery by pulmonary autograft patch. Eur J Cardiothorac Surg. 2004;2521-5.

29. Gussenhoven EJ, Essed CE, Frietman P, et al. Intravascular ultrasonic imaging: histologic and echographic correlation. Eur J Vasc Surg 1989;3:571.

30. Nishimura RA, Edwards WD, Warness CA, et al. Intravascular ultrasound imaging: in vitro validation and pathologic correlation. J Am Coll Cardiol 1990;16:145.

31. Nishimura RA, Higano ST, Holmes DR, et al. Use of intracoronary ultrasound imaging for assessing left main coronary artery disease. Mayo Clin Proc 1993;68:134-40

Chapter 6

Value of Magnetic Resonance Imaging, Angiography and Fractional Flow Reserve to Evaluate the Left Main Coronary Artery after Direct Surgical Angioplasty.

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Abstract

Background. Direct surgical angioplasty of the left main coronary artery is aimed to restore a more physiological blood flow through the left main coronary artery compared to conventional bypass surgery and allows subsequent percutaneous coronary interventions of more distal coronary lesions. Some data on anatomic evaluation with coronary angiography and MRI are known, and we conducted a study to report the physiologic evaluation.

Methods. Coronary angiography, MRI and fractional flow reserve measurements were performed in 18 patients 8 years after direct surgical angioplasty of the left main coronary artery.

Results. At coronary angiography and MRI a dilated funnel shaped left main coronary artery was seen in all 18 patients, but both methods failed to demonstrate a flow-limiting lesion in the distal left main coronary artery in 1 patient. The functional severity was shown by fractional flow reserve measurement and subsequently this patient underwent repeated bypass surgery.

Conclusion. MRI is a safe and non-invasive modality to visualise the left main coronary artery also after direct surgical angioplasty of the left main coronary artery but due to the low resolution properties quantitative assessment of a lesion is not reliable. Fractional flow reserve measurements are mandatory to evaluate the hemo-dynamic properties of the left main coronary artery after direct surgical angioplasty.

Introduction

Any significant stenosis of the left main coronary artery (LMCA) has a dismal prognosis with only medical therapy, with 4 and 6 year survival rates of 65% and 44% respectively (1). Therefore treatment traditionally is by coronary artery bypass grafting or percutaneous coronary intervention (PCI) (2,3). Also direct surgical angioplasty of the left main coronary artery (LMDSA) has been advocated over the years with the perspective to restore physiologic flow in the LMCA (4).

The limitations of coronary angiography to assess LMCA stenosis are well recognized, therefore a number of newer anatomic and physiologic methods, both invasive and non-invasive, have been suggested to evaluate left main coronary artery disease (5,6,7). The usefulness of magnetic resonance imaging (MRI) to evaluate the anatomic properties of the LMCA and fractional flow reserve (FFR) measurements to evaluate its physiologic properties are well documented (8,9).

In some case reports and small studies anatomic evaluation of the result after LMDSA is reported with coronary angiography, MRI, intra-vascular ultrasound (IVUS), spiral computed tomography or even trans-oesophageal echocardiography (10-13).

In this study we evaluated the physiologic properties of the LMCA after LMDSA and compared non-invasive MRI with invasive coronary angiography and FFR measurements of the LMCA in 18 patients 8 years after LMDSA.

Patients and Methods

Patient population

Between January 2004 and December 2004, 18 patients who underwent LMDSA between January 1996 and December 1997, were included in the present study. The patients had already been attending clinical follow-up for an 8 year period. In the present study, the LMCA after LMDSA was evaluated by MRI, coronary angiography and FFR measurements.

The indication for these investigations was surveillance and was not symptom driven.

The study was approved by the institutional review board and written informed consent was obtained from all patients before the follow-up investigations.

Surgical technique

The LMCA was approached from the anterior. The incision was started on the anterior aspect of the aortic root and was extended across the left lateral wall towards the LMCA. A curved incision was made into the right lateral aortic wall towards the LMCA, and the pulmonary root was unrolled towards the left by traction sutures to ease exposure. The anterior aspect of the LMCA was incised across the stenosis. A venous onlay patch was used to enlarge not only the LMCA but also the adjacent 2 centimetres of the aortic incision, so as to give the LMCA ostium a funnel shape, which favours a laminar blood flow (4).

Magnetic resonance imaging

MRI was performed on a 1.5t system (Intera CV: Philips Medical Systems, Best, The Netherlands) equipped with high performance gradients (60 mT/m, 150 mT/m/second rise time) and dedicated cardiac imaging software (release 10.3). A phased-array coil and vectorcardiographic monitoring were used. A scout localizer sequence in three orthogonal directions was performed to localize the left coronary artery and to place the navigator as described previously (14). Using these scout images, subsequently a transverse 3D imaging volume encompassing the proximal left coronary artery was defined. The navigator was placed vertical through the dome of the right hemi-diaphragm. An end-expiratory 5 mm gating window was used for acceptance of image acquisition data. To define an imaging window in the mid diastolic part of the cardiac cyc1e, a balanced turbo fast field echo cine sequence in a four chamber plane (defined using real time interactive imaging) was performed in which the right coronary artery and the circumflex artery were axially trans-sected. This cine run was used to define a mid-diastolic imaging window with minimal cardiac and coronary movement.

Next, coronary MRI's were acquired by using a vectorcardiographic triggered free breathing navigator-gated multi-section 3D segmented transverse balanced fast field echo sequence with fat suppression and T2 preparation prepulses. The imaging parameters were 5.6/2.8 (TRJTE), a 110 degrees flip angle, a 270 mm field of view, a 272x272x20 matrix reconstructed to 512x512x40 pixels, and a turbo fast field echo factor (number of shots per heartbeat) of 16, which resulted in an acquired spatial resolution of lxlx3 mm reconstructed to 0.5xO.5x1.3 mmo. The MRI images were acquired during the previously defined mid-diastolic time window of 90 milliseconds. The whole imaging protocol was performed within 15 minutes. (15).

Coronary angiography and FFR measurements

After administration of 5000 units of heparin, a left coronary guiding catheter was advanced in the left coronary ostium, 200 micrograms of intra-coronary nitroglycerin was administered and coronary angiograms were performed in at least two orthogonal views. There after a 0.014" pressure guidewire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden) was advanced to the tip of the guiding catheter and after equal pressures were confirmed at that location, the wire was advanced across the LMCA . Intravenous adenosine 140 microg/kg/min was administered via the femoral vein to induce maximum coronary hyperaemia (16).

The FFR, which is considered the gold standard for physiologic assessment of the coronary artery, was ca1culated by the ratio Pd/Pa at steady-state maximum hyperaemia, where Pd equals mean coronary pressure distal of the LMCA (recorded by the pressure wire) and Pa mean aortic pressure (recorded by the guiding catheter) as described before.(16,17). FFR measurements where performed twice with the pressure wire once in the anterior descending artery and once in the circumflex artery. After the second measurement a pullback curve was performed at sustained hyperaemia to localize the pressure drop if present.

Analysis of data

All QCA data, FFR and MRI measurements were stored digitally and analysed off-line by an independent experienced reviewer. Because of the funnel shape of the LMCA after LMDSA, no reference diameter for QCA and MRI measurements were available and therefore the results off these methods are expressed as minimal lumen diameter and minimal square area.

FFR is expressed as usual by a number between 0 and 1, expressing the achieved maximum Blood flow as a fraction of the normal maximum blood flow if no LMCA disease would be present at all. All data are expressed as mean +/- standard deviation with ranges.

Results

Procedural results

This cohort of18 consecutive patients consisted of 13 men and 5 women, and their mean age was 62 years (range from 44 to 79 years) All of them underwent LMDSA 8 years earlier. All patients complete evaluation of the LMCA was performed with MRI, coronary angiography and FFR measurements.

Clinical follow-up

After 8 years of clinical follow-up,16 of the 18 patients were in angina class I according to the Canadian cardiovascular society and 2 were in angina class II. No additional interventions or repeated surgery had been necessary in any of these patients up to the moment of the invasive and non-invasive investigations. The baseline characteristics of these patients are presented in table 1.

Table1. Baseline characteristics (n=18)

Characteristics	No.
Male	12
Female	6
Age	63 (48-69)
Previous infarction	1
Previous CABG	0
Previous PCI	0
Smoking	5
Diabetes	3
Hyperchol.	13
Hypertension	8
Fam. History	6
Angina class	
I	0
II	0
III	7
IV	11
Ejection fraction	0.63 ± 0.07

CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention.

Invasive follow-up: coronary angiography and FFR measurements

Invasive follow-up was performed in all patients 8 years after LMDSA and consisted of coronary angiography and FFR measurements.

At coronary angiography, a wide open funnel shaped LMCA was seen in all patients. In one patient a non significant stenosis was present at the distal LMCA and in another patient a severe stenosis was present in the left anterior descending artery just distal of the first diagonal branch.

At QCA the minimal lumen diameter was 3.1 +/- 0.77 mm.

At coronary pressure measurement, the FFR was 0.93 +/- 0.09 (range, 0.66-1.00). In 1 patient, the FFR was below 0.75, considered as the threshold for a significant stenosis , and in this patient underwent repeated coronary bypass surgery. The patient with a stenosis in the distal left anterior descending artery underwent a percutaneous coronary intervention (PCI). The clinical follow-up, angiographic and physiologic data are presented in Table 2.

Non-invasive follow-up: MRI

MRI was performed in all patients included in this study. At MRI a wide open funnel shaped LMCA was visualised, but no definitive judgement could be made about the distal LMCA due to the low resolution of the MRI in the planar view (1-2 square mm)

The MRI data are also presented in Table 2.

Table 2. Clinical, angiographic, MRI and physiologic data 8 years after LMDSA (n=18)

Patient	Angina class	QCA (mld)	MRI (mld)	FFR	Repeat intervention
1	I	4.4	4.2	1.00	None
2	I	3.5	3.1	0.93	None
3	II	2.0	3.2	0.66	CABG
4	I	2.3	4.4	0.96	None
5	I	3.1	3.2	0.93	None
6	I	4.9	4.2	0.98	None
7	I	3.8	3.6	0.95	None
8	I	3.0	3.2	0.98	None
9	I	2.6	3.1	0.96	None
10	II	2.9	3.4	0.73	PCI
11	I	3.2	4.0	0.96	None
12	I	2.6	3.9	0.98	None
13	I	2.4	3.8	0.95	None
14	I	2.1	4.0	0.93	None
15	I	3.6	4.2	0.96	None
16	I	2.8	3.5	1.00	None
17	I	2.5	4.0	0.98	None
18	I	4.1	4.2	0.96	None

mld: minimal lumen diameter (mm)

CABG=coronary artery bypass grafting; FFR=fractional flow reserve; mld=minimal lumen diameter in mm; LAD=left anterior descending artery; MRI=magnetic resonance imaging; PCI=percutaneous coronary intervention; QCA=quantitative coronary angiography

Comment

Although coronary angiography is still considered to be the gold standard for evaluation of the coronary tree, the pursuit of a non invasive technique for visualisation of coronary artery disease has an avid interest. In the majority of patients, MRI is limited to visualise proximal coronary arteries; however distal vessels remain difficult to evaluate (18). In this perspective 64-slice computed tomography is a more promising technique in evaluating the whole coronary tree (19), but it was not used in this study because it was not available in our hospital when the study was performed.

The most common cause of LMCA stenosis is arteriosclerosis affecting particularly the mid part and distal bifurcation, often associated with two or three vessel disease. LMCA stenosis is present in 9% of the patients undergoing bypass surgery. Coronary artery bypass surgery is an excellent treatment of LMCA stenosis but with some potential limitations such as complete graft depending perfusion due to progressive occlusion of the LMCA and the risk of arteriosclerotic changes or occlusion of bypass grafts (20,21). It has also been suggested that perfusion of a large area of the myocardium retrograde would be sub-optimal (22).

