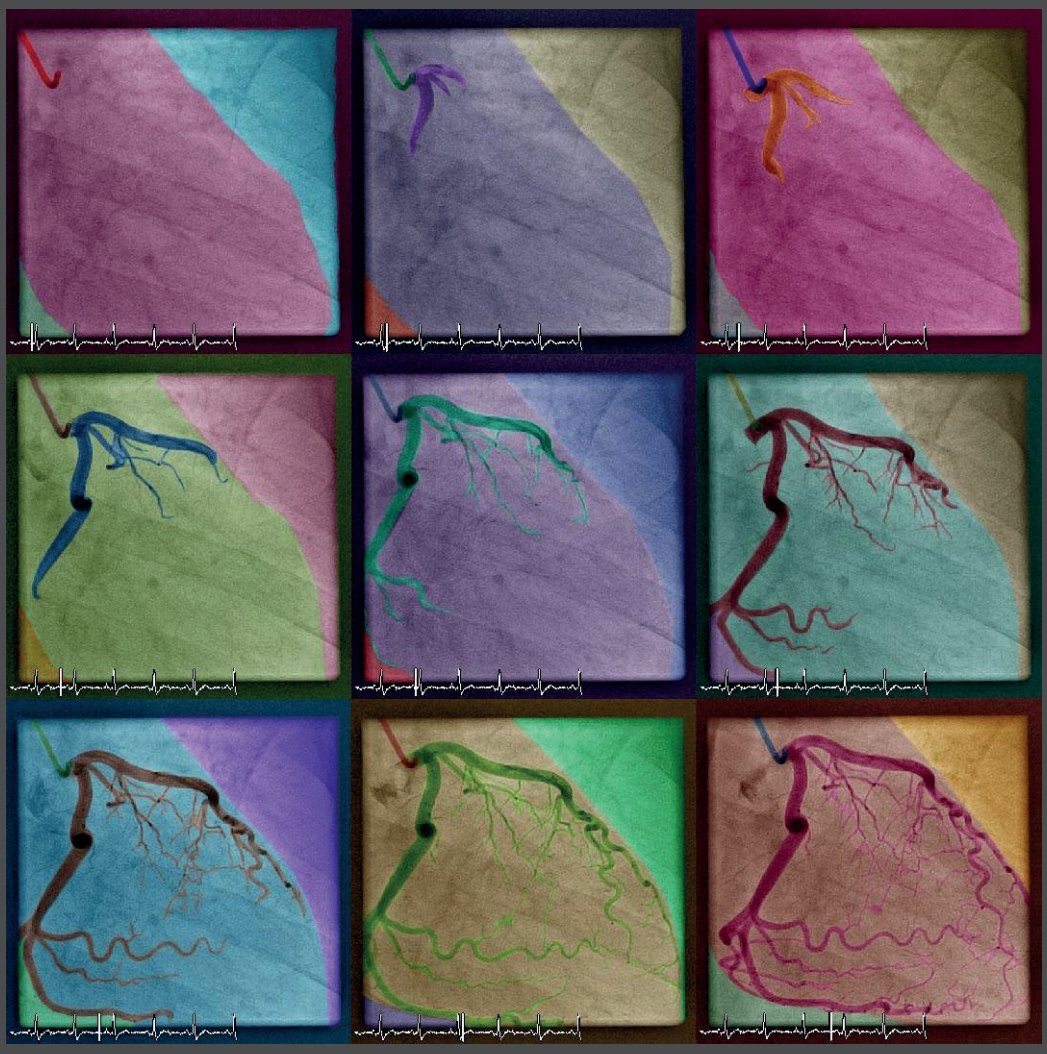

ANGIOGRAPHY AND CORONARY FUNCTION, A CLINICAL APPROACH

Martin Stoel

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CONTENTS

Chapter 1

Introduction and Outline of the Thesis

Anatomic assessment of coronary arteries by means of angiography

Selective coronary cine-angiography was first performed in 1958 by Dr. F.M. Sones Jr.[1] For a long time, anatomical assessment by means of coronary angiography (CAG) remained the 'gold standard' for the evaluation of both, extent of coronary artery disease and severity of coronary stenoses.[2]

In patients with symptoms and/or signs of myocardial ischemia, a CAG-based lumen diameter stenosis of more than 50%, as compared to the lumen dimensions in the adjacent normal (reference) vessel segments, generally was (and sometimes is) considered significant, and thus, a reasonable indication for coronary revascularization.[3] However, further research subsequently led to the knowledge that (so-called) "intermediate" coronary lesions with anatomically significant lumen diameter stenoses of 50-70% are often functionally non-significant, as only a minority of them cause myocardial ischemia.[4,5]

Semi-quantitative assessment of coronary flow from coronary angiography

In the 1980s, CAG was first used to qualify coronary flow velocity in the setting of patients with acute myocardial infarction. The Thrombolysis in Myocardial Infarction (TIMI) study group introduced the assessment of TIMI flow grade, with grade 3 representing normal coronary flow, grade 2 being flow that filled the entire artery but slower than in other coronary vessels, grade 1 representing partial filling, and grade 0 showing no filling of the coronary lumen beyond the obstructive lesion.[6]

One decade later, the same research group refined the TIMI flow grades by the introduction of the TIMI frame count (TFC) approach.[7] Using predefined distal anatomic landmarks of the three major coronary vessels, TFC determines the number of frames required to fill the entire artery with dye, which allows to quantify coronary flow velocity.

As in normal coronary arteries the TFC of the left anterior descending (LAD) was found to be significantly higher than that of the left circumflex (LCX) and right coronary artery (RCA), TFC measurements of the LAD were corrected by a factor (i.e., divided by 1.7) to determine the (so-called) corrected TFC (CTFC). Thereafter, this corrected index of coronary flow velocity was used in various clinical studies and randomized trials.[8-12]
It is noteworthy that the value of TFC measurements is influenced by the cine frame rate of the CAG. The acquisition rate of the X-ray systems is dependent on the frequency of the electricity network. Therefore, in Europe the cine frame rate is 12.5 or 25 frames-per-second (50 Hertz electricity supply), while in the USA that rate is 15 or 30 frames-per-second (60 Hertz).[13]

As restoration of epicardial coronary flow does not necessarily restore microvascular perfusion, CAG-based assessment of myocardial blush grade was introduced as a semi-quantitative angiographic measure of myocardial perfusion in patients with acute

myocardial infarction.[14] In brief, this approach evaluates ease of and degree by which dye enters the microvasculature and, consecutively, is washed out of the myocardium.

Measurement of coronary flow velocity reserve with a Doppler guidewire

In the 1990s, the intracoronary Doppler guidewire became available, which did not only allow to quantify coronary flow velocity but also to determine coronary flow velocity reserve (CVR), the ratio of hyperemic to basal average peak flow velocity.[15] Pharmacologically induced hyperemia is generally achieved by the intravenous or intracoronary administration of adenosine. In general, a CVR value > 3.0 is considered entirely normal in adults. The comparison of the CVR of an obstructed coronary artery to that of an angiographic 'normal' reference vessel (in the same patient) permits the calculation of relative coronary flow velocity reserve (rCVR), a parameter that is corrected for potential abnormality of microvascular function in a subject to be assessed.[16,17]

In intermediate coronary lesions with unknown functional significance (i.e., lesions with 50-70% lumen diameter stenosis), a CVR value > 2.0 and a rCVR value > 0.65 are considered being appropriate cut-off values to defer percutaneous coronary angioplasty (PCI).[18,19] In addition, in the absence of a coronary stenosis, CVR can be used to evaluate microvascular function and to predict left ventricular function recovery following myocardial infarction.[20-22] The reproducibility of coronary flow velocity measurements with Doppler guidewires is high and CVR became an established way to assess the function of the coronary vasculature.[23]

Nevertheless, the method has shortcomings with respect to the assessment of PCI indication as it is not lesion-specific; CVR evaluates the function of an entire coronary vessel, including the microvasculature. In addition, Doppler guidewire derived CVR does not represent an examination under truly physiological conditions because it is affected by coronary perfusion pressure and metabolic state of the myocardium.[24] For instance, when evaluating coronary lesion significance, a false normal CVR (> 2.0) may be found, when baseline flow velocity is low, and a false abnormal CVR (< 2.0) is possible, when baseline flow velocity is high (e.g., after myocardial ischemia) or minimal microvascular resistance is high (e.g., in the presence of arterial hypertension or diabetes).[25]

Assessment of fractional flow reserve with a pressure guidewire

While being introduced in the 1990s, pressure guidewire-derived fractional flow reserve (FFR) measurement significantly gained in importance throughout the last decade. During that period, several important clinical trials showed an advantage of the FFR method in deferring PCI and/or selecting appropriate target lesions for PCI.[26-28] As these trials showed that the pressure guidewire-derived measurement of FFR is a reliable method to measure the hemodynamic significance of intermediate coronary lesions,

the method of FFR measurement rapidly replaced CVR measurement in most PCI centers.