Direct surgical angioplasty of the LMCA was suggested as a good alternative by restoring the native ante-grade flow and allowing PCI of more peripheral lesions as coronary artery disease progresses (23).

The two technical methods described to get access to the LMCA are the posterior and anterior approach. The anterior approach was used in the present study (4,22).

Different methods have been used to evaluate the result of LMDSA but not on a regular basis or systematically in follow-up studies. Most reports have used coronary angiography, IVUS, MRI, trans-oesophageal echocardiography or ultra fast computed tomography and concern just one or a few patients (10-13).

The techniques we used for evaluating the LMCA after direct surgical angioplasty in our present study were MRI, coronary angiography and FFR measurements, in order to obtain both anatomic and physiologic information. In our opinion, intravascular ultrasound is suboptimal for evaluating the LMCA after surgical angioplasty. Owing to the wide funnel shape of the LMCA, the intravascular ultrasound catheter cannot be positioned centrally n the LMCA (4).

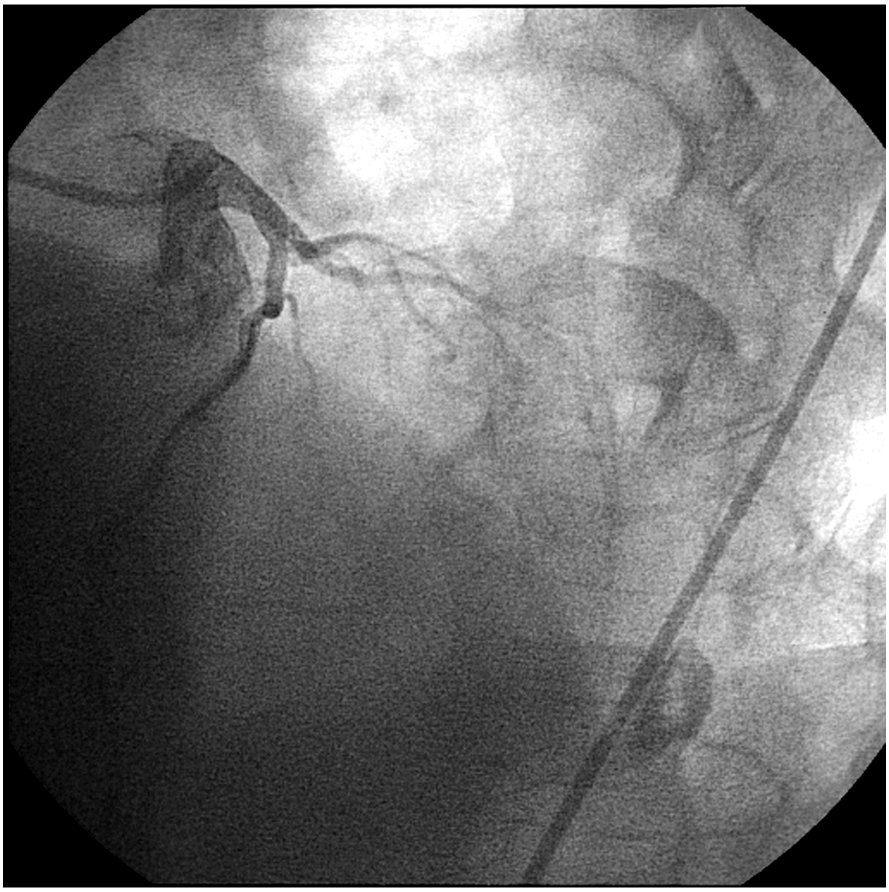
Previous reports have shown the feasibility of using MRI to evaluate the LMCA after surgical angioplasty (12). The advantage of MRI over coronary angiography is its non-invasive character and its relatively short time to perform a MRI for evaluating the LMCA. The disadvantage of MRI compared with coronary angiography is the low resolution of MRI (1-2 square mm in the present study) making quantitative assessment of a specific stenosis more difficult, although angiographic determination of degrees of narrowing of the LMCA is subject to considerable error. The angiographic errors appear to result primarily from the presence of arteriosclerotic plaque in the LMCA and an insufficient number of angiographic projections (5).

The same problem was encountered in our series of 18 patients evaluated 8 years after LMDSA . Angiography, although projections were made from different angles and MRI both failed to give specific information about the distal LMCA with respect to the functional severity of a lesion in the distal LMCA in 1 patient. This lesion appeared non-significant on angiography and could not be seen on MRI, although both modalities gave a good anatomic view of the LMCA.

The problem of anatomic evaluation of a stenosed LMCA is the poor correlation with the physiologic properties of the LMCA as we showed in previous work (9).

This emphasizes the general problem that anatomic evaluation of the LMCA often poorly corresponds with the physiologic severity of an eventual stenosis, a problem not only present in classic coronary angiography but also inherent to any anatomic method used to evaluate the LMCA.

So far, no information was available about the hemo-dynamic and physiologic properties of the LMCA after direct surgical angioplasty. An average FFR of 0.93+/_0.09, indicates that a good functional operative result was present in most patients 8 years after LMDSA. Only in 1 patient was a significant pressure drop present at the distal LMCA , which was not recognised either by coronary angiography or MRI (figure 1).This patient underwent repeated bypass surgery.



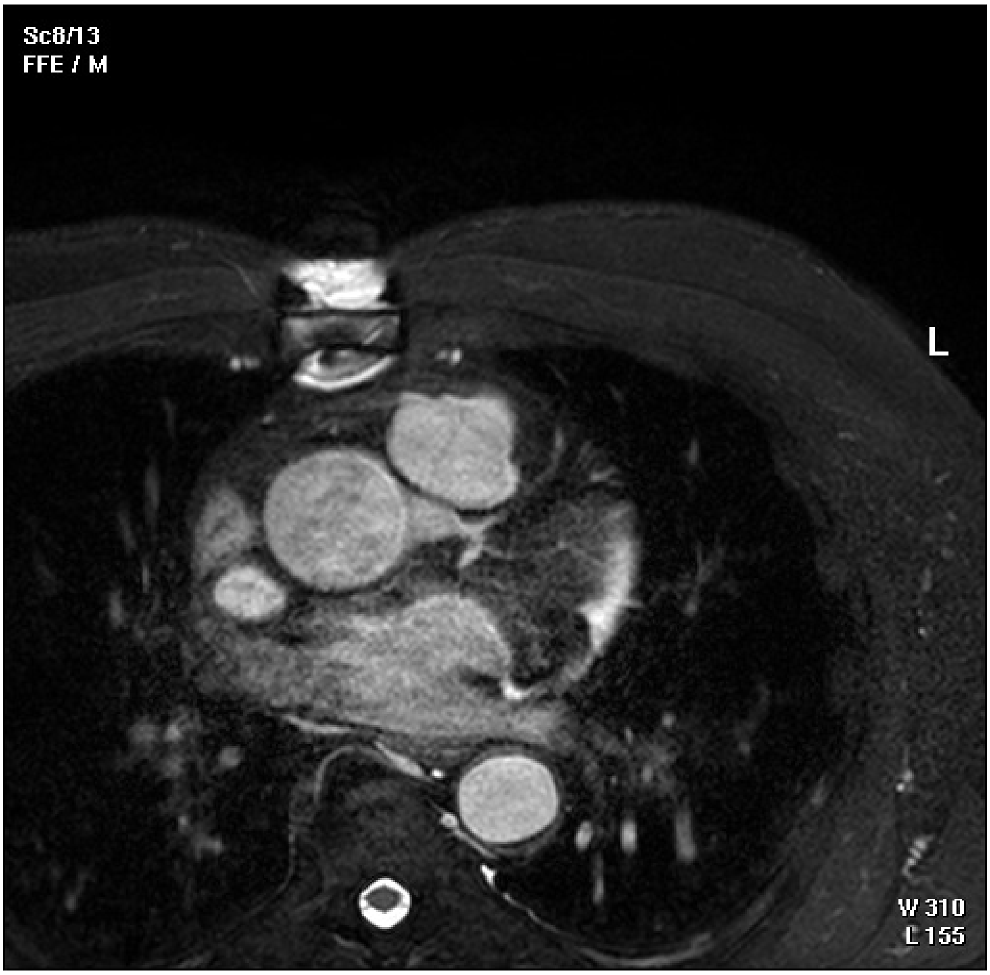


Figure 1. *A nonsignificant lesion of the distal left main coronary artery is shown with coronary Angiography. No lesion is seen with magnetic resonance imaging. Although this lesion was anatomically nonsignificant, it proved to be significant with fractional flow reserve measurement This patient underwent reoperation.*

The remaining 17 patients showed a FFR > 0.90 in the LMCA indicating there was no significant hyperaemic pressure drop in the LMCA even after 8 years of follow-up. This ruled out any flow obstruction in the LMCA after LMDSA regardless of its funnel-shaped morphology. In this cohort, 17 of 18 patients had an excellent functional result of direct surgical angioplasty after long-term follow-up

Conclusion

MRI is a safe and non-invasive way to visualize the LMCA after LMDSA, but shares the same intrinsic limitation of coronary angiography: how to assess flow obstruction. In this respect, FFR measurements are superior to evaluate the hemodynamic properties of the LMCA after LMDSA.

Invited commentary

(Ann Thorac Surg 2007;83:495)

We also believe that the surgical angioplasty of the left main coronary artery is a valuable technique inasmuch as it maintains the patency of the left main stem and antegrade perfusion, and it spares bypass material. It should be emphasized that not only ostial stenosis are amenable for surgical angioplasty, and this is important to state in an era of "all lesions" stenting. Provided that the exposure is correct, it is also a safe procedure.

The authors (3) have to be commended for their excellent clinical results and for the completeness of their angiographic and magnetic resonance follow-up after 8 years. In 1 patient, a distal stenosis of the left anterior descending artery was found, still being accessible for percutaneous transluminal coronary angioplasty, which is one of the advantages of the technique. In another patient a significant stenosis at the end of the left main coronary artery was only established after the calculation of the fractional flow reserve, which was completely missed by the magnetic resonance image, and angiography only revealed a nonsignificant narrowing.

In addition, intravascular ultrasound would have probably confirmed it, although it is also an invasive tool.

Magnetic resonance imaging has failed, but hopefully the 64-slice and even more recent the 128-slice computed tomography scan will definitively supplant all other (non-invasive) imaging modalities.

We should thank the authors for the precise analysis of their results and this important word of caution concerning the reliability of magnetic resonance imaging in this field.