The FFR is the ratio of the (adenosine-induced) hyperemic intracoronary pressure distal to a coronary stenosis and the proximal coronary arterial pressure as measured through the guiding catheter. Based on previous validation work, a stenosis with a pressure ratio of less then 0.75 - 0.80 is assumed to be functionally significant.[29-32] However, due to small vessel disease causing high hyperemic microvascular resistance, FFR can be false normal.[33] In clinical practice, limitations of CVR and FFR may lead to discordant results in more then a quarter of the intermediate lesions.[34] The combination of both, flow and pressure measurements, permits the calculation of the hyperemic stenosis resistance index (i.e., ratio of hyperemic pressure gradient and flow velocity), which has been shown to most accurately assess coronary lesion severity.[35]

Composition and function of the coronary vasculature

The function of coronary circulation is to provide sufficient blood supply to the myocardium, blood supply that matches the actual metabolic demands of the heart. The extent of coronary blood flow is dependent on the perfusion pressure (arterial blood pressure minus blood pressure in the right atrium) and the resistance of the coronary vasculature. In case of changes in perfusion pressure and/or metabolic state of the myocardium, alteration of coronary resistance is the adjusting screw that allows to customize blood supply in order to match myocardial demands.[36]

The coronary vasculature consists of different elements with dissimilar significance for coronary resistance. Epicardial coronary arteries with a diameter of more than 0.5 mm are conductance vessels that (in the absence of a coronary stenosis) merely account for 10% of total coronary resistance. Pre-arterioles and arterioles, however, which are most important for the regulation of coronary blood flow, account for 80% of total coronary resistance. The branched out capillary net is most important for the exchange of oxygen/carbon dioxide, supply of the myocardium with energy, and for clearing the myocardium from metabolic products. Capillaries and coronary veins, the latter being essentially conductance vessels that transport blood back to the heart and lungs, together account for another 10% of total coronary resistance.

Within the section of pre-arterioles and arterioles, which together account for 80% of the total coronary resistance, the pre-arterioles (vessel diameter of 200 to 500 µm) cause 25% of total coronary resistance. In order to preserve adequate distal perfusion pressures, these vessels are able to dilate or constrict in reaction to blood flow velocity (i.e., shear stress) and blood pressure. This regulatory function of these vessels is dependent on functioning endothelium and several mediators such as for instance nitric oxide (NO). Arterioles with vessel diameters < 200 µm account for the vast

majority of coronary resistance. While larger arterioles with diameters between 100 and 200 µm act in the same way as pre-arterioles that facilitate blood flow, smaller arterioles between 40 and 100 µm regulate coronary blood flow in reaction to stretch of vascular smooth muscle cells (i.e., dilation in response to decrease in pressure). The smallest arterioles with vessel diameters < 40 µm are mainly influenced by metabolic demands of the myocardium (i.e., these vessels dilate with increasing metabolic demands) that are transmitted through several neural factors such as – for instance – adenosine.[37]

Principle and possible side effects of adenosine-based hyperemia induction

Adenosine is a purine nucleoside that is one of the mediators of metabolic regulation of coronary blood flow. It is used worldwide to induce myocardial hyperemia for the assessment of FFR. Originally, adenosine was administrated intravenously (140 µg/kg per minute), preferably trough a central venous line because of its very low half-life time of less than 10 seconds.

However, intracoronary injection of a bolus of adenosine is more rapidly performed and generally as effective as the continuous intravenous administration. In addition, intracoronary administration of a bolus of adenosine has less side effects (e.g., chest pain, flushing, drop in blood pressure, rise in heart rate) as is seen during intravenous administration of adenosine. Most important side effect of an intracoronary injection of adenosine is a temporary atrioventricular block, especially after administration of adenosine into the right coronary arteries, which is rarely seen with intravenous administration of adenosine.

On the other hand, the intracoronary injection method may be technically somewhat more demanding. In narrow coronary ostia or if the guiding catheter has a tendency to slip into a deep seating position, it is of paramount importance to withdraw the guiding catheter into the aorta following the adenosine bolus injection. Otherwise, if the guiding catheter limits maximal coronary flow and dampens the aortic pressure signal, FFR values may be false normal. In addition, intracoronary administration of a bolus of adenosine requires particular attention to the position of the guiding catheter tip to avoid an unintentionally non-selective administration of adenosine into the aorta. Moreover, in case of serial coronary lesions, a pressure pullback recording during ongoing hyperemia by intravenous administration of adenosine may be more accurate than serial measurements with intracoronary bolus injections. Bronchial hyperreactivity is a contraindication for intravenous, but not for intracoronary administration of adenosine.

In the search for maximal hyperemia for the purpose of FFR measurement, incremental doses of intracoronary adenosine have been used. These dose of intracoronary bolus

injections of adenosine started in the 1990s with 12 and 16 µg in the right and left coronary arteries, respectively, evolved then to 100 µg, and finally accumulated into intracoronary injections of as much as 600 µg of adenosine.[38]

Potential advantages of avoiding of transducer-equipped guide wires

Even if carefully performed by experienced interventional cardiologists, the invasive interrogation of coronary arteries with transducer-equipped guidewires bears a small but relevant risk of vascular complications. In addition, use of these guidewires to measure intracoronary pressures and coronary flow velocity increases the financial burden of medical care. Novel computed tomography-based approaches for the assessment of FFR may be of interest in the future,[39] but nowadays, straight-forward coronary angiography already provides valuable, generally unused information which can be analyzed with a simple angiographic method (i.e., without need for transducer-equipped guide wires) that determines maximum coronary flow velocity and minimum coronary resistance in coronary lesions of uncertain hemodynamic significance. In addition, in the absence of focal coronary stenoses, the angiographic evaluation of hyperemic coronary flow velocity may be of clinical use in patients with suspected microvascular dysfunction or diffuse stenosis of the epicardial coronary arteries.

OUTLINE OF THIS THESIS

In this thesis, we explore several aspects of angiographic evaluation of coronary flow velocity and function. In addition, we evaluate approaches to optimize coronary flow in the setting of acute myocardial infarction. ***Chapter 1*** provides an introduction to the topic of this thesis and various techniques relevant for this subject.

In ***chapter 2***, we assess the impact of dye injection on intracoronary pressure, using a pressure guidewire during coronary angiography in patients without significant coronary stenoses. Although previous studies have showed that both, size of the guiding catheter and rate of contrast injection do not significantly alter TFC,[40-42] the magnitude of intracoronary pressure rise was still unknown. Knowledge on the mean pressure rise during dye injection might be of interest for the TFC method.

The corrected TFC takes into account the greater length of the LAD (compared to the length of RCA and LCx).[7] However, the correction for coronary artery length might be improved by considering the mean length of each of the three major coronary vessels. For that purpose, we measured the distance between ostium and distal landmark of the

arteries with an intracoronary guidewire. By this means, a more accurate TFC method could be derived, the so-called frame count velocity (FCV). In ***chapter 3***, we compare both methods, FCV and CTFC.

The TFC is determined manually by subtracting the cine frame number at the start of the dye injection from the number of the cine frame, on which the dye reaches the distal coronary landmark. For the most accurate calculation of FCV, individual measurement of the selected vessel length with an intracoronary guidewire is required, as outlined above. However, this increases the complexity of the procedure, the costs of the examination, and last but not least the risk of procedure-related complications to the coronary vessel. Therefore, an automated method should be preferable. In ***chapter 4***, we present a three and four-dimensional coronary model that is used to determine vessel length and TFC. With this method, automated determination of FCV is possible.

In ***chapter 5***, an angiographic method for determining coronary flow reserve is presented, which does not require use of a coronary guidewire. The frame count reserve (FCR) is the ratio of basal to hyperemic TFC. To compensate for possible microvascular dysfunction, relative FCR (rFCR) is calculated using the FCR of a non-culprit (reference) vessel. In this chapter, we compare the (r)FCR with Doppler guidewire-derived (r)CVR. In addition, the length of each coronary artery was measured with a guidewire, which allowed calculation of mean coronary flow velocity, absolute coronary flow, and an index of minimal coronary resistance.

A substantial proportion of patients, treated with PCI for acute ST-segment elevation myocardial infarction (STEMI) – so-called “primary PCI” – do not show normalization of coronary flow (i.e., no reflow). This is reflected in persistent ST-segment elevation on the electrocardiogram (ECG). In our experience, supported by several previous studies,[43-46] high-dose intracoronary infusion of adenosine can ameliorate or even normalize coronary flow and ST-segment elevation. To investigate this, we performed a randomized, placebo-controlled study as presented in ***chapter 6***. Endpoints of the study were early (after PCI) and late (after 90 minutes) ST-segment resolution (STR) as well as angiographic parameters, including TFC and coronary resistance index.

The optimal moment to determine STR on an ECG after primary PCI in relation to clinical events and prognosis is unknown. In ***chapter 7***, we assess in 223 STEMI patients treated with primary PCI the prognostic value of early, late, and absent ST-segment resolution with regard to one-year mortality and rehospitalization for major cardiac events.

In patients undergoing primary PCI for acute STEMI, manual aspiration of coronary thrombus through dedicated aspiration catheters can ameliorate myocardial reperfusion and decrease mortality.[47,48] However, before and during this procedure, (fragments of) thrombus may be embolized into the distal vasculature, which frequently cause suboptimal reperfusion and limit myocardial salvage. When an embolized thrombus is large enough to get lodged in a distal epicardial vessel, extraction is sometimes possible by use of an aspiration catheter. In **chapter 8**, we describe 3 successful cases of thrombus aspiration from distal epicardial coronary segments, leading to optimization of coronary reflow and myocardial perfusion.

Chapter 9 contains the summery, conclusions, and future perspectives of this thesis.

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Chapter 2

Impact of Dye Injection on Intracoronary Pressure

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EuroIntervention 2009,5:272-276

ABSTRACT

Aims: Coronary angiography is widely used to estimate coronary blood flow velocity, as in the TIMI frame count method. However, it is unknown to what extent the injection of dye elevates intracoronary pressure which may accelerate coronary blood flow velocity. In the present study, intracoronary pressure was measured during coronary angiography.

Methods and results: In 25 patients with non-significant coronary lesions, assessed by fractional flow reserve measurement with a pressure guidewire, we recorded intracoronary pressure during dye injection for coronary angiography in the ostium of the coronary artery as well as distal to the lesion. There was a rise in mean intracoronary pressure during dye injection in both ostial and distal coronary arterial segments (from 90.8±17.2 mmHg to 96.8±18.5 mmHg and from 89.7±15.3 mmHg to 93.6±17.3 mmHg, respectively; p<0.001). Nevertheless, the absolute and relative increase in pressure was small (6.0±4.2 mmHg {6.7±4.9%} in the ostium, and 3.9±5.5 mmHg {4.2±5.7%} distally).