References

1. De Mots H, Rosch J, McAnulty JH, Rahimtoola SH. Left main coronary artery disease. Cardiovasc Clin 1977;8:201-211
2. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery : Executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 1999;100:1464-1480
3. Park SJ, Park SW, Hong EK, et al. Stenting of unprotected left main coronary artery stenosis: Immediate and late outcomes. J Am Coll Cardiol 1998;31:37-42
4. Dion R, Verhelst R, Matta A, et al. Surgical angioplasty of the left main coronary artery. J Thorac Cardiovasc Surg 1990;99:241-250
5. Isner JM, Kishel J, Kent KM, et al. Accuracy of angiographic determination of left main coronary arterial narrowing. Circulation 1981;63:1056-1064

6. Post JC, van Rossum AC, Hofman MB, et al. Clincal utility of two-dimensional magnetic resonance imaging in detecting coronary artery disease. Eur Heart J 1997;18: 426-433
7. Jasti V, Ivan E, Yalamanchili V, et al. Correlations between fractional flow reserve and intravascular ultrasound in patients with ambiguous left main coronary artery stenosis. Circulation 2004;110:2831-2836
8. Appelbaum E, Botnar RM, Yeon SB, Manning WJ. Coronary magnetic resonance imaging: current state-of-the-art. Coron Artery Dis 2005;16:345-353
9. Bech GJ, Droste H, Pijls NH, et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. Heart 2001;86:547-552
10. Sharoni E, Erez E, Shapira Y, et al. Transesophagal echocardiogaphy evaluation and follow-up left main coronary artery patch angioplasty. Eur J Cardiothorac Surg 2003;23:585-588
11. Spencker S, Hetzer R, Kreps P, et al. Surgical angioplasty of the left main coronary artery. Evaluation and postoperative follow-up with intravascular ultrasound. Kardiol 2002;91:846-852
12. Briffa NP, Clarke S, Kugan G, et al. Surgical angioplasty of the left main coronary artery: follow-up with magnetic resonance imaging. Ann Thorac Surg 1996;62:550-552
13. Meseguer J, Hurle A, Fernandez-Latorre F, et al. Left main coronary angioplasty : mid term experience and follow-up with spiral computed tomography. Ann Thorac Surg 1998;65:1594-1598
14. Stuber M, Botnar RM, Danias PG, et a. Double-oblique free-breathing high resolution three-dimensional coronary magnetic resonance angiography. J Am Coll Cardiol 1999;34:524-531

15. Shellock F, Kanal E. Policies, guidelines and recommendations for MR imaging safety and patient management. J Magn Reson Imaging 1991;1:97-107

16. Pijls NHJ, van Gelder B, van der Voort P, et al. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation 1995;92:3183-3193

17. Pijls NHJ, de Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenosis. 1996;334:1703-1708

18. Kim WY, Danias PG, Stuber M, et al. Coronary magnetic resonance imaging for the detection of coronary stenosis. N Engl J Med 2001;345:1863-1869

19. Cademartiri F, Malagutti P, Belgrano M, et al. Non-invasive coronary angiography with 64-slice computedtomography. Minerva Cardioangiol 2005;53:465-472

20. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Circulation 1995;91:2325-2334

21. Gomberg J, Klein LW, Seelaus P, et al. Surgical revascularisation of left main coronary artery stenosis: determents of preoperative and long-term outcome in the 1980s. Am Heart J 1988;116:440-446

22. Hitchcock JF, Robles de Medina EO, Janbroes G, et al. Angioplasty of the left main coronary artery for isolated left main coronary artery disease. J Thorac Cardiovasc Surg 1983;85:880-884

23. Dion R, Elias B, El Khoury G, et al. Surgical angioplasty of the left main coronary artery. Eur J Cardiothorac Surg 1997;11:857-864

Chapter 7

Percutaneous Coronary Intervention or Bypass Surgery in Multivessel Disease? A Tailored Approach Based on Coronary pressure measurement

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Abstract

Background: In patients with multivessel disease, fractional flow reserve (FFR), calculated from coronary pressure measurement, is a reliable index to identify which of several stenoses are culprit (i.e. functionally significant). Aim of the present study was to compare long-term outcome after selective percutaneous coronary intervention (PCI) of culprit lesions only (FFR <0.75) to bypass surgery (CABG) of all stenoses.

Methods and Results*:* In 150 patients with multivessel disease referred for CABG, FFR was determined in 381 coronary arteries considered for bypass grafting.

If FFR was less than 0.75 in 3 or more stenoses or in 2 stenoses including the proximal left anterior descending (LAD) artery, CABG was performed (CABG-group). If only 1 or 2 lesions were culprit (not including the proximal LAD), PCI of those lesions was performed (PCI-group). Out of 150 patients, 87 classified for CABG and 63 for PCI. Both groups had completely similar angiographic and other baseline characteristics. At 2-year follow-up, no differences were seen in adverse events, including repeated revascularization

(event free survival 74% in CABG-group and 72% in PCI-group). A similar number of patients were free from angina (84% in the CABG-group and 82% in the PCI-group). Importantly, the results in both groups were as good as the surgical group in previous studies comparing PCI and CABG in MVD.

Conclusion*:* In patients with multivessel disease, PCI in those with 1 or 2 culprit lesions as identified by FFR <0.75, yields a similar favorable outcome as bypass surgery in those with 3 or more culprit lesions, despite similar angiographic extent of disease.

Introduction

Although percutaneous coronary intervention (PCI) was initially intended as a treatment for single vessel coronary artery disease, technical progress including the development of coronary stents, has allowed PCI to be considered as an alternative to bypass surgery (CABG) in patients with multivessel disease (MVD)[1,2].

A number of randomized studies comparing CABG and PCI in patients with MVD suggest similar outcomes with respect to death and acute myocardial infarction (AMI).However, in these studies PCI was invariably associated with an increased repeated revascularization rate and more angina pectoris at follow-up[3,4,5].

Numerous studies have shown that in patients with a similar angiographic degree of disease, the most important prognostic index to predict outcome, is the extent and severity of inducible ischemia[6,7]. Moreover, both from a symptomatic and prognostic point of view, revascularization is indicated for functionally significant stenoses only, i.e. stenoses responsible for inducible ischemia[8,9,10].

Therefore, treating all patients with MVD disease in the same way, either by PCI or CABG , is a rather crude approach and makes little sense as large differences with respect to myocardium at risk may exist between different patients with otherwise similar angiographic characteristics[6,7].

In patients with MVD, determining the physiologic significance of each lesion is challenging with noninvasive metods(11, 12). Fractional flow reserve (FFR), measured with a coronary pressure wire is an accurate and lesion-specific index for determining the functional significance of a specific stenosist[13-16].

The aim of this study is to evaluatea tailored approach to treating patients with MVD, in which the physiologic significance of each lesion is interrogated by measuring the FFR and the information is used to determine whether PCI or CABG is the most appropriate treatment strategy. In patients with three vessels with physiologically significant lesions or two vessels with physiologically significant stenosis including the proximal left anterior descending (LAD) artery, CABG was performed; the remaining patients underwent PCI of the physiologically significant lesion(s) only.

We hypothesize that the preferred revascularsation therapy in MVD can be effectively determined by measurement of individual coronary lesion hemodynamics, and that when individual lesion hemodynamics are used to guide patient selection for CABG or PCI, the relief of anginal symptoms and freedom from major adverse events will be similar.

Methods

Patient selection and study protocol

One hundred and fifty patients (105 males; 45 females; age 64 ± 13 years) were included in this study who fulfilled the following criteria: referred for mechanical revascularization of multivessel disease; suitability for both CABG and PCI of all lesions from a technical point of view; no specific contraindications for either CABG or PCI such as very severe obstructive lung disease, end-stage renal failure, or bleeding disorders. In these patients a second angiogram was performed 1-2 days before the planned CABG and FFR was measured in al diseased coronary arteries. A stenosis was defined as physiologically significant if FFR was equal to or below 0.75. In patiens with 3 vessels with physiologically significant stenosis or 2 vessels with physiologically significant stenoses involving the proximal LAD bypass surgery of all arteries with angiographically significant lesions (> 50% by quantitative coronary agiography) was performed as previously planned and according to routine. In all other patients, instead of the planned CABG, PCI was performed on the physiologically significant lesion(s) only according to standard PCI techniques in our hospital at the time of this study.

Follow-up was performed during 2 years. The study was approved by the institutional review board of the hospital and informed consent was obtained from all patients prior to the study.

Cardiac catheterization and coronary pressure measurement

After administration of 10.000 U of heparin, a right and/or left guiding catheter was advanced into the coronary ostium, 200 µg of NTG was administered intracoronarily, and angiograms were made from at least 2 orthogonal views as usual.

Thereafter, a 0.014" pressure guide wire (PressureWire, Radi Medical Systems, Uppsala, Sweden) was advanced to the tip of the guiding catheter and after equal pressures were confirmed at that location, the wire was advanced across the respective stenosis. Next, intravenous adenosine 140 µg/kg/min was administered by a femoral venous sheath to induce maximum coronary hyperemia. FFR was calculated by the ratio P_d / P_a at steady state maximum hyperemia, where P_d is mean distal coronary pressure (recorded by the pressure wire), and P_a mean aortic pressure (recorded by the guiding catheter), as described previously[11,15,16].

All measurements were performed in-duplo and after the second measurement, a pressure pullback recording was always made during sustained hyperemia to verify the appearance and disappearance of the hyperemic gradient at the site of the respective stenosis and to check for pressure drops along the coronary artery at other locations[15-17].

Study endpoints and follow-up

Clinical follow-up was performed during 2 years (with outpatient-clinic visits at 6 weeks, 6 months, 1 year, and 2 years). The primary endpoint was occurrence of major adverse cardiac events (MACE), defined in an hierarchical order as death from any cause, myocardial infarction (AMI), (repeated-) bypass surgery, or (repeated-) PCI. To avoid bias in favor of PCI, the diagnosis of AMI in surgical patients during hospital stay was only made if both the CK-MB value was greater than 5 times the upper limit of normal and new Q-waves or akinetic segments on a echocardiogram were present (3). For PCI patients , and for all patients after the discharge from the hospital, either abnormal Q-waves or enzymatic changes were sufficient.

Secondary endpoints were the functional status of the patient according to CCS-classification at 1 and 2 years and use of antianginal medication. To prevent reintervention on angiographic grounds only, invasive follow-up was not routinely performed, but only if clinically indicated.

Quantitative Coronary Angiography

QCA was performed in all patients from two orthogonal views. Reference diameter (RD), minimal lumen diameter (MLD) and stenotic diameter (SD) were calculated as the mean of both views using the guiding catheter as a scaling device.

Statistical Analysis

All comparisons were made on an intention-to-treat basis. Comparisons between continuous data were tested using the paired and unpaired *t* test. Categorical data were tested using the Fisher exact test or the Chi-square test. Patient survival curves for the absence of cardiac events were estimated according to the method of Kaplan and Meier and compared by the log-rank test. A *P* -value <0.05 was considered significant; all tests were 2-tailed. Values are presented as mean ± SD.

Results

Patient characteristics and angiographic data

Baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline characteristics used for univariate analysis of the study population and both treatment groups

	All patients n=150	CABG N=87	PCI n=63	P-value
Age (years)	64 (37-81)	63 (37-81)	65 (44-79)	0.18
Gender (M/F)	105/45	61/26	44/19	1.00
Risk factors (%)				
Smoking	45%	41%	49%	0.32
Hypertension	29%	29%	29%	1.00
Diabetes	24%	24%	24%	1.00
Hyperchol.	69%	72%	63%	0.29
Family history	50%	47%	54%	0.51
Angina Class at entry (%)				
CCS 1	0%	0%	0%	1.00
CCS 2	20%	19%	21%	0.98

CCS 3	38%	38%	38%	1.00
CCS 4	42%	43%	41%	0.98
1-v disease	0	0	0	---
2-v disease	45%	46%	44%	0.86
3-v disease	55%	54%	56%	0.87
# angiographic stenoses/pat	2.7	2.9	2.6	0.79
Ejection Fraction (%)	62±7	62±8	62±7	0.85

A total of 410 stenotic arteries were evaluated with an average of 2.7 per patient.

In a total of 101 stenotic arteries, FFR was >0.75, and in 259 arteries FFR was <0.75.

In addition, 16 total occlusions and 5 lesions which could not be crossed by the pressure wire were present precluding pre-interventional FFR measurement. Those stenoses were considered as culprit by definition. Moreover, in 29 angiographically significant lesions FFR was not measured because the respective patients had qualified already for CABG on the basis of FFR measurement in the other arteries.

Angiographic characteristics of Physiologically significant and not significant stenoses are presented in table 2. Although the average stenosis severity was slightly larger in the arteries with FFR <0.75, this difference was not significant and the overlap was so large that angiography was not suitable to identify which stenoses were culprit or not (Table 2).