Conclusion: In coronary arteries without significant stenosis, coronary angiography causes only a minor increase in intracoronary pressure. The limited impact of dye injection on intracoronary blood pressure confirms the value of coronary angiography for estimation of coronary flow velocity.

INTRODUCTION

Coronary blood flow velocity can be estimated from coronary angiography by measuring TIMI frame count (TFC) (1,2) and TIMI frame count velocity (FCV) (3,4). Previous studies showed that both size of the guiding catheter (5) and rate of contrast injection (6,7) do not significantly alter TFC. Nevertheless, during angiography the force of dye injection could temporarily elevate intracoronary pressure to some extent, which may increase coronary blood flow velocity. Coronary blood flow during dye injection has previously been studied (8), but we are not aware of a study that may have prospectively investigated the effect of dye injection on (proximal and distal) intracoronary pressure in human coronary arteries in vivo. We therefore studied this relationship during standard coronary angiography procedures.

METHODS

Study population

We examined a total of 25 consecutive patients, who were in sinus rhythm and scheduled for fractional flow reserve (FFR) measurement of an intermediate coronary lesions which turned out to be insignificant (FFR>0.75). Patients with atrial fibrillation, anatomically significant ostium stenosis (diameter stenosis >50% by quantitative coronary angiography) or damping of the pressure curve were not considered for inclusion.

Interventional procedure

All patients were examined through the femoral artery using 6F guiding catheters without side holes (Cordis Europa, Roden, The Netherlands) and received a bolus of 5.000 IU of heparin and an intracoronary bolus of 200-300 µg of nitroglycerin. The contrast medium Iodixanol (Visipaque 320, Amersham Health, Eindhoven, The Netherlands) was used for coronary angiography with manual dye injections. We performed standard quantitative coronary angiography (QCA) analyses (Pie Medical Imaging, Maastricht, the Netherlands) of the proximal and distal reference vessel segments and the target lesion.

Pressure recordings and analysis

Pressure sensor-equipped guide wires (Radi Medical Systems, Uppsala, Sweden) that permit intracoronary pressure tracings without flow obstruction were used to measure intracoronary pressure as previously described (9 -13)**.** FFR was determined after bolus injection of 50 µg of adenosine into the right coronary artery and 100 µg into the left

coronary artery. After coronary hyperemia was no longer present, coronary angiography was done. During dye injection we performed simultaneous measurements of both the pressure inside the coronary arteries (by the pressure sensor on the pressure guide wire) and the pressure in the proximal part of the guiding catheter (by the fluid filled pressure sensor on the manifold). The pressure sensor of the guide wire was positioned first distally to the target lesion and secondly in the proximal segment of the coronary artery, just a few millimetres distal to the ostium. Systolic and diastolic arterial pressure was recorded digitally for both sites. All pressure recordings started at least one cardiac cycle before the dye injection and ended after at least one cardiac cycle after contrast injection was finished. In figure 1, a typical pressure tracing during the injection of dye is shown. The mean arterial pressure (MAP) was calculated as: (1x systolic pressure + 2x diastolic pressure) divided by 3.

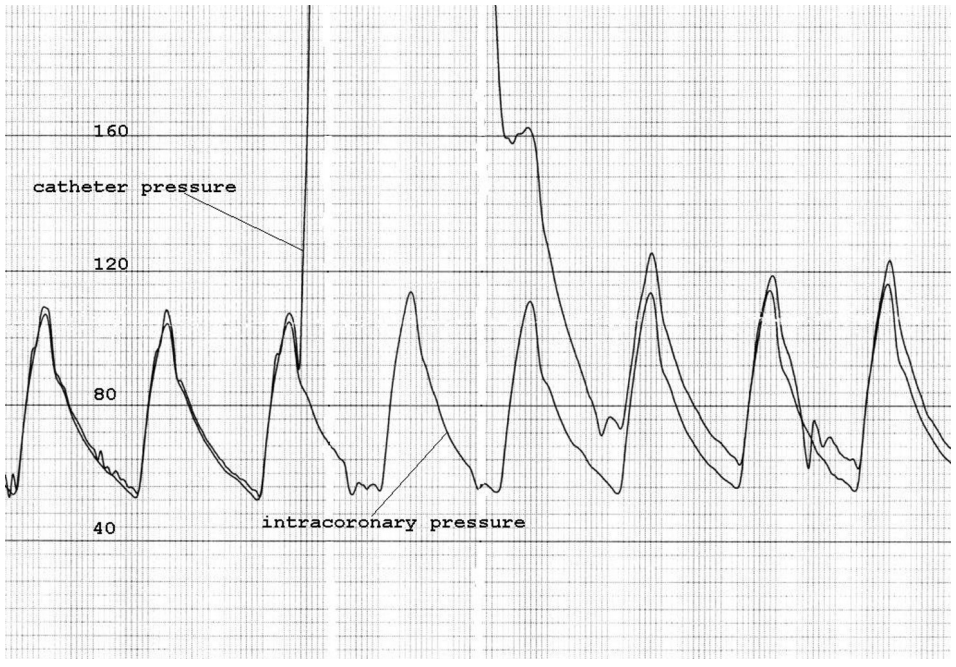

Figure 1 Example of catheter and pressure guidewire tracings (mm Hg) during dye injection with pressure sensor located in left main coronary artery, showing minor elevation of intracoronary systolic pressure during injection of approximate 10 mm Hg.

In an additional group of 6 patients, intracoronary pressure during dye injection was recorded at the coronary ostium as well as in the coronary artery at a distance of 3, 6 and 9 cm from the ostium. These distances were determined by the length of the radio-opaque distal part of the pressure guidewire.

Statistical analysis

Analyses were performed with SPSS 16.0 (SPSS Inc., Chicago, Illinois). Dichotomous data are presented as frequencies. Quantitative data are presented as mean±1SD and compared using repeated measurements analysis (Random intercept) with post-hoc comparisons according to the method of Sidak. A p-value <0.05 was considered significant.

RESULTS

The characteristics of the 25 patients are presented in Table 1. The procedure and lesion characteristics are shown in Table 2. There were 21 measurements in the left main coronary artery (LCA), 5 in the ostium of the right coronary artery (RCA) and 32 measurements distal to intermediate lesions (17 left anterior descending (LAD), 10 left circumflex (LCx), and 5 RCA). In one patient, measurements were performed in the LCA as well as in the RCA, and in 6 patients measurements were performed both in LAD and LCx.

Table 3 shows the systolic, diastolic, and mean intracoronary pressure before, during, and after dye injection, both in the coronary ostium and distal to the intermediate lesion. During dye injection, there was an increase in systolic and diastolic blood pressure (mean pressure from 90.8±17.2 mmHg to 96.8±18.5 mmHg, p<0.001 for ostial pressure measurements, and from 89.7±15.3 mmHg to 93.6±17.3 mmHg, p<0.02 for distal measurements). Nevertheless, this increase remained small. The mean pressure in the ostium of the coronary artery increased during dye injection by 6.0±4.2 mmHg (6.7±4.9%), while distal to the insignificant lesion the intracoronary pressure increased by 3.9±5.5 mmHg (4.2±5.7%). There were no significant differences for the increase in pressure in the LCA compared to the RCA (6.6±4.4 mmHg and 3.6±2.8 mmHg, respectively, p=NS)

Figures 2 and 3 illustrate the individual changes in systolic and diastolic pressure for ostial and distal positions of the pressure wire sensor, respectively.

In 6 patients intracoronary pressure was recorded at the coronary ostium and in the coronary artery at 3, 6 and 9 cm from the ostium (3 LAD, 2 LCx and 2 RCA). The change in mean intracoronary pressure during dye injection compared to the mean

Table 1 Patient Characteristics.

Patients, *n*	**25**
Age, y	64±9.8
Male, %	80
Diabetes mellitus, %	12
Hypertension, %	40
Dyslipidemia, %	40
Smoker, %	24
Family history of coronary disease, %	32
Medication, %	
Acetylsalicylic acid	100
Beta-blockers	68
Statins	76
ACE inhibitors	44
Calcium-channel blockers	40
Nitrates	32
Previous myocardial infarction, %	12
Previous CABG, %	0
Previous PCI, %	24

ACE = angiotensin-converting enzyme;
CABG = coronary artery bypass grafting;
PCI = percutaneous coronary intervention

Table 2 Lesion and Procedure Characteristics.

	All	**Ostial (n=26)**	**Distal (n=32)**
LCA, *n*		21	-
LAD, *n*		-	17
LCx, *n*		-	10
RCA, *n*		5	5
Vessel reference diameter, mm		4.3±1.1	3.1±0.4
Diameter stenosis, %		-	49.2±5.7
Systolic blood pressure, mmHg	135±31		
Diastolic blood pressure, mmHg	68±11		
Heart Rate, bpm	65±12.9		
FFR		-	0.85±0.07

LCA = left coronary artery; LAD = left anterior descending; LCx= left circumflex coronary artery;
RCA = right coronary artery; FFR = fractional flow reserve

Table 3 Intracoronary Pressure Before, During and After Dye Injection.

		Before	**During**	**After**	**p***
Ostial pressure (mmHg)	Systolic	136.0±33.6	145.1±33.9	138.3±34.8	<0.001
	Diastolic	68.2±11.0	72.6±12.4	68.9±10.6	<0.001
	Mean	90.8±17.2	96.8±18.5	92.1±17.1	<0.001
Distal pressure (mmHg)	Systolic	134.1±28.9	140.4±31.1	137.2±31.7	<0.001
	Diastolic	67.5±10.9	70.3±13.3	68.7±12.1	0.016
	Mean	89.7±15.3	93.6±17.3	91.5±16.8	<0.001

*p for pressures during dye injection compared to before the injection, and for after dye injection compared to during injection.

pressure before and after injection is shown in figure 4. Mean change in intracoronary pressure during dye injection, measured from proximal to distal was 6.9±1.2, 4.0±1.4, 4.5±1.3 and 3.1±1.5 mmHg.

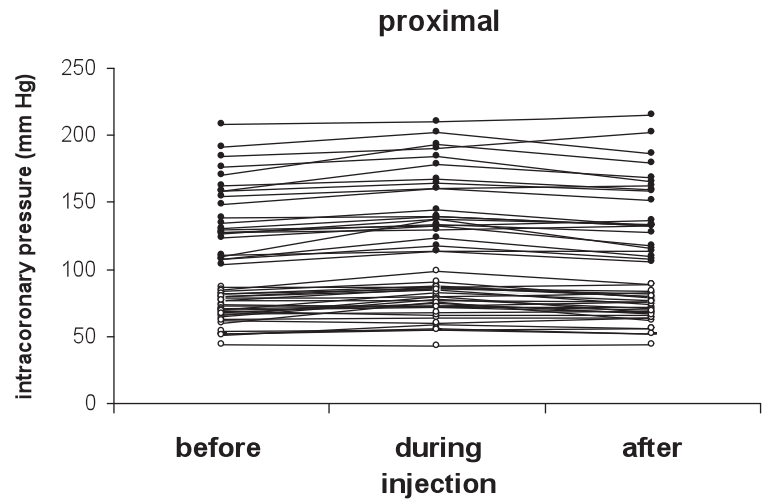

Figure 2 Systolic (•) and diastolic (○) intracoronary pressures (mmHg) before, during, and after dye injection for all measurements with the pressure sensor located in the coronary ostium (n = 26).

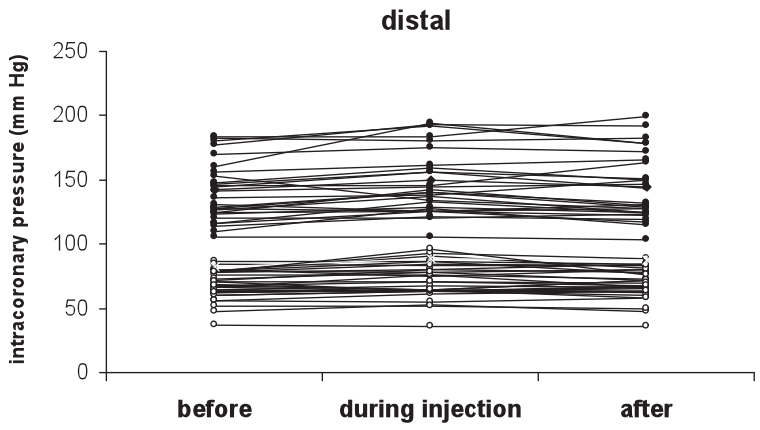

Figure 3 Systolic (•) and diastolic (◦) intracoronary pressures (mmHg) before, during, and after dye injection for all measurements with the pressure sensor located distal to the target lesion (n = 32).

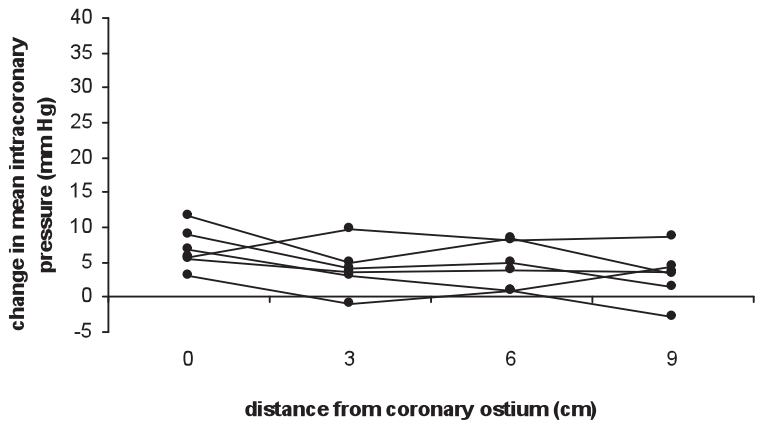

Figure 4 Change in mean intracoronary pressure (mmHg) during dye injection compared to mean pressure before and after injection, with the pressure sensor located at the coronary ostium and 3, 6 and 9 cm distal to the ostium (n = 6).

DISCUSSION

The present study shows that manual injection of dye for coronary angiography causes a measurable, statistically significant rise in intracoronary pressure, which is relatively small and can be observed particularly in the proximal segments of the left and right coronary arteries. In fact, such a small increase in systolic and diastolic pressure is negligible compared to normal variations in blood pressure such as – for instance – caused by respiration. The results of this study confirm the use of coronary angiography for estimation of coronary blood flow velocity with the TIMI frame count (3), and for evaluation of microvascular perfusion with the Myocardial Blush Grade (14). In addition, the manual injection of saline that is used to estimate coronary flow and microvascular resistance (15-17), is likewise of limited influence on intracoronary pressure en blood flow velocity.

Previous studies

Our data explain why the rate of dye injection does not significantly influence blood flow velocity, as was shown by Dodge et al. and Abaci et al. (6,7), and confirm the value of using coronary angiography to estimate coronary blood flow velocity with TFC and FCV(1-4). In addition, the findings of the present study are in accordance with data of Hodgson et al., who found only a small increase (<1.5%) in coronary blood flow during the initial phase of dye injection (8).

Factors that may affect coronary pressure during angiography

There is a critical ratio between the size of the guiding catheter and the coronary orifice, above which the high pressure inside the guiding catheter (during dye injection) propagates into the coronary artery. The exact value of this critical ratio is unknown. For that reason, it was essential to assure an easy backflow of dye into the ascending aorta during dye injection, which resulted in stable intracoronary pressure. Of note, our study was performed with 6F guiding catheters in coronary arteries without significant ostial disease or damping of the pressure signal in the guiding catheter.

In addition, in case of hemodynamic significant coronary stenosis, dye injection may increase proximal intracoronary pressure more pronounced compared to normal coronary arteries. However, we limited our study to the assessment of pressure in coronary arteries without hemodynamic significant coronary stenosis (FFR >0.75 in all vessels studied).

Implications for TIMI frame count

The rise in mean arterial pressure in the ostium of the coronary arteries during dye injection was 6.0±4.2mmHg. Compared to baseline, this is an increase by 6.7±4.9%. In

general, the rise in pressure is lasting the whole period of time in which the frames for the TFC are counted.

Assuming that coronary resistance (epicardial and microvascular) does not change, this pressure rise should augment coronary blood flow velocity during TFC measurements by approximately 6.7% (compared to the state before dye injection). Left anterior descending (LAD), left circumflex (LCx), and right (RCA) coronary arteries without significant stenosis have a mean TFC of 35.1±17.0, 25.1±9.5, and 17.0±2.5 respectively (25 frames/sec) (4). Consequently, the dye injection for TFC measurement may increase coronary flow velocity and lower TFC, with a decrease on average of 2.3, 1.9 and 1.1 frames for LAD, LCx, and RCA respectively, less then corresponding standard deviations.

For the assessment and comparison of the TFC in daily practice and in scientific studies, it makes no sense to perform a correction of the measurements as TFC requires dye injection as an essential part of the method. Nevertheless, we feel that it is interesting to know and realize the abovementioned facts.

Limitations

Standard manual dye injection may show more variability in force than an automated dye injection with an injection pump. Nevertheless, the manual approach resembles the routine practice in the vast majority of catheterization laboratories, both in routine practice and scientific studies, and our findings can be transferred to most clinical scenarios. All measurements were done using 6F guiding catheters. It is possible that the use of 8F guiding catheters causes more pronounced elevation of intracoronary pressure during dye injection. This could be a subject of future studies. In the calculation of mean blood pressure and the relation to coronary flow velocity, the predominant diastolic coronary flow was not accounted for. The higher viscosity of dye compared to blood may reduce flow velocity to a certain extent; this issue could not be addressed in this clinical study and may not be relevant as it is inherent to the technique. The sample size of 25 patients was not large but adequate to assess the relation between dye injection and intracoronary pressure. Finally, blood pressure variation caused by respiration could have influenced pressure measurements to a limited degree.

Conclusion

In coronary arteries without significant stenosis, coronary angiography causes only a minor increase in intracoronary pressure. Our data are in line with previous findings which suggested that the impact of dye injection on coronary blood flow velocity is limited and confirm the value of coronary angiography for estimation of coronary blood flow velocity.

Acknowledgements

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Chapter 3

Corrected TIMI Frame Count and Frame Count Velocity

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ABSTRACT

Background

Little is known about the differences between the corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (CTFC) and the 'frame count velocity' (FCV), an estimate of blood flow velocity derived from the TFC and the length of the related vessel, in each of the three epicardial coronary arteries.

Methods

After angioplasty of 119 coronary vessels, 50 left anterior descending (LAD), 27 left circumflex (LCx) and 42 right coronary artery (RCA), the CTFC was compared to the FCV assessed by measuring the length of the coronary arteries with an intracoronary guidewire.