Table 2. Angiographic characteristics of the culprit (FFR ≤0.75) and non-culprit stenoses (FFR >0.75)

	FFR ≤0.75	**FFR>0.75**	**P-value**
n	259	101	
RD	2.78 ± 0.51	2.85 ± 0.54	0.23
% stenosis	54 ± 12	53 ± 10	0.77
MLD	1.27 ± 0.45	1.35 ± 0.42	0.09

FFR, fractional flow reserve; RD, reference diameter; Mld, minimal luminal diameter

CABG group and PCI group

According to the study protocol, 87 patients underwent bypass surgery (CABG group) and 63 patients underwent PCI (PCI group). Except for the results of the coronary pressure measurements, both groups were similar with respect to baseline characteristics, risk factors, and angiographic extent of disease (table 1).

In the CABG-group, 270 bypasses were placed with an average of 3.1 bypasses per patient. At least one internal mammarian artery was used in 94% of them. Out of 270 bypass placed, 21 bypasses were placed on vessels not recognized as stenotic by the operator at cardiac catheterisation and therefore not evaluated by FFR, but considered as having an >50% stenosis by the cardiac surgeon.

In the PCI group, an average of 1.4 stenoses was dilated per patient and one or more stents were used in 67% of the patients, which is in accordance with the stent rate in our hospital at the time of the study.

In-hospital mortality was 1.2% in the CABG group and 0% in the PCI group and peri-procedural AMI was 1.2% and 1.6% respectively (Table 3).

Table 3. Adverse events at hospital discharge and at 2-year follow-up

	CBG group (n = 87)		PCI group (n = 63)	
	Number	%	Number	%
Adverse events at hospital discharge				
(re-) CBG	1	1.2%	0	0%
(re-) PCI	0	0%	1	1.6%
Infarction	1	1.2%	1	1.6%
Death	1	1.2%	0	0%
Total events	3	3.5%	2	3.2%
Adverse events at 2 years				
(re-) CBG	3	3.4%	3	4.8%
(re-) PCI	7	8.1%	7	11.2%
Infarction	4	4.6%	2	3.2%
Death	2	2.3%	0	0%
Total events	16	18.4%	12	19.1%

Early re-operation was not necessary in any of the patients from the CABG group and in-hospital re-intervention was performed in 1 patient from the PCI group. Other serious in-hospital complications did not occur in either of the groups.

Adverse events and CCS Class at follow-up

MACE rate at discharge from the hospital and after 2 years is presented in table 3 and event-free survival in figure 1.

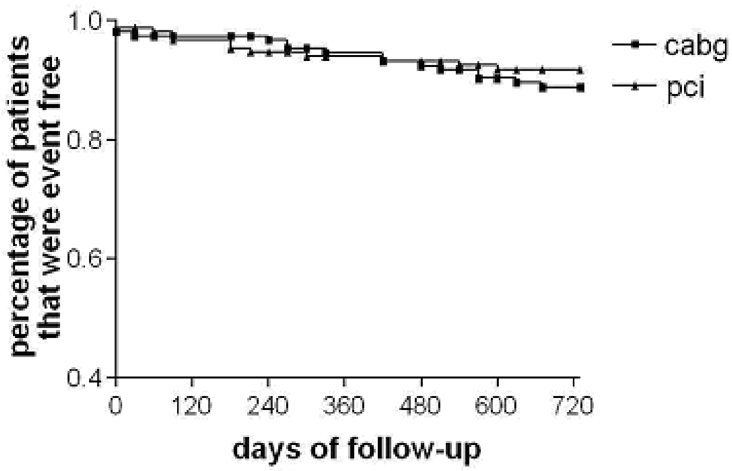

Figure 1. *Event-free survival up to 2 years in the CABG group and he PCI group in the present study.*

No differences in mortality, AMI, the need for repeat revascularization or functional class were observed between the two groups. Total MACE rate at 2 years was 18.4% in the CABG group and 19,1% in the PCI group (P=NS; table 3).

Percentage of patients free from angina after 2 years was 84% in the CABG group and 82% in the PCI group (P=NS; table 4). No differences in use of antianginal medication were present between the two groups after 2 years.

Table 4. Angina class (CCS) at 1-year and at 2-year follow-up

	CBG group (n = 85)		PCI group (n = 63)	
Class	Number	%	Number	%
Angina class (CCS) 1-year follow-up				
I	75	88%	54	86%
II	10	12%	9	14%
III	0	0%	0	0%
IV	0	0%	0	0%
Angina class (CCS) 1-year follow-up				
I	71	84%	52	82%
II	11	13%	10	16%
III	3	3%	1	2%
IV	0	0%	0	0%

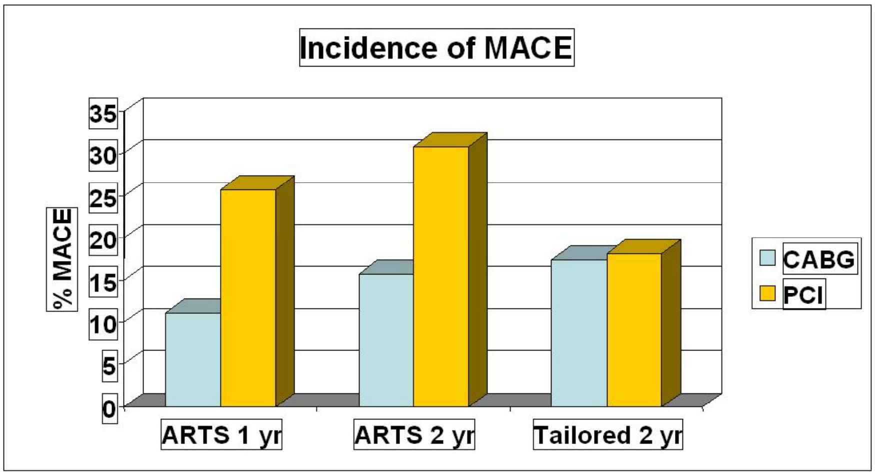

Figure 2. *Incidence of MACE in the ARTS study and in the Tailored approach (the present study) after 1 and 2 years in the CABG group and the PCI group.*

In figure 2, the MACE rate for both groups in this study is compared to the in part simultaneously performed and recently published Arterial Revascularization Therapy Study (ARTS). In the ARTS study the inclusion criteria and the extent of angiographic disease were similar to the present study, but in the ARTS study patients were assigned to CABG or PCI by randomization, without taking in account the functional significance of the individual stenoses. In the ARTS study, CABG was superior to multivessel PCI in terms of adverse events and functional class at follow-up . In contrast, as shown in Figure 2, the FFR-based tailored approach in the present study showed similarly favorable outcome in both the PCI and CABG groups, comparable the best group (CABG group) in the ARTS study[3].

Discussion

This study was not designed to answer the question of wether CABG or PCI is a better treatment in all patients with multivessel disease, but to investigate what is the optimum treatment in an individual patient with MVD.

By measuring FFR in all stenotic arteries, the population with MVD referred for bypass surgery was divided in 2 groups, not distinguishable by the extent and severity of angiographic abnormalities but by a different functional extent of coronary artery disease. Subsequently, patient who underwent CABG had more extensive coronary artery disease compared to those who underwent PCI. By performing this tailored treatment, favorable results were obtained in all patients, and were comparable to those of CABG in previous randomized studies comparing PCI and CABG in MVD disease[3,4] (figure 2). These results are clinically important because this means that in patients with MVD referred for CABG, additional functional measurements can identify a subgroup of almost 50% in whom PCI can performed with an equivalent outcome to CABG, not only with respect to death and AMI, but also with respect to the need of repeat revascularisation and anginal status.

The observation that treatment based upon the functional extent of disease, makes more sense than using strictly angiographic criteria, is not surprising. It has been known for years and demonstrated in numerous studies, that the prognosis and outcome of patients with coronary artery disease, are determined by the presence and extent of inducible ischemia and not solely by the angiographic severity of disease[6-9]. As recently described by Beller and Zaret in a large meta-analysis in 12.000 patients, the mortality and myocardial infarction rate were 12 higher in those with abnormal nuclear perfusion studies compared to those wih a normal or only mildly abnormal test, despite similar angiographic characteristics[6].

More recently, the DEFER-trial confirmed these data invasively, showing that revascularization of a physiologically non-significant stenosis (with FFR >0.75), did not influence event rate or functional class[8,9]. Although such patients had a risk for cardiac events which was slightly higher than in normal subjects, the absolute risk for cardiac death or AMI was only 1% per year and the risk for intervention less than 5% per year.

Several previous studies have been performed to evaluate the efficacy of PCI when treating culprit (i.e., hemodynamically significant) stenoses only[12,18,19,20]. However, in these studies culprit lesions were defined angiographycally or by nuclear perfusion imaging, both of which have important limitations in patients with MVD. For example, two stenosis with similar angiographic appearances may have distinctly different physiologic effects based on the extent of myocardium supplied by each vessel.

In addition, nuclear perfusion imaging is limited inits ability to identify culprit lesions in patients with MVD [11,17,21,22]. In contrast, measuring FFR is an ideal method for identifying the physiologic significance of individual stenosis in such patients andeven allows hemodynamic assessment of several stenosis within one coronary artery or plaques whether or not superimposed on diffuse epicardial disease[14,21,23,24]. Moreover, FFR accounts for the myocardial distribution of a vessel and the presence of collaterals[13-15] .

Therefore, we believe that the discrimination of stenoses responsible for reversible ischemia was more specific in the present study explaining the favorable outcome in the PCI group. Finally, it has been demonstrated recently that also narrowed coronary arteries with angiographycally mild disease may be responsible for considerable pressure gradients due to angiographycally inapparent diffuse disease[15]. Such vessels might not have been recognized and treated in earlier studies but may have benefited from revascularization in the present study.

Figure 3.

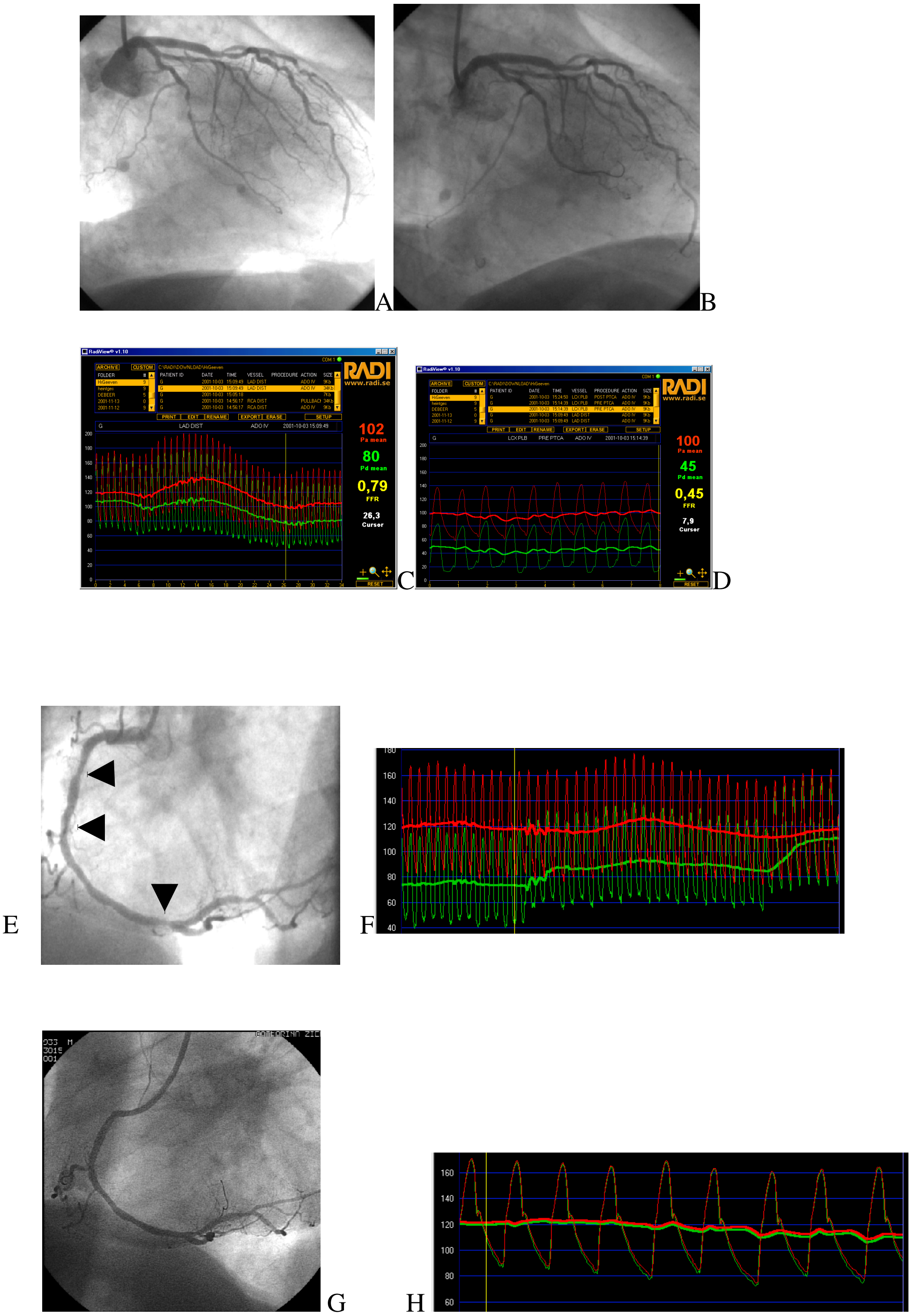

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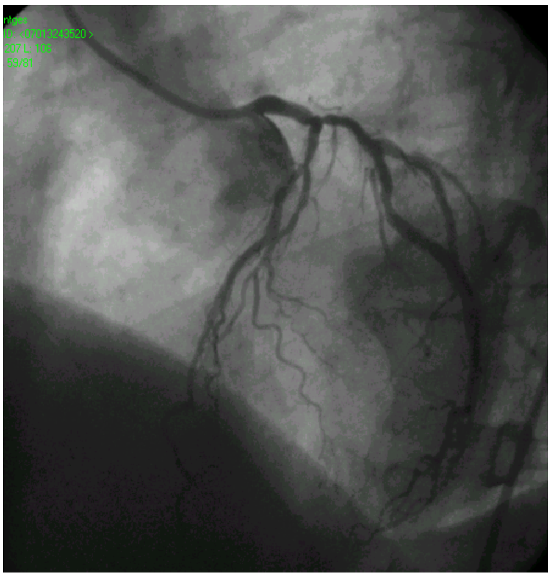
Figure 3. *Left coronary artery of a 68 year old male with angiographic three vessel disease. There is a intermediate stenosis in the mid LAD and a significant stenosis in the LCX (A). The RCA is shown in E. The LAD stenosis is not physiologically significant, as reflected by a FFR of 0.79 (C). Therefore this patient has physiologically 2 vessel disease and qualified for PCI. The LCX stenosis is significant, FFR = 0.45 (D). This lesion was subsequently treated with PCI with a good result (B). The right coronary artery shows diffuse disease (E). FFR distal in the RCA equals 0.62 (F). The pressure pullback curve at hyperemia shows that two of the multiple plaques are hemodynamically significant. The other plaques do not have hemodynamic significance. Consequently, two stents were placed at the hemodynamically significant locations; there ater a good angiographic and excellent functional result were obtained with normalization of the FFR (G and H).*

Figure 4.



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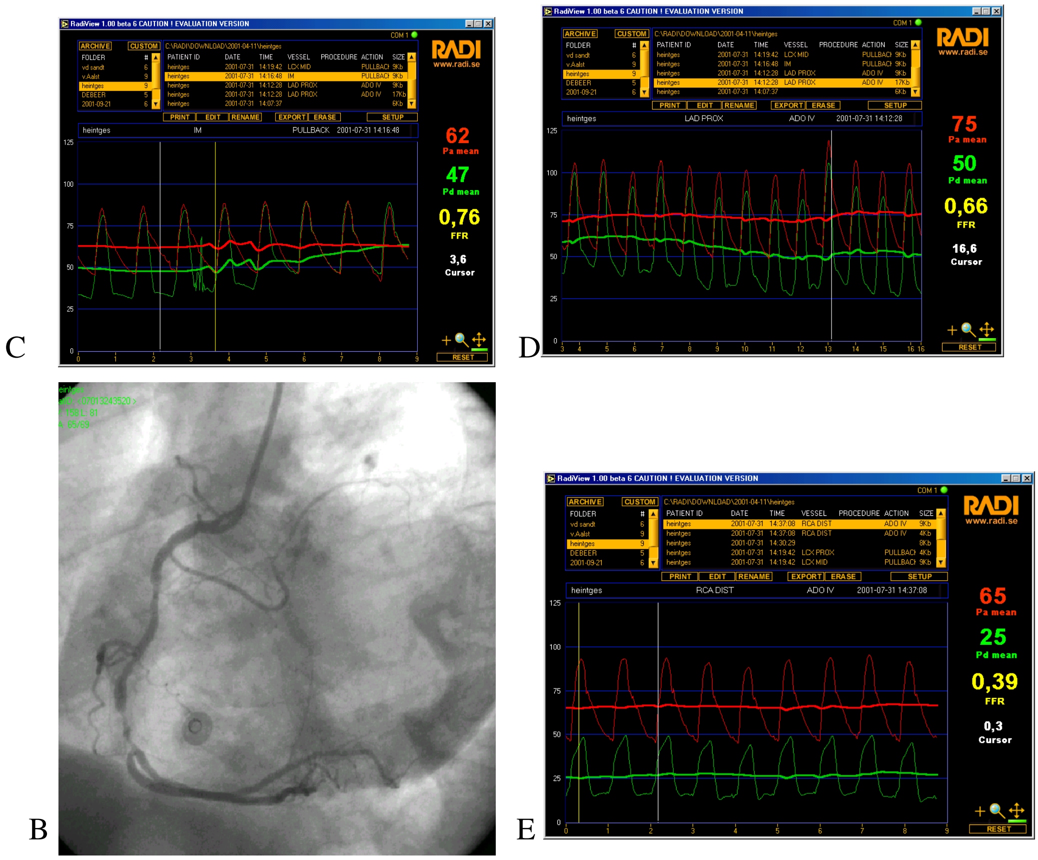

Figure 4. *Fifty-nine year old male with angina class 3 with a 50% stenosis in the LAD , 50% stenosis in the proximal LCX, and a 90% stenosis in the RCA (A and B, respectively). Despite the moderate stenosis in the LAD en LCX, these stenosis were physiologically significant, as was the lesion in the RCA (C, D, and E respectively). According o the study protocol, this patient this patient underwent bypass surgery.*

Consequences of this study in drug-eluting stent era

The present study was performed using CABG and PCI technology as available in 1999-2001. Technical progress since than, such as the development of less invasive surgical techniques and drug-eluting stents, influence the results of this study. For example, drug-eluting stents should improve outcomes further by lowerinf the revascularisation rate in those treated with PCI. Moreove, drug-eluting stents may allow percutaneous treatment of patients with diffuse disease who might otherwise have undergone CABG.

Furthermore, measuring FFR to determine the physiological significance of a lesion will be particulary important in patients with multiple lesions in the same vessel as often seen today Coronary pressure measurement and, especially the hyperemic pressure pull-back recording as used in this study, is an easy and accurate method to perform such a segmental analysis of all abnormalities along the coronary artery[15,17]. Figures 3 and 4. This tailored approach should allow appropriate use of costly drug-eluting stents, identify those spots or segments where stenting is necessary and prevent overstenting, increasing costs, and risk without benefit for the patient.

Study limitations

The present study was not randomized; treatment assignment was based on the coronary pressure measurements. This was unavoidable, however, as the intent of the study was not to compare PCI to CABG but to evaluate an FFR-guided approach t treating patients with MVD.The number of patients in this study was smaller than in previous trials comparing CABG and PCI in patients with MVD. However, given the comparable outcomes, it is unlikely that an relevant differences were missed.

Conclusions

In patients with MVD disease, coronary pressure measurement and calculation of FFR is are useful tools to identify which of several stenoses are functionally significant and contribute to reversible ischemia. In this way, patients with similar angiographic characteristics can be divided in 2 groups according to the functional extent of disease and number of physiologically significant lesions. Performing PCI in those with 1 or 2 significant lesions (42% in this study) and CABG in the group with 3 or more culprit lesions, yields a similar favorable outcome not only with respect to survival and adverse events but also with respect to the need for repeated revascularization and functional class at 2-year follow-up. Using this approach, a considerable number of patients referred for CABG can be treated as effectively with PCI

References

1. Rigter H, Meijler AP, McDonnell J, et al. Indications for coronary revascularisation: a Dutch perspective. *Heart 1997;77:211-8.*
2. Patil CV, Nikolsky E, Boulos M, et al. Multivessel coronary artery disease : current revascularization strategies. *Eur Heart J. 2001;22:1183-1197.*
3. Serruys PW, Unger F, Eduardo Sousa J, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med, 2001;345:1117-1124.*
4. Alderman EL, Andrews K, Bost J, et al. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization (BARI) Investigators. *N Engl J Med. 1996;335:217-225.*
5. Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet 1995;346:1184-9.*
6. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation. 2000;101:1465-1478.*
7. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med 1999;341:70-6.*

8. Bech GJW, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation. 2001;103:2928-2934.*
9. Wilson RF. Looks Aren't everything: FFR B4 U PTCA. *Circulation 2001;103:2873-2875.*
10. Pijls NHJ, De Bruyne B. Coronary pressure measurement and fractional flow reserve. *Heart 1998;539-542.*
11. Pijls NHJ, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med. 1996;334:1703-1708.*
12. Chamuleau SAJ, Meuwissen M, Van Eck-Smit BLF, et al. Fractional flow reserve, absolute and relative coronary flow velocity reserve in relation to the results of technetium-99 sestamibi SPECT in patients with two-vessel coronary disease. *J Am Coll Cardiol. 2001;37:1316-1322.*
13. Abe M, Tomiyama H, Yoshida H et al. Diastolic fractional flow reserve to assess the functional severity of moderate coronary artery stenoses: comparison with fractional flow reserve and coronary flow velocity reserve. Circulation 2000;102:2365-2370.
14. De Bruyne B, Pijls NHJ, Bartunek J, et al. Fractional Flow Reserve in patients with prior myocardial infarction. *Circulation. 2001;14:157-162.*
15. De Bruyne B, Hersbach F, Pijls NHJ, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "normal" coronary angiography. *Circulation. 2001;104:2401-2406.*
16. Pijls NHJ, Van Gelder B, Van Der Voort P, et al. Fractional Flow Reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation. 1995;92:3183-3193.*

17. Pijls NHJ, De Bruyne B, Bech GJW, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: Validations in humans. *Circulation. 2000;102:2371-2377.*

18. Ezechiels JP, Laarman GJ, Kiemeneij F, et al. Complete versus incomplete revascularisation in patients with multivessel coronary artery disease who are eligible for PTCA. *Cardiologie 2000;471-465.*

19. Faxon DP, Ghalilli K, Jacobs AK, et al. The degree of revascularization and outcome after multivessel coronary angioplasty. *Am Heart J 1992;123:854-859.*

20. Bourassa MG, Yeh W, Holubkov R, et al. Longterm outcome of patients with incomplete vs. complete revascularization after multivessel PTCA. *Eur heart J 1998;19:103-111.*

21. Gould KL, Nakagawa Y, Nakagawa K, et al. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by non-invasive positron emission tomography. *Circulation. 2000;101:1931-1939.*

22. Travin MI, Katz MS, Moulton AW, et al. Accuracy of dipyridamole SPECT imaging in identifying individual coronary stenoses and multivessel disease in women versus men. *J Nucl Cardiol 2000;7:213-220.*

23. Kern MJ. Coronary physiology revisited: practical insights from the cardiac catheterization laboratory. *Circulation 2000;101:1344-1351.*

24. Kern MJ, Meier B. Evaluation of the culprit plaque and the physiological significance of coronary atherosclerotic narrowings. *Circulation 2001;103:3142-3149*

Chapter 8

General Discussion and Conclusion

Blood Flow through bypass grafts

The aim of coronary bypass surgery is to restore normal coronary blood flow to diminish angina and to improve the prognosis of a patient. Although coronary bypass surgery has been performed for several decades, till recently the physiological properties of bypasses have never been studied. It has been suggested that resistance in an internal thoracic artery would be higher than in a venous bypass graft. In earlier studies it has even been suggested that resistance in an internal thoracic artery would be so high that myocardial ischemia could result, especially shortly after the operation when a large myocardial territory is depending upon this graft.