Results

The three vessels show a significant difference in mean length (the LAD was 14.5 ± 1.6 cm, the LCx 12.8 ± 1.9 cm and the RCA 11.3 ± 1.4 cm, $p<0.001$ for all comparisons), making it possible to convert the TFC to the FCV with reasonable accuracy without having to use a guidewire. The mean length of the LCx and the RCA was considerably longer than in previous reports on which the CTFC is based. In addition with this method the estimation of the coronary blood flow velocity in the RCA is significantly higher compared with the LAD and LCx (23.0 ± 7.9 cm/sec versus 17.6 ± 7.4 cm/sec and 16.4 ± 6.3 cm/sec, respectively, $p<0.001$).

Conclusion

With the TFC and the average length of the related coronary artery presented in this study, the FCV can be calculated for each of the three vessels resulting in a simple and, compared with the CTFC, more accurate angiographic estimation of the coronary blood flow velocity.

INTRODUCTION

To quantitate coronary blood flow velocity, Gibson et al introduced the Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC), determined by the number of cineframes required for contrast to reach standard distal coronary landmarks.[1] Since the TFC of the left anterior descending (LAD) was found to be significantly higher compared to the TFC of the left circumflex (LCx) and right coronary artery (RCA), the TFC of the LAD was divided by a factor of 1.7 to calculate the corrected TFC (CTFC). These measurements were, however, made in patients referred for diagnostic cardiac catheterization who may have had different coronary anatomy and blood flow velocity compared to patients referred for coronary angioplasty.

Since the (corrected) TFC is only an inversed index of coronary blood flow velocity, the same group introduced a simple method to estimate absolute blood flow velocity, by measuring the distance of a guidewire from the catheter-tip to the distal landmark of a coronary artery.[2] However, because of the use of a guidewire, this technique is limited to patients undergoing coronary angioplasty. Therefore, the aim of the present study was to compare the CTFC with this 'frame count velocity' (FCV) in each of the three epicardial vessels.

METHODS

Patients and procedure

Consecutive patients undergoing percutaneous transluminal coronary angioplasty of native coronary arteries were studied. In all patients both the (C)TFC and FCV were determined after angioplasty. Included were patients undergoing elective angioplasty and patients with acute coronary syndromes. Excluded were patients with tortuous coronary arteries that were straightened by the guidewire (decreasing the bends of the vessel resulting in an underestimation of its length), if the distal landmark could not be reached, a guiding-catheter was used with side-holes or damping of the pressure signal occurred. In addition, patients were excluded if a residual stenosis >50% was present in the culprit vessel, if there was persisting absent or partial filling of the coronary artery (TIMI flow grade 0 and 1) or in case of hemodynamic instability.

All procedures were done by the same investigator using 7 French Judkins and Amplatz guiding-catheters (Guidant) and ioxaglaat (Hexabrix 320, Laboratoire Guerbet, France). The mean arterial pressure was recorded during the procedure and all patients received 0.2-0.4 mg intracoronary nitroglycerine every 10-20 minutes.

TFC

Frames were numbered digitally (Philips Integris 2000, 25 frames/second) and counted, the first frame being the one with >70% of the arterial lumen filled with dye and the last one in which dye appears first in the landmark. The distal, apical bifurcation was used as the landmark of the LAD, for the LCx the distal bifurcation of the segment with the longest total distance that includes the culprit lesion was used and the landmark of the RCA was the first branch arising from the RCA distal of the origin of the RDP.[1] By dividing the TFC of the LAD by a factor of 1.7 the CTFC was calculated and it was multiplied with a factor of 1.2 to convert to a speed of 30 f/s making direct comparison to earlier reports possible. The TFC was determined without a guidewire in the coronary artery.

FCV

After angioplasty, the distal end of the guidewire was positioned 1-3 mm in the area of the landmark and marked outside the guiding catheter, then withdrawn inside the catheter until 1-3 mm of the distal end was still visible and marked again. The length between the markers was measured after the procedure, and multiplied with 25/TFC to calculate the frame count velocity.[2]

Statistical analysis

Continues variables are expressed as mean ± 1 standard deviation with their range. The Fisher exact test and the Student unpaired *t* test were used. A p-value <0.05 was considered significant.

RESULTS

A total of 218 consecutive coronary angioplasties was performed. Excluded were 99 procedures; in 37 the culprit vessel was the LAD, in 14 the LCx, in 27 the RCA, and in 21 the left main or a side branch. The most important reasons for exclusion were severe tortuositas of the vessel and residual stenosis. The final analysis included 119 coronary arteries in 117 patients.

The characteristics and results are listed in table 1. The RCA was significantly shorter (11.3 ± 1.4 cm), and the LAD significantly longer (14.5 ± 1.6 cm) than the LCx (12.8 ± 1.9 cm), p<0.001 for both comparisons as illustrated in figure 1. Compared to LAD and LCx, the TFC of the RCA was significantly lower (16.6 ± 6.4 versus 30.5 ± 15.5 and 27.1 ± 12.4 p<0.0005) and the FCV significantly higher (23.0 ± 7.9 cm/sec versus 17.6 ± 7.4 cm/sec and 16.4 ± 6.3 cm/sec p<0.001), while there were no significant differences between the LAD and LCx. The CTFC of the LCx however was significantly higher compared to LAD and RCA (27.1 ± 12.4 versus 17.9 ± 9.1 and 16.6 ± 6.4, p<0.001).

Table 1 Characteristics and results

	LAD	LCx	RCA	total	p-value
Number	50	27	42	119	
Age (y) mean	60.5	60.2	63.4	61.6	NS
Male gender (%)	84.0	88.9	64.3	78.1	0.027 *
Acute coronary syndromes (%)	66.0	40.7	59.5	58.0	NS
AMI (%)	22.0	11.1	19.0	18.5	NS
Stented target vessels (%)	80.0	55.5	69.0	70.6	0.034 †
Mean arterial pressure (mm Hg)	94.1 ± 15.8	93.9 ± 14.9	93.1 ± 14.0	93.7 ± 14.8	NS
Heart rate (beats/min)	66.3 ± 14.7	67.4 ± 22.4	63.3 ± 12.0	65.5 ± 15.9	NS
Length to landmark (cm)	14.5 ± 1.6 9.5 – 17.5	12.8 ± 1.9 8.9 – 16.7	11.3 ± 1.4 8.6 – 15.5	13.0 ± 2.1 8.6 – 17.5	<0.001 ‡
TIMI frame count (30 f/s)	30.5 ± 15.5 10.8 – 72.0	27.1 ± 12.4 8.4 – 72.0	16.6 ± 6.4 7.2 – 37.2	24.8 ± 13.7 7.2 – 72.0	<0.0005 §
Corrected TIMI frame count (30f/s)	17.9 ± 9.1 6.4 – 42.4	27.1 ± 12.4 8.4 – 72.0	16.6 ± 6.4 7.2 – 37.2	19.5 ± 8.9 6.4 – 72.0	<0.001 ¶
Frame count velocity (cm/s)	17.6 ± 7.4 6.0 – 38.9	16.4 ± 6.3 6.0 – 37.1	23.0 ± 7.9 10.0 – 43.3	19.2 ± 7.9 6.0 – 43.3	<0.001 §

* RCA compared to LCx; † LCx compared to LAD; ‡ between the three vessels;
¶ LCx compared to LAD and RCA
§ RCA compared to LAD and LCx, p = NS between LAD and LCx;
AMI = acute myocardial infarction; LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery; SD = standard deviation; NS = not significant

In Figure 2 the conversion from TFC (30f/s) to FCV (frame count velocity = mean vessel length × 30/TFC) is shown for the three coronary arteries separately (using the mean length of each related vessel). The standard deviation expressed as the percentage of the mean length, and thus the FCV, is 11% for the LAD, 15% for the LCx and 12 % for the RCA. The conversion from TFC to FCV for the three coronary arteries combined, using the mean length of 13.0 ± 2.1 cm (17%) is illustrated in Figure 3 A, while in Figure 2 B the CTFC is converted to the FCV, using the 'corrected' mean length of 10.5 ± 2.2 cm (21%).

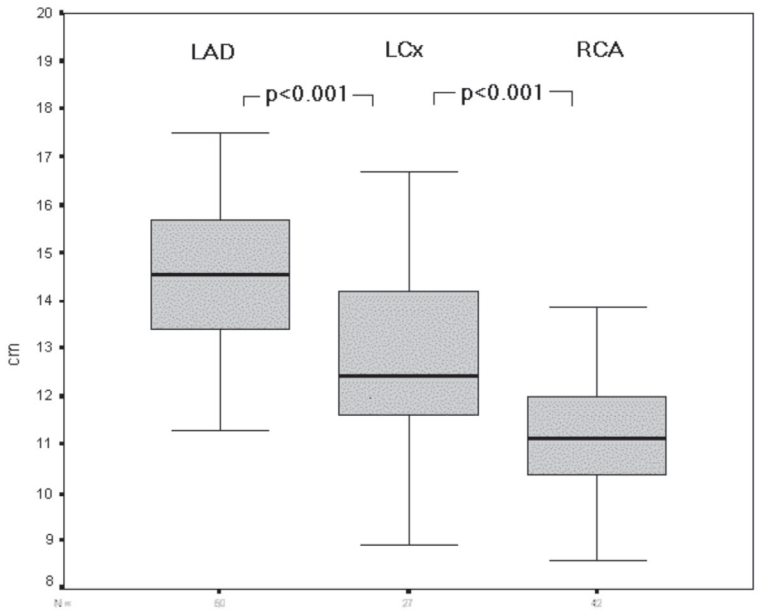
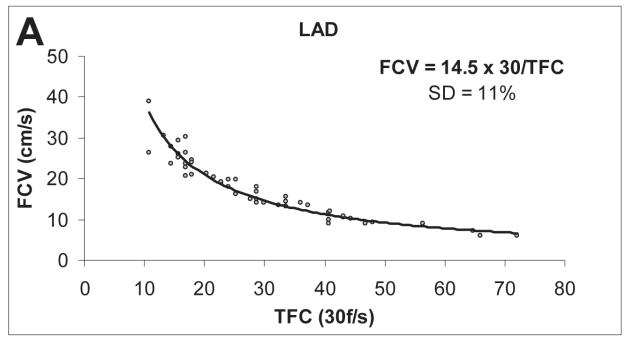


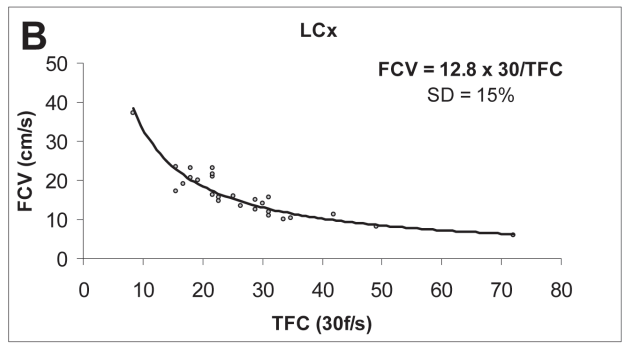
Figure 1 Box plot of the median length, standard deviation and range of the left anterior descendens (LAD), left circumflex (LCx) and right coronary artery (RCA).

DISCUSSION

The CTFC is a commonly used index for coronary flow velocity. With the FCV the flow velocity can be estimated more accurate by normalizing the TFC to the length of the related vessel. With the results shown in Figure 2 it is possible to convert the TFC of a coronary artery to its corresponding FCV without the need of using a guidewire to measure its length. Because of the modest variation in length of the significantly different arteries, in this group of patients the standard deviation of the FCV derived from the TFC and the related mean vessel length is 11% for the LAD, 12% for the RCA and 15% for the LCx.

Gibson et al introduced the corrected TIMI frame count because in a group of patients without myocardial infarction, the TFC for the LAD (36.2 ± 2.6) was significantly higher than for the RCA (20.4 ± 3.0) and the RCX (22.2 ± 4.1).[1] This finding was supported by a previous study of Dodge et al in which a three-dimensional angiographic model was used to determine the length of the coronary arteries approximate to their distal landmarks.[3] They reported an average length of 14.7 cm for the LAD, 9.3 cm for the LCx





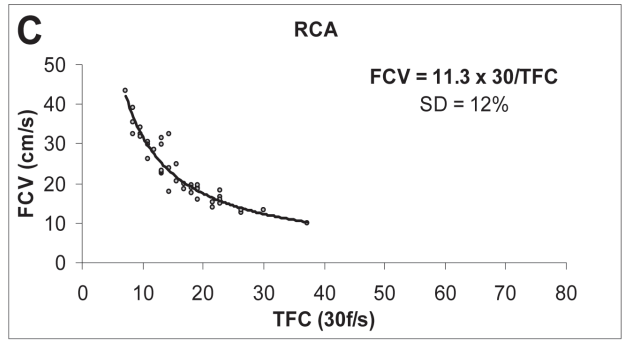
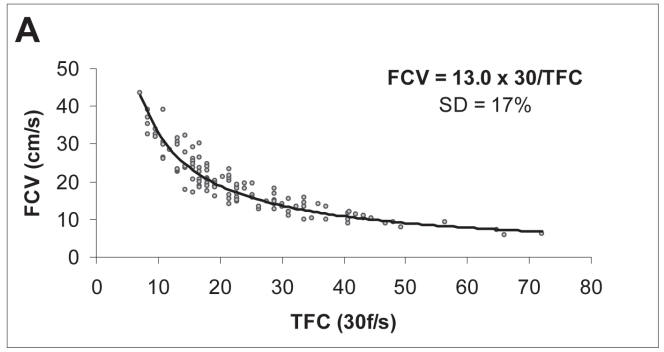


Figure 2 Conversion from TIMI frame count (TFC) to frame count velocity (FCV): FCV = mean length of related vessel x film speed/TFC. **A**, left anterior descending (LAD), n=50; **B**, left circumflex (LCx), n=27; **C**, right coronary artery (RCA), n=42, SD=standard deviation.

and 9.8 cm for the RCA. Based on these observations the TFC was corrected by dividing the TFC for the LAD by a factor of 1.7.



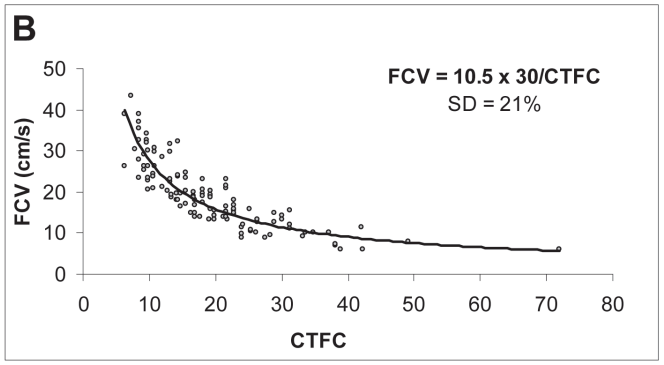


Figure 3 Conversion from **A**, TIMI frame count (TFC) and **B**, TFC corrected for the left anterior descending (CTFC), to frame count velocity (FCV): FCV = mean (corrected) length of the 3 vessels combined x film speed/(C)TFC, n=119, SD=standard deviation.

The present study confirms the observations of Dodge et al with respect to the length of the LAD (mean 14.5 cm).[3] However, the mean length of both the LCx and RCA was considerably longer (12.8 and 11.3 cm respectively). In addition it was found that the difference between the mean TFC of the LAD and LCx (30.5 vs. 27.1) was not significant while the difference between the mean TFC of the RCA (16.6) compared with the LAD and LCx was very significant ($p<0.0005$, Table 1).

Therefore, in this study-group of patients, dividing the TFC of the LAD by a factor of 1.7 results in an over-correction, and increases the standard deviation of the blood flow velocity from 17% to 21% (Figure 3 A and B).

The observed differences in length and TFC of the three coronary arteries compared to the previous studies might be related to differences in patient selection. In the

present study all patients were selected for angioplasty and the target vessels were therefore possibly bigger and longer compared to the control group of patients reported by Gibson et al.[1] This could be especially true for the LCx because the location of its landmark varies considerably. In contrast to the previous reports the present study included also patients with an old or acute myocardial infarction with subsequent possible dilatation of the left ventricle and associated "stretching" of the coronary arteries. In addition, the guidewire method used to measure the length of the coronary arteries is probably more accurate than quantitative angiography as used by Dodge et al,[3] because angiography is likely to result in shortening of the vessels. However, because the guidewire takes the shortest route inside the lumen by cutting off the curves, this method can also result in underestimation of the length of the artery.

The FCV in the RCA in this study is significantly higher than in the LAD and the LCx (23.0 vs. 17.6 and 16.4 cm/s). This could be explained by the fact that compared to the LCA the TFC of the RCA is less dependent on the moment of dye injection in relation to the cardiac cycle because the coronary flow velocity is relatively more influenced by the lower resistance of the vasculature of the right ventricle. This observation is supported by a higher systolic-diastolic ratio seen in the proximal RCA compared to its left ventricular branches and the LCA.[4]

A possible limitation of this study is the relatively small number of measurements in the LCx. There was also a smaller percentage of stent-implantations in this group, but since procedures with a residual diameter stenosis >50% were excluded, it is not likely this fact had major influence on the measured flow velocities. Another limitation is the fact that the injection of the dye was not synchronized with the cardiac cycle. This has been shown to influence the TFC.[5] The measurements were done a varying time after angioplasty, and post-ischemic hyperemia could have influenced the TFC and FCV. However, these influences were probably the same for all three arteries. Finally, in this study there was no comparison with coronary flow velocity measured with an intracoronary doppler wire. The pressure wave generated by the contrast injection and the viscosity of the contrast medium could have influenced the flow velocity measurements.

CONCLUSION

Because the TFC, used as an index for coronary flow velocity, is dependent on the length of the related vessel, it was corrected for the longer length of the LAD to calculate the CTFC. However, the present study shows that correction can be done more precise by normalizing the TFC to the significantly different mean length of each of the three

coronary vessels. In this way the 'frame count velocity' can be calculated without having to use an intracoronary guide wire. Therefore, the frame count velocity is a fast, simple and, compared to the CTFC more accurate angiographic method to estimate coronary blood flow velocity.

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Chapter 4

Automated TIMI frame counting using 3-d modeling

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ABSTRACT

Three dimensional coronary modeling and reconstruction can assist in the quantitative analysis of coronary flow velocity from 2-d coronary images. In this paper a novel method to assess coronary flow velocity is proposed. First, 3- d models of the coronary arteries are estimated from bi-plane X-ray images using epipolar constraint energy minimization for the selected fiducial points like bifurcations, and subsequently 3-d B-spline energy minimization for the arterial segments. A 4-d model is assembled from a set of 3-d models representing different phases of the cardiac cycle. The 4-d model is fitted to the 2-d image sequences containing basal or hyperemic blood flow information. Then, by counting the frames in analogy with TIMI frame counting, an index of the mean coronary flow velocity can be estimated. Our experimental results show that the algorithm correlates with r = 0.98 (P<0.0001, 95% CI 0.92–0.99) to the clinical measurements of the TFC.