Both from the resistance model and the in vitro-model we used (chapter 3) is was concluded that an internal thoracic artery has indeed a higher intrinsic resistance than a venous bypass graft, reflected by the observation that the FFR measured distal of the anastomosis with the arterial conduit never reaches the value of 1.0 meaning that completely normal maximum blood flow is not achieved. In contrast, in the case of a venous bypass graft, normal maximum blood flow can mostly be achieved irrespective of the severity of the stenosis in the coronary artery.

In the clinical setting we also have observed this phenomenon. The FFR measured distal of the anastomosis with an arterial conduit is between 0.85 and 0.90 but does not reach the normal value of 1.0 as is seen with venous bypass grafts.

In this respect it is interesting to note that in a rather large clinical studie of Glineur at al, almost the same observations were made in patients undergoing FFR measurements in coronary bypass grafts 6 months after operation. In this study in patients without complaints, 12 left internal thoracic arteries, 10 right internal thoracic arteries and 21 venous bypass grafts were analysed. All these grafts were angiographically normal. FFR equalled 0.90±0.04, 0.95±0.03 and 0.96±0.03

respectively for the left internal thoracic arteries, right internal thoracic arteries and venous bypass grafts, thus confirming our predictions in humans (chapter 4).

A normal venous bypass has an intrinsic resistance which is almost negligible and therefore is comparable in this respect to a normal coronary artery. In the left internal thoracic artery the intrinsic resistance is higher but amply above the treshold at which myocardial ischemia might occur.

Competitive flow

As mentioned before, coronary artery bypass grafting is a well established treatment for patients with obstructive coronary artery disease. However, occlusion or narrowing of these bypasses may occur over time. During the first year after surgery thrombosis and/or fibro-intimal proliferation of the graft predominate, while later on atherosclerosis appears.

It has been suggested that grafting of less critical stenosis, which may imply lower flow rates through the bypass graft may be a risk factor for early dysfunction (within 1 year after surgery) of the graft.

Most data about bypass graft dysfunction are retrospective. It has been suggested that the patency of internal thoracic arteries would decrease as coronary competitive flow increases due to less severe stenosis rate. However, this was only concluded retrospectively so far and coronary angiography was only performed in the presence of symptoms, which might bias interpretation of data.

In the mathematical model we used (chapter 3), it was shown that the flow through the arterial conduit decreases rapidly when the FFR exceeds 0.75, which is considered as the treshold for a hemodynamically significant stenosis. The flow through the venous bypass was only slightly influenced by the flow through the coronary artery and did not decrease significantly, not even when it was placed on a almost normal coronary artery.

Measurements in the in vitro model (chapter3) showed identical findings: The flow through the arterial conduit was more influenced by the stenosis severity of the coronary artery than of the venous bypass graft.

Till recently, no prospective study was performed to assess the relation between stenosis severity using FFR and graft patency at follow-up.

In the cohort, described in chapter 4 of this thesis, 525 lesions in 152 patients were analysed pre-operatively with FFR, grafted, and after one year the patency of the bypass grafts was evaluated by coronary angiography. The primary endpoint of this study was graft patency in relation to functional stenosis severity. We found a patency rate of 91.1% of grafts on functionally significant lesions and 78.6% on non-significant lesions (p-value < 0.0001). Although the finding of a significant difference between patency rates of bypass grafts on functionally significant and functionally non-significant lesions was to be expected, the patency rate of bypass grafts on non-significant lesions is higher than mentioned in the literature. An explanation for this finding is the avoidance of negative selection of only patients in whom coronary angiography was performed because of coronary events and/or recurrent angina.

Bypass grafts on functionally significant lesions showed a patency rate of 86.3% for arterial conduits and a patency rate of 94.1% for venous bypass grafts (p-value 0.02). This finding seems surprising, but the higher intrinsic resistance of arterial conduits may lead to lower flow through these conduits accompanied by lower patency rate after one year.

The somewhat disappointing results of arterial revascularisation are attributed to the low patency rates of the radial artery conduits. The patency of the left internal thoracic artery was 93.8%, in accordance with literature.

The low patency rate of radial artery conduits in our study is attributed to the fact that these conduits were often anastomosed on the right or circumflex coronary artery with a diameter < 2.0 mm. It is know that the patency of radial artery conduits is strongly related to stenosis severity, diameter of the stenosed coronary artery, and site of the anastomosis.

Another surprising finding in our study is the high patency rate of venous grafts after one year, which is 94% and higher than in previous literature. Also this finding can be explained, at least in part, by the fact that this was a prospective study with a complete follow-up. Repeat angiography was performed in all patients and was not driven by angina or coronary events.

Bypass grafts on functionally non-significant lesions showed no difference in patency rate between arterial or venous bypass grafts after one year (78.1% versus 80%). These patency rates are higher than reported in previous studies, which were not prospective and symptom-driven.

It is concluded that competitive flow influences the patency rate of bypass grafts in a negative way, which effect is more pronounced in arterial conduits than in venous conduits. However this finding is of less importance for the individual patient: as expected, patients with patent or occluded bypass grafts on non-significant lesions did not suffer from an excess of angina or repeat coronary interventions.

Therefore, when a patient is scheduled for coronary artery bypass surgery and no functional information is available, it might be adequate to bypass also intermediate lesions, given the limited reliability of the angiogram and the relative harmlessness of grafting a non-significant stenosis. For optimum treatment in terms of physiology, all such lesions in the coronary arteries should be measured before any revascularization.

Morphology or physiology

Fundamentally, two principal approaches are available to assess the severity of a coronary stenosis, the morphological approach and the physiological approach. The different morphological methods and physiological methods are described in chapter 2. For optimum diagnosis and treatment of coronary artery disease, in fact angiographic and physiologic approaches play a complementary role.

Till recently, coronary angiography was the gold standard of these morphological methods and is still used as such in many centers. The interpretation of coronary angiograms is of vital interest to cardiologists and cardiac surgeons if they have to make informed decisions about their patients. Also in the future, coronary angiography will play a pivotal role in providing a road map for the interventionalist to be guided to the locations of coronary lesions. However, the interpretation of the stenosis severity is often difficult and different angiographers may interpret the stenosis severity quite different.

Several alternative anatomic approaches have been introduced but none of them can replace coronary angiography.

IVUS has several unique properties in the detection and quantification of coronary artery disease. Not only the lumen of the vessel is visualised, but also the wall of the coronary artery. But IVUS is time-consuming, expensive and requires skills beyond that of the regular angiographer.

Also the role of MRI has been somewhat disappointing so far: Coronary arteries are small structures and follow a tortuous course, and are intimate with many surrounding structures, making them difficult to visualize by MRI. This problem is also encountered with MSCT, calcium deposits in coronary arteries, previous stent implantation, an irregular rhythm and motion artefacts makes interpretation of the views difficult and non-reliable.

The physiological significance of a stenosis cannot be established by the morphologic methods mentioned above. FFR is the gold standard for physiological stenosis severity assessment and a value below 0.75 indicates a functionally significant stenosis.

In chapter 5 and 6 two studies are described comparing morphological methods with FFR measurements to assess the result of surgical left main angioplasty after 8 years of follow up. We showed that it is feasible to evaluate the left main after surgical angioplasty with MRI and IVUS, but these modalities shares the same intrinsic limitation as coronary angiography: They were not always reliable to indicate impaired flow. In this respect FFR measurements are superior and indispensable to evaluate the hemodynamic properties of the left main coronary artery after surgical angioplasty.

Multi-vessel disease

Percutaneous coronary intervention (PCI) was initially intended to treat single vessel disease, but due to improvement of the techniques and the introduction of coronary stents its use has been extended to treat multi-vessel disease. Data of randomised studies comparing coronary bypass surgery (CBG) with multi-vessel PCI shows equal results in preventing death and acute myocardial infarction. However, excess repeated interventions and more angina at follow-up was invariably associated with PCI for multivessel disease.

It is well known that in patients with the same degree of angiographic disease, the extent and severity of inducible ischemia are the most important prognostic factors. In other words only revascularisation of the lesions responsible for inducible ischemia, the “culprit” lesions, is warranted both from a symptomatic and prognostic point of view. Therefore, treating multivessel disease with CBG or PCI irrespective of the functional significance of the different lesions makes little sense.

To investigate the optimum treatment in patients with multi-vessel disease we measured the FFR in all stenotic coronary arteries in a population of 150 patients (chapter 7). This population with multi-vessel disease was split up in two groups, not distinguishable by the severity of angiographic abnormalities but by the severity of functional disease. In patients with anatomic and functional 3-vessel-disease, CBG was performed; whereas in patients with functional 1-or 2-vessel-disease (not including the proximal LAD artery) 1- or 2-vessel PCI was performed. This was called the 'tailored approach'. Both groups did equally well after 2 years of follow-up.

This tailored approach shows that in patients with multi-vessel disease, from the symptomatic and prognostic point of view, functional assessment of the different stenoses is more important than angiographic evaluation. Moreover, almost 50% of the patients with multi-vessel disease can equally well be treated by PCI instead of CBG if all stenoses are functionally evaluated before any revascularization.

Conclusions

From the studies, performed within the scope of this thesis, the following conclusions can be drawn:

1. Coronary artery bypass surgery is a highly effective and durable treatment to restore blood flow in atherosclerotic coronary heart disease. This is not new in itself but the patency rate, and thereby the efficiency of treatment, was extremely high in this prospective study in a large patient cohort with almost complete follow-up.

A patency rate of 94% at one year for venous grafts has never been described before, whereas the patency rate of 94% for the internal mammarian artery grafts is in accordance with literature.

Also the rather low patency rate of radial grafts is in accordance with previous literature.

2. There is a strong inverse correlation between graft patency at one year and physiologic (hemodynamic) significance of the original stenosis in the grafted artery.

   Such inverse correlation is also present for anatomic stenosis severity but not as strong as the former one.

3. Especially arterial grafts, the radial more than the internal thoracic, are vulnerable to graft occlusion in case of grafting to a hemodynamically non-significantly narrowed coronary artery.

   In case of doubt with respect to using an arterial graft to bypass a coronary artery with an equivocal stenosis, measurement of FFR is indicated.

4. Premature occlusion of a bypass graft to a hemodynamically non-significantly narrowed coronary artery seldom leads to complaints or adverse events

5. It is feasible to evaluate the left main coronary artery after surgical angioplasty by MRI and IVUS, but these methods share the same intrinsic limitation as coronary angiography: how to assess flow impairment. In this respect FFR measurements are superior and indispensable to evaluate the hemodynamic properties of the left main coronary artery after surgical angioplasty.