INTRODUCTION

Coronary artery disease, or more specific a stenosis, may lead to a reduction in coronary blood flow. This is manifested in a reduced flow velocity of blood through the coronary arteries. TIMI frame counting is a practical method to index blood flow velocity and quantize coronary flow velocity reserve using measurements in basal and hyperemic conditions.[10] Coronary flow velocity reserve is an important measure for heart assessment.[7,19,20] In clinical practice the method of TIMI frame counting can be considered as a qualitative flow velocity assessment using 2-d monoplane X-ray images.[22] This method, however, is manually performed by a cardiologist and requires catheter measurements to provide information about vessel length. The standard minimally invasive modality to assess coronary arteries is mono-plane X-ray angiography, which is a two dimensional method. Three dimensional and also non-invasive methods are computed tomography (CT) and magnetic resonance imaging (MRI). Several 3-d semi-automatic modeling methods have been proposed using mono-plane[9] and bi-plane X-ray.[6] 4-d models with motion analysis are shown by Chen et al.[2,5] Tomographic reconstruction techniques require multiple projection angles which are obtained in CT or rotational angiography. This requires measuring of the electrocardiogram to perform ECG-gated recording or retrospective ECG gated reconstruction. Tomographic reconstruction requires a calibrated system in which the projection geometry is well defined and at least three projections are required to get reasonable results.[11] Several improvements of this algorithm are proposed.[12,17,18] Coronary models can be used, for example, in intervention planning[23] or fusion with other modalities like IVUS.[15]

In this paper we propose a method using two standard, uncalibrated, mono-plane X-ray image sequences to create a 3-d model of the coronary arteries. Our main research goal is to automate the measurement of mean coronary flow velocity. In our previous research,[3] we have aimed at using the 2-d X-ray angiography data directly, but quantization of flow velocity requires the length of the vessel which can only be obtained using 3-d information. Furthermore our 2-d analysis required coronary model fitting in which the model ideally should be 3-d. A set of 3-d models is created resulting in a 4-d model of the coronary arteries covering the complete cardiac cycle. This is accomplished by creating a temporal 3-d model using the basic 2-d X-ray information acquired by standard assessment procedures. A minimum of two projection angles is required to estimate a 3-d model from the 2-d data, as shown in Fig. 1.

The estimated 4-d model T is used as a template to find the coronary arteries in the 2-d X-ray images I. A 3-d model is selected from T corresponding to the normalized cardiac phase of the 2-d image. Then, a 2-d projection of the 3-d model M is fitted onto the 2-d image by slightly adapting the 3-d model. This adaptation is controlled by

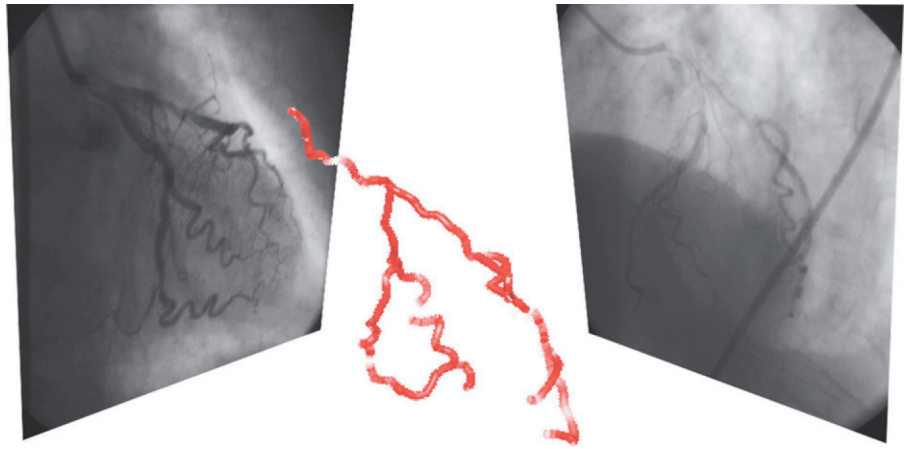

Figure 1 B4-d model *T* creation using mono-plane X-ray sequences at two different projection angles. The frames are selected using retrospective ECG gating. The 4-d cardiac cycle is covered by a set of 3-d models $T = [M_0, \ldots, M_1]$ estimated from the 2-d images *I*.

deforming the 3-d model until the mean squared distance between the projection of the model wire-frame and the vessel centerlines in the 2-d image is minimized. This process is repeated for every image in the sequence.

After a satisfactory fit of the 3-d model the contrast agent density at the location of the vessel centerline is measured. Combining the 4-d model with these measurements results in a 4-d model including information about coronary blood flow from which we can estimate coronary blood flow velocity.

METHODS

TIMI frame counting (TFC) is a manual method to give a flow velocity index by counting the number of frames between the appearance of the contrast agent at the main trunk and at the apical bifurcation of a vessel.[10] When the blood flow velocity is artificially increased by inducing hyperemic conditions using an injection of dipyradimole, papaverine or adenosine, the frame count is in general significantly decreased. The ratio between basal and hyperemic state frame counting can be defined as the frame count reserve. Flow limiting factors, such as the presence of a stenosis, will show a limited decrease of flow velocity during the hyperemic condition compared to basal conditions. Our approach to find TFC values automatically is to extract time density curves from the all images. These time density curves are represented as an image, called a contrast

flow map, which is subsequently analyzed by standard image processing algorithms. In this paper we want to locate the vessels and measure, using densitometry, the contrast density at the vessel centerlines. Coronary vasculature is difficult to obtain from the low contrast images from only one 2- d view. It limits the temporal analysis of a single 2-d X-ray image sequence, because the information is not sufficient to resolve the ambiguities like vessel overlap and foreshortening. Therefore, we will reconstruct a 3-d model of the coronary arteries.

Fig. 2 clarifies the procedure. On top are the angiographic sequences used as input to the algorithm, we firstly use two sequences, the primary and secondary angular view, to estimate a 3-d coronary model. From the primary and secondary input sequence one

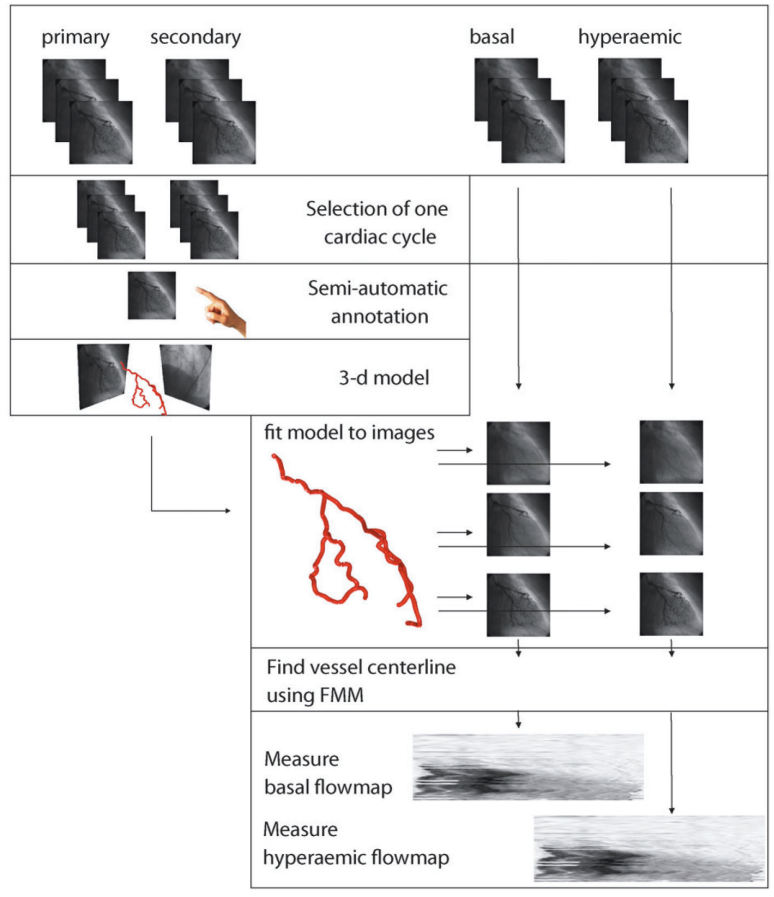

Figure 2 Overview of the creation of flow maps from X-ray angiography image sequences.

cardiac cycle is selected which contains maximum opacification of the coronary arteries. In these images the start and end points of the main arteries and the most important bifurcations are manually annotated in one image resulting in a set of points. Then this annotation is propagated through the remaining images using template matching, the user is able to correct the automatic annotation. The annotated sequence covering one cardiac cycle from two viewpoints is used to create a 3-d model. This model is used to find the location of the vessels in the X-ray sequences of the basal and hyperemic acquisitions. The next section will explain this process in more detail.

Imaging geometry

The 3-d coronarary reconstruction method using planar X-ray images follows the computer vision methods described by Hartley and Zisserman [13]. After the creation of the model, the model is fitted to the two dimensional image sequence using 3-d deformation and projection. Finally, a densitometric measurement results in flow maps from which we can estimate TFC.

The center of the heart coincides with the center of rotation of the C-arm, this is because the images in this research are acquired with a full-view of the coronary arteries centered in the imageplane. A small center offset can sufficiently be corrected by a table motion correction algorithm, which is discussed in Section 2.4. From this point of view, we can use the uncalibrated information in the DICOM file to construct the geometry of the C-arm. In our case the known variables are the size of the image plane N in [pixels] and the width of the intensifier D in [mm]. We assume that the focal distance f in [mm] is equal to the distance source to detector. Based on this assumption we can calculate the detector element (pixel) size μ = D/N. We also introduce a displacement vector in the image plane $\mathbf{d} = [d_x, d_y]$. Variables f, N and D can be extracted from the DICOM info structure from fields *Distance Source to Detector, Rows* and *Intensifier Size*, respectively. These variables define the camera calibration matrix K:

$$\mathbf{K} = \begin{bmatrix} f\mu & 0 & \frac{1}{2}N + d_t \\ 0 & f\mu & \frac{1}{2}N + d_y \\ 0 & 0 & 1 \end{bmatrix} \quad (1)$$

The rotation matrix R can be formed using the primary (RAO/LAO) and secondary angle (CAUD/CRAN) information from the DICOM info structure:

$$\mathbf{R}_x(\beta) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\beta) & -\sin(\beta) \\ 0 & \sin(\beta) & \cos(\beta) \end{bmatrix} \quad (2)$$

$$\mathbf{R}_y(\alpha) = \begin{bmatrix} \cos(\alpha) & 0 & \sin(\alpha) \\ 0 & 1 & 0 \\ -\sin(\alpha) & 0 & \cos(\alpha) \end{bmatrix} \quad (3)$$

$$\mathbf{R}(\alpha, \beta) = \mathbf{R}_x(\beta)\,\mathbf{R}_y(\alpha) \quad (4)$$

The primary angle corresponds to RAO ($\alpha \leq 0$) and LAO ($\alpha > 0$) projection and the secondary angle to the CAUD ($\beta \leq 0$) and CRAN ($\beta > 0$) projection, see Fig. 3. The translation vector $\mathbf{t}$ is the position of the camera relative to the center of rotation. The z-axis points towards the ceiling, so the camera is *f/2* out of the center of rotation in z direction:

$$\mathbf{t} = \begin{bmatrix} 0 \\ 0 \\ f/2 \end{bmatrix} \quad (5)$$

The camera matrix is now:

$$\mathbf{P} = \mathbf{K}\begin{bmatrix} \mathbf{Rt} \end{bmatrix} \quad (6)$$

3-d modeling

Fallavollita and Cheriet [9] have proposed a method to estimate coronary arteries using snakes. Our method uses this approach with the main difference that a FMM speed-map

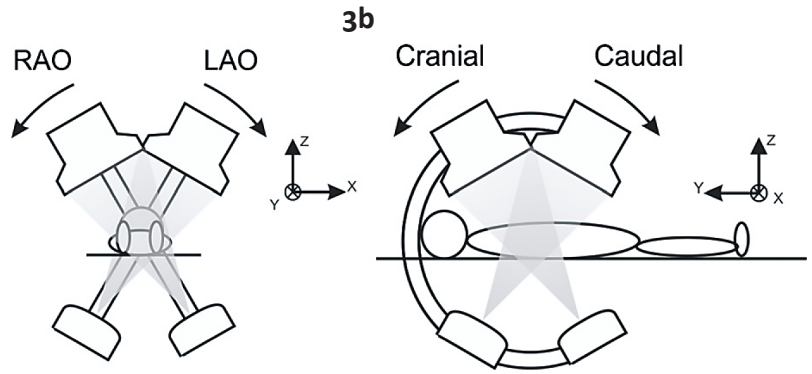

Figure 3 The C-arm can rotate about two angles, the primary angle α (RAO/LAO), see Fig. 3(**a**), and the secondary angle β (Caudal/Cranial), see Fig. 3(**b**). The origin of the coordinate system is placed at the center of rotation of the C-arm. The C-arm is at anterior-posterior (PA) position when $[\alpha, \beta] = [0, 0]$. (a) Primary angle (α) and (b) secondary angle (β).

is used as force function. The force function is important because it controls the deformation of the 3-d snake. The snake is described by a 3-d-curve or B-spline $v(s)$. The deformation is controlled by an energy minimization function:

$$E(v) = \int_0^1 (E_{int}(v) + E_{ext}(v))ds \tag{7}$$

where $E_{int}(v)$ is the internal energy, preserving smoothness, and $E_{ext}(v)$ is the external energy, attracting the snake to image features. E_{int} can be described by:

$$E_{int}(v) = \gamma \left| \frac{v}{s} \right|^2 + \lambda \left| \frac{^2 v}{s^2} \right|^2 \tag{8}$$

where γ and λ are constants controlling the tension and rigidity of the snake respectively. The external energy E_{ext} can be described by:

$$E_{ext}(v) = \phi^{-1}(\mathbf{x}_1, \mathbf{x}_2, \mathbf{P}_1, \mathbf{P}_2) - \mathbf{X} \tag{9}$$

where ϕ^{-1} is the retro-projection operator. This operator reconstructs a 3-d point from two given 2-d points $\mathbf{x}_n$ in two projection planes $n = 1, 2$ described by camera matrix $\mathbf{P}_n$:

$$\mathbf{X} = \phi^{-1}(\mathbf{x}_1, \mathbf{x}_2, \mathbf{P}_1, \mathbf{P}_2) \tag{10}$$

$\mathbf{x}_n$ are the original points $\mathbf{q}_n$ with a movement depending on the force maps $\mathbf{F}_n$:

$$\mathbf{x}_n = \mathbf{q}_n - \nabla \mathbf{F}_n(\mathbf{q}_n) \tag{11}$$

where $\mathbf{q}_n$ are the projections of on projection planes $n = 1, 2$ and $\mathbf{F}_n$ are the used force maps, which will be discussed in the next section.

The numerical implementation of the snake algorithm requires approximation of the derivatives with finite differences. Conversion to vector notation with $v_i = (x_i, y_i, z_i)$ [1] results in:

$$E_{int}(v) = \gamma \left| v_i - v_{i-1} \right|^2 + \lambda \left| v_{i-1} - 2v_i + v_{i+1} \right|^2 \tag{12}$$

$$\begin{aligned} \gamma \left| \frac{v_i}{s} \right|^2 &\approx \gamma \left| v_i - v_{i-1} \right|^2 \\ &= \gamma \left((x_i - x_{i-1})^2 \right. \\ &+ (y_i - y_{i-1})^2 \\ &+ \left. (z_i - z_{i-1})^2 \right) \end{aligned} \tag{13}$$

$$\begin{aligned} \lambda \left| \frac{^2 v_i}{s^2} \right|^2 &\approx \lambda \left| v_{i-1} - 2v_i + v_{i+1} \right|^2 \\ &= \lambda \left((x_{i-1} - 2x_i + x_{i+1})^2 \right. \\ &+ (y_{i-1} - 2y_i + y_{i+1})^2 \\ &+ \left. (z_{i-1} - 2z_i + z_{i+1})^2 \right) \end{aligned} \tag{14}$$

The distance between the points is kept equidistant (Euclidean distance) by redistribution of the points along the snake using cubib B-spline interpolation. Discretization of the integral in Eq. (7) gives:

$$E = \sum_{i=0}^{N-1} (E_{int}(v_i) + E_{ext}(v_i)) \tag{15}$$

for a snake with N nodes.

Minimization of E allows us to rewrite Eq. (15) to be solved using dynamic programming:

$$\begin{aligned} E(v_1, v_2, \ldots, v_N) &= E_1(v_1, v_2) \\ &+ E_2(v_2, v_3) + \ldots \\ &+ E_{N-1}(v_{N-1}, v_N) \end{aligned} \tag{16}$$

In case of, for example, $N = 5$ nodes we can calculate the minimal energy using sub-functions $s_k(v_{k+1})$:

$$\begin{aligned} s_1(v_2) &= \min_{v_1} E_1(v_1, v_2) \\ s_2(v_3) &= \min_{v_2} (s_1(v_2) + E_2(v_2, v_3)) \\ s_3(v_4) &= \min_{v_3} (s_2(v_3) + E_3(v_3, v_4)) \\ \min_{v_1, \ldots, v_5} E(v_1, \ldots, v_5) &= \min_{v_4} (s_3(v_4) + E_4(v_4, v_5)) \end{aligned} \tag{17}$$

The recurrence relation is now stated as (for clarity the second order term is not presented):

$$s_k(v_{k+1}) = \min_{v_k} \left\{ s_{k-1}(v_k) + E_{ext}(v_k) + \left| v_{k+1} - v_k \right|^2 \right\} \tag{18}$$

Each stage consists of 26 possibilities, the neighbors $[3 \times 3 \times 3] - 1$, to calculate. The internal energy is stored at each stage. The indices of node position with the minimum energy cost are stored in the position matrix. The minimum energy can now be found by back-tracing in the position matrix using Dijkstra's shortest path algoritm [8].

Force map

The force map is specifically constructed for each vessel segment to prevent interference from other vessel segments during the minimization process of the 3-d-snake. The begin and endpoint of each vessel segment is annotated. With this annotation we can generate a force map from each vessel segment using the fast marching method (FMM) [21]. This force map is used to find the vessel centerline using the minimal cost path algorithm. The 2-d vesselcenterline is plotted in a 2-d grid. From this grid a euclidean distance map is calculated. The gradient of the distance map is used as force map in the snake energy minimization algorithm.

The vessel centerline is found using the 2-d multi-stencils fast marching method (FMM) [14]. This FMM is used to build a map containing the travel time between the start-point and all other points using a force function, which can be considered as the speed. The FMM solves the Eikonal equation:

$$\left|\left|\nabla T\,(x,\,y)\right|\right|\,\left|\left|\,F\,(x,\,y)\,=\,1\right.\right. \tag{19}$$

in which $T(x, y)$ is the arrival time of the front and $F(x, y)$ is the force function. The contrast enhanced image $I_c(x, y)$ is used as input $F(x, y)$ for the fast marching method:

$$F\,(x,\,y)\,=\,(1\,-(G_\sigma \otimes I_c))^{\gamma} \tag{20}$$

Now the vessel centerline is the minimum cost path from the starting point to the end point, the back-tracing of the minimal cost past is performed using a fourth order Runge–Kutta approximation. The centerline, see Fig. 4, is defined by $v(s) = (x(s), y(s))$ where x and y are the coordinate functions and $s \in [0, 1]$ is the parametric domain which describes the vessel from start to endpoint.

Table motion compensation

Table motion is compensated using image plane shifting. The only requirement for this algorithm is the annotation of the catheter-tip