   Surgical left main coronary angioplasty for isolated left main disease is not recommended as first choice treatment, but should be in the armourmement of the cardiac surgeon.

6. In patients with multivessel coronary artery disease, systematic measurement of fractional flow reserve enables to divide these patients in two groups: one group in whom

physiologic 3-vessel-disease is present and one group with physiologic 1- or 2-vessel-disease. One- or 2-vessel PCI in the latter group is equally effective as bypass surgery in the first group (having similar anatomic but more severe functional disease). This conclusion is valid for PCI with bare metal stents and might be modified in the drug-eluting stent era.

Chapter 9

Summary

Chapter 1

The objectives of this thesis are: 1. to acquire more insight in the mutual influence of native coronary artery blood flow and bypass function, both from the theoretical point of view and in a prospective clinical study; 2. to compare functional methods, especially fractional flow reserve (FFR), with anatomic standards (both invasive and non-invasive) in subsets of patients after bypass surgery; and 3. to investigate the usefulness of FFR in patients with multi-vessel disease to stratify them in one arm suitable for percutaneous intervention (PCI) and another arm more suitable for coronary bypass surgery (CBG), the so-called "tailored" approach.

Chapter 2

This chapter shows an overview of the different morphological and physiologic approaches to evaluate the severity of coronary artery disease.

Invasive morphological methods as coronary angiography and intra-vascular ultrasound (IVUS) are described . Coronary angiography is still the anatomically gold standard to evaluate coronary artery disease, but has several limitations in interpretation of the filmed views. IVUS has unique properties to detect and quantify coronary artery disease, but fails to provide adequate functional information about a stenosis.

Magnetic resonance imaging (MRI) and multi-slice computed tomography (MSCT) are non-invasive morphologic entities to evaluate coronary artery disease. However, detection and quantification of coronary disease with the present state of technology is still inferior to angiography and not accurate enough for clinical decision making.

Two physiological methods to assess functional severity of a coronary stenosis are described: 1. coronary flow reserve (CFR) and 2. fractional flow reserve (FFR). Although the concept of CFR has largely contributed to the understanding of coronary physiology, this index has limited value for the functional assessment of stenosis severity. In contrast, FFR is now recognized as the gold standard for functional assessment of epicardial stenosis severity with a circumscribed threshold of 0.75 to detect ischemia

Chapter 3

For both arterial and venous conduits, early graft dysfunction is a well known problem after coronary bypass surgery. Although this phenomenon is not completely understood, it has been suggested that grafting non-significantly stenosed coronary arteries promotes this condition.
A mathematical and in vitro model were used to establish the influence of the functional severity of a stenosis in a coronary artery (reflected by fractional flow reserve) on the flow in an arterial or venous bypass graft.
Both models showed that the flow through arterial conduits is more influenced by the severity of the stenosis in a native coronary artery than flow in venous conduits due to the difference in intrinsic resistance. The flow through an arterial conduit decreases more rapidly with less severe stenosis in a coronary artery compared to flow trough a venous conduit. Moreover, in both models myocardial blood flow never reaches its normal value when using an arterial conduit. When using a venous conduit, the normal myocardial blood flow could be achieved.
In conclusion, decrease of flow in an arterial or venous conduit anastomosed on a coronary artery with a mild stenosis can contribute to early dysfunction of such graft.
Arterial conduits are more susceptible to this phenomenon than venous conduits.

Chapter 4

After coronary bypass surgery occlusion or narrowing of bypass grafts may occur over time. It has been suggested that grafting of less critical stenosis may be a risk factor for early dysfunction of the graft. This hypothesis, although important, has never been tested prospectively in patients.
In 164 patients eligible for coronary bypass surgery, not suitable for percutaneous intervention and with at least one intermediate lesion, fractional flow reserve was measured in all lesions to be grafted to establish if a lesion was functionally significant or not. The surgeon was blinded to the results of these measurements. One year after surgery coronary angiography was performed to establish bypass graft patency.
At coronary angiography after one year 8.9% of all bypass grafts on functionally significant lesions were occluded and 21.4% of all bypass grafts on functionally non-significant lesions were occluded. There was no difference in angina class or repeat interventions between patients with or without occluded bypass grafts.
The patency of bypass grafts on functionally significant lesions is significantly higher than the patency of bypass grafts on non-significant lesions, however this finding has little clinical relevance as patients with patent or occluded bypass grafts on non-significant lesions did not suffer from an excess of angina or repeat interventions.

Chapter 5

Direct surgical angioplasty of the left main coronary artery is aimed to restore a more physiological flow of the left coronary artery compared to conventional bypass surgery and allows subsequent percutaneous coronary interventions of more distal coronary lesions if necessary. Only few data are known on long-term outcome in these patients.

In 1996 and 1997, in 31 patients in our hospital, surgical angioplasty of the left main coronary artery was attempted. The left main coronary artery was approached in the anterior way. Follow-up was performed during 8 years and concluded by invasive anatomic and functional evaluation of the left main coronary artery.

In 4 of these patients, the procedure was converted to conventional bypass surgery due to calcification of the left main coronary artery. Of the remaining 27 patients, 3 patients died in the peri-operative period and 4 other patients died during follow-up. In 18 of the 20 survivors, coronary angiography was performed after 8 years and the left main coronary artery was also evaluated by intra-vascular ultrasound (IVUS) and coronary pressure based fractional flow reserve measurement (FFR). At angiography and IVUS, a dilated funnel shaped left main coronary artery was seen in all of these patients. In 1 patient, a hemodynamical significant left main coronary artery stenosis was present (FFR < 0.75) and in this patient coronary-artery bypass surgery was performed.

Although the majority of the survivors had a satisfactory anatomic and physiologic result after direct surgical angioplasty of the left main coronary artery, the total mortality of 23% was disappointing and we do not recommend this procedure as a first choice treatment for left main coronary artery disease.

Chapter 6

Few data on anatomic evaluation with coronary angiography and MRI are known, but no physiologic evaluation has been reported yet.

In the 18 patients described in chapter 5, also MRI was performed and these data were compared to FFR measurement. MRI showed a similar dilated funnel shaped left main coronary artery in all 18 patients, but failed to demonstrate a flow-limiting lesion in the distal left main coronary artery in 1 patient. The functional severity was shown by fractional flow reserve measurement and subsequently this patient underwent repeated bypass surgery.

MRI is a safe and non-invasive modality to visualise the left main coronary artery also after direct surgical angioplasty of the left main coronary artery but due to the low resolution properties quantitative assessment of a lesion is not reliable. Fractional flow reserve is mandatory to evaluate the hemo-dynamic properties of the left main coronary artery after direct surgical angioplasty.

Chapter 7

In patients with multivessel disease, fractional flow reserve (FFR), calculated from coronary pressure measurement, is a reliable index to identify which of several stenoses are culprit (i.e. functionally or hemodynamically significant). Aim of the present study was to compare long-term outcome after selective percutaneous coronary intervention (PCI) of culprit lesions only (FFR <0.75) to bypass surgery (CBG) of all stenoses.

In 150 patients with multivessel disease referred for CBG, FFR was determined in 381 coronary arteries considered for bypass grafting.

If FFR was less than 0.75 in 3 or more stenoses or in 2 stenoses including the proximal left anterior descending (LAD) artery, CBG was performed (CBG-group). If only 1 or 2 lesions were culprit (not including the proximal LAD), PCI of those lesions was performed (PCI-group).
Out of 150 patients, 87 classified for CBG and 63 for PCI. Both groups had completely similar angiographic and other baseline characteristics. At 2-year follow-up, no differences were seen in adverse events, including repeated revascularization (event free survival 74% in CBG-group and 72% in PCI-group). A similar number of patients were free from angina (84% in the CBG-group and 82% in the PCI-group). Importantly, the results in both groups were as good as the surgical group in previous studies comparing PCI and CBG in MVD, like the ARTS-I study.
In patients with multivessel disease, PCI in those with 1 or 2 culprit lesions as identified by FFR <0.75, yields a similar favourable outcome as bypass surgery in those with 3 or more culprit lesions, despite similar angiographic extent of disease.

Chapter 8

In this chapter, the data collected within the several studies of this thesis are discussed within a wider scope and the most important conclusions are summerized.

Chapter 10

Summary in Dutch

Hoofdstuk 1

De doelstellingen van dit proefschrift zijn de volgende: 1. het verkrijgen van meer inzicht in de wederzijdse invloed van de bloedstroom door een kransslagader (coronair arterie) en de functie van een omleiding (bypass); 2. het vergelijken van verschillende functionele onderzoeksmethoden, met name de fractionele flow reserve (FFR), met de gangbare anatomische onderzoeken (zowel invasief als niet invasief) bij groepen patiënten die een hartoperatie hebben ondergaan; 3. het onderzoeken van de bruikbaarheid van FFR bij patiënten meer meertaks coronaria lijden, om onderscheid te maken in twee groepen, één groep die geschikt is voor het ondergaan van een percutane coronaire interventie (PCI) en een andere groep die geschikt is om een bypass operatie (CBG) te ondergaan. Dit wordt de zogenaamde "tailored" approach genoemd, hetgeen wil zeggen een op maat gesneden behandeling.

Hoofdstuk 2

In dit hoofdstuk wordt een overzicht gegeven over de verschillende morfologische en fysiologische methoden om de ernst van het coronaria lijden te evalueren.
Invasieve morfologische methoden zoals coronair angiografie en intra-vasculaire echo (IVUS) worden beschreven. Coronair angiografie is nog steeds de gouden standaard als het gaat om de evaluatie van de kransslagaders, maar dit onderzoek heeft een aantal beperkingen als het gaat om de interpretatie van het angiogram. IVUS heeft unieke eigenschappen om coronaria lijden te ontdekken en te quantificeren, maar kan geen functionele informatie over de ernst van een vernauwing (stenose of lesie) geven. Magnetic resonance imaging (MRI) en multi-slice computed tomography (MSCT) zijn niet-invasieve methoden om coronaria lijden te evalueren, echter op dit

moment zijn zij nog inferieur aan coronair angiografie en niet betrouwbaar genoeg om er klinische besluitvorming op te baseren.

Twee fysiologische methoden om de functionele ernst van een stenose te bepalen worden eveneens beschreven: 1. coronaire flow reserve (CFR) en 2. fractionele flow reserve (FFR). Hoewel het concept van de CFR veel heeft bijgedragen tot het begrip van de coronaire fysiologie, heeft deze index een beperkte waarde om de functionele ernst van een stenose te bepalen. In tegenstelling hiermee wordt de FFR erkend als de gouden standaard voor het bepalen van de functionele ernst van een stenose waarbij er een duidelijke cut-off waarde is van 0.75 om het tekort aan zuurstofgehalte (ischemie) te detecteren.

Hoofdstuk 3

Zowel voor arteriele als veneuze omleidingen is vroege dysfunctie van een omleiding een bekend probleem na bypass chirurgie. Hoewel dit fenomeen niet volledig wordt begrepen, wordt gesteld dat het aanleggen van een bypass op een niet significant vernauwde coronair arterie zulk een dysfunctie bewerkstelligt. Een mathematisch en in-vitro model werden gebruikt om de invloed van de functionele ernst van een stenose in een coronair arterie (weergegeven door de fractionele flow reserve) vast te stellen op de flow in een arteriele of veneuze bypass.

Beide modellen lieten zien dat de flow door een arteriele bypass meer wordt beinvloed door de ernst van de stenose in een coronair arterie dan de flow in een veneuze bypass. Dit wordt verklaard door het verschil in intrinsieke weerstand van deze omleidingen. De flow door een arteriele bypass neemt sneller af bij afnemende ernst van een stenose in een coronair arterie dan de flow door een veneuze bypass. Sterker, in beide modellen bereikte de myocardiale bloedstroom nooit zijn normale maximale waarde als er een arteriele omleiding werd gebruikt.

Bij gebruik van een veneuze bypass werd de normale maximale myocardiale bloedstroom wel bereikt. Concluderend kan gesteld worden dat de afname van flow in een arteriele of veneuze bypass die geplaatst is op een coronair arterie met een milde stenose kan bijdragen tot vroege dysfunctie van een omleiding. Arteriele omleidingen zijn hier gevoeliger voor dan veneuze omleidingen.

Hoofdstuk 4

Na bypass chirurgie kan na verloop van tijd een vernauwing en afsluiting optreden van de geplaatste omleidingen. Zoals al in hoofdstuk 3 vermeld is, wordt aangenomen wordt dat het plaatsen van een omleiding op een coronair arterie met een niet ernstige stenose een risico factor kan zijn voor het optreden van vroege dysfunctie of afsluiting van een omleiding. Deze hypothese is van belang maar was tot op heden nooit prospectief in een klinische studie onderzocht.
Bij 164 patiënten, die geaccepteerd waren voor bypass chirurgie, en tenminste één intermediaire stenose hadden werd de fractionele flow reserve gemeten in alle bloedvaten waarop omleidingen geplaatst zouden worden om vast te stellen of de betreffende bloedvaten functioneel significant vernauwd waren of niet. De chirurg was niet op de hoogte van de resultaten van deze hemodynamische metingen. Eén jaar na de operatie werd een her-angiografie verricht om de omleidingen te beoordelen.
Hierbij bleek dat 8.9% van de omleidingen die waren geplaatst op functioneel significant vernauwde bloedvaten afgesloten waren en 21.6% van de omleidingen die op niet-significant vernauwde bloedvaten waren geplaatst. Er was geen verschil in angina pectoris klasse of re-interventies tussen patiënten met of zonder afgesloten omleidingen.

Hoofdstuk 5

Het eerste deel van de linkerkransslagader wordt de hoofdstam genoemd en de behandeling van vernauwingen in deze hoofdstam brengt specifieke problemen met zich mee. Eén behandelingsmogelijkheid is een zogenaamde hoofdstam plastiek met als doel het herstellen van fysiologische flow in de linker coronair arterie in vergelijking met conventionele bypass chirurgie. Bovendien kan dan indien nodig via de hoofdstam nog een percutane interventie worden verricht van meer distaal gelegen lesies. Data betreffende long-term follow-up van dit soort patiënten zijn schaars.

In 1996 en 1997 werden 31 patiënten in ons ziekenhuis voor een chirurgische hoofdstam plastiek gepland. De patiënten werden gedurende 8 jaar gevolgd waarna een invasieve anatomische en functionele evaluatie verricht werd van de hoofdstam.

In 4 patiënten werd de ingreep geconverteerd naar conventionele bypass chirurgie, als gevolg van calcificatie van de hoofdstam. Van de overige 27 patiënten overleden er 3 in de peri-operatieve periode en 4 gedurende verdere follow-up. Bij 18 van de 20 overgebleven patiënten werd een coronair angiogram verricht na 8 jaar follow-up en de hoofdstam werd verder nog geevalueerd met intravasculaire echo (IVUS) en fractionele flow reserve (FFR). Zowel bij aniografie als bij IVUS werd een gedilateerde trechter vorm van de hoofdstam gezien bij alle patiënten. Bij 1 patient werd er een hemodynamisch significante (FFR < 0.75) afwijking gevonden in de hoofdstam en deze patient onderging een bypass operatie.

Hoewel de meerderheid van de overlevenden een goed anatomisch en fysiologisch resultaat van de chirurgische hoofdstam plastiek hadden, was de totale mortaliteit van 23% teleurstellend en wordt deze chirurgische techniek niet als eerste keus voorgesteld bij een vernauwing van de hoofdstam.

Hoofdstuk 6

Er zijn weinig gegevens beschikbaar betreffende angiografie en MRI van de hoofdstam na chirurgische hoofdstam plastiek. Een fysiologische evaluatie is in dit kader nooit verricht.

Bij de 18 patiënten die in hoofdstuk 5 invasief werden geevalueerd, werden de resultaten van MRI vergeleken met de FFR metingen. MRI liet een gedilateerde trechter vorm zien van de hoofdstam bij alle patiënten. Bij één patient echter werd een hemodynamisch significante lesie in de distale hoofdstam gemist. De functionele ernst van deze lesie werd wel aangetoond met FFR meting en vervolgens onderging deze patient een bypass operatie.

MRI is een veilige en niet-invasieve modaliteit om de hoofdstam te evalueren ook na chirurgische hoofdstam plastiek, maar tengevolge van de lage resolutie is functionele analyse van een vernauwing niet betrouwbaar. Fractionele flow reserve metingen zijn nodig om de hemo-dynamische eigenschappen van de hoofdstam na chirurgische hoofdstam plastiek te evalueren.

Hoofdstuk 7

De fractionele flow reserve (FFR) berekend met coronaire druk metingen is een betrouwbare index om functioneel of hemodynamisch significante vernauwingen vast te stellen. Met significant wordt bedoeld dat zulk een vernauwing gepaard gaat met induceerbaar zuurstofgebrek van de hartspier. Het doel van de studie zoals beschreven in hoofdstuk 7 was om bij patiënten met meertaks coronaria lijden de resultaten van selectieve percutane coronaire interventie (PCI) van uitsluitend significante stenosen te vergelijken met bypass chirurgie (CBG) van alle stenosen na 2 jaar follow-up.

Bij 150 patiënten met coronaire meertaks lijden die verwezen waren voor CBG, werd de FFR gemeten in 381 kransslagaders die in aanmerking kwamen voor een omleiding.

Indien de FFR kleiner was dan 0.75 in 3 of meer vaten of in 2 vaten inclusief de proximale ramus descendens anterior (LAD) werd een bypass operatie verricht (CBG-groep). Als er slechts in 1 of 2 vaten, exclusief de proximale LAD, een significante stenose aanwezig was werd er een PCI verricht (PCI-groep).

Van de 150 patiënten kwamen er 87 in aanmerking voor CBG en 63 voor PCI. Beide groepen hadden dezelfde angiografische karakteristieken. Ook wat betreft overige variabelen kwamen zij overeen. Na 2 jaar follow-up werden er geen verschillen gezien in mortaliteit, aantal hartinfarcten of herhaalde interventie. (74% van de patiënten in de CBG-groep en 72% van de PCI-groep waren vrij van complicaties). Een vergelijkbaar aantal patiënten had geen angina pectoris meer (84% in de CBG-groep en 82% in de PCI-groep). Bovendien waren de resultaten van beide groepen even zo goed als die van de chirurgische groep in eerdere studies die PCI en CBG vergeleken bij patiënten met meertaks coronaria lijden zoals de ARTS-I studie.

Niet alleen wat betreft overleving, hartinfarcten, re-operaties of re-PCI maar ook wat betreft de kwaliteit van leven (functionele klasse) waren de beide groepen dus even goed af.

Hoofdstuk 8

In dit hoofdstuk worden de gegevens verkregen uit de verschillende studies in een breder perspectief besproken en worden de belangrijkste conclusies samengevat.

Chapter 11

Publications of the author

1. Botman CJ, Hillen HF, Sanders HW. Thymus hyperplasia in Graves disease. Ned Tijdschr Geneesk 1987 ;131:1002-4.
2. Botman CJ, Mulder AW, Hoorntje SJ. Kidney insufficiency following use of enalapril for congestive heart failure. Ned Tijdschr Geneesk. 1987 ;131:1402-4.
3. Botman CJ, El Gamal M, El Deeb F, et al. Percutaneous transluminal coronary angioplasty more than twice for the same coronary lesion. Eur Heart J 1989;10:112-6.
4. Hillen HF, Breed WP, Botman CJ. Scalp cooling by cold air for the prevention of chemotherapy-induced alopecia. Neth J Med 1990;37:231-5.
5. Van Gelder BM, Bracke FA, Oto A, Yildirir A, Haas PC, Seger JJ, Stainback RF, Botman KJ, Meijer A. Diagnosis and management of invertently placed pacing and ICD lead in the left ventricle: a multicentre experience and review of the literature. Pacing Clin Electrophysiol 2000;23:877-83
6. Romberg-Camps MJ, Korsten HH, Botman CJ, et al. Right ventricular failure in acute respiratory distress syndrome. Neth J Med 2000;57:94-7.
7. Roeffel S, Bracke F, Meijer A, Van Gelder B, Van Dantzig JM, Botman CJ, Peels K. Transesophagal echocardiographic evaluation of tricispid valve regurgitation during pacemaker and implantable cardioverter defibrillator lead extraction. Pacing Clin Electrophysiol. 2002;25:1583-6
8. Botman KJ. Zoektocht, een reisverhaal (roman). Servo uitgevers. April 2003.
9. Aarnoudse WH, Botman KJ, Pijls NH. False-negative myocardial scintigraphy in balanced three-vessel-disease, revealed by coronary pressure measurement. Int J Cardiovasc Intervent. 2003;5:67-71.

10. Botman KJ, Pijls NH, Bech JW, et al. Percutaneous intervention or bypass surgery in multivessel disease? A tailored approach based on coronary pressure measurement. Catheter Cardiovasc Interv. 2004;63:184-91.
11. Berger A, Botman KJ, MacCarthy PA, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. J Am Coll Cardiol. 2005;46:438-42.
12. Aarnoudse W, Geven M, Barbato E, Botman KJ et al. Effect of phentolamine on the hyperemic response to adenosine in patients with microvascular disease. Am J Cardiol. 2005;96:1627-30.
13. Botman CJ, Aarnoudse W, Penn O, Pijls NH. Long-term outcome after surgical left main coronary angioplasty. Ann Thorac Surg. 2006;81:828-34.
14. Aarnoudse W, Botman CJ, Pijls NH. Pressure wire. P Lanzer Ed. Mastering Endovascular Techniques. Lippincott, Williams and Wilkins. 2007.
15. Botman CJ, Post H, Penn O, Pijls NH. Value of magnetic resonance imaging, angiography, and fractional flow reserve to evaluate the left main coronary artery after direct surgical angioplasty. Ann Thorac Surg 2007;83:490-4.
16. Pijls NH, Botman KJ. Functional assessment of bypass grafts by fractional flow reserve. Eur J Cardiothorac Surg. 2007;31 :381-2.
17. Botman CJ, Schonberger J, Koolen J, Penn O, Botman H, Dib N, Eeckhout E, Pijls NH. Does stenosis severity of native vessels influence bypass graft patency ? A prospective fractional flow reserve-guided study. 2007;83:2093-7.

Chapter 12

Acknowledgements (Dutch)

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Chapter 13

About the author

The author was born on september the 19th 1958 in the city of Hoorn, in The Netherlands.
He attended primary school in Medemblik and Bunnik and secondary school at the Stedelijk Gymnasium in the city of Utrecht.
He entered medical school at the Vrije Universiteit in the city of Amsterdam in 1977, and obtained his medical degree in 1984.
From 1985 to 1989 he worked as a resident in internal medicine in the Catharina hospital Eindhoven under supervision of Dr. H. Hillen. In 1989 he started working as a resident in cardiology also in the Catharina hospital Eindhoven under the supervision of Dr. Mamdouh El Gamal.
After his registration as cardiologist he worked for three year in the Gooi Noord hospital Blaricum. In 1997 he returned to the Catharina hospital to be trained as an interventional cardiologist and became a member of the staff in 2000.
From 2000 on he combined his work as a interventional cardiologist with the studies performed within the scope of this thesis.
He has 5 children and is married to Hilde Baggerman . They share the same affection to old cars, gardening and animals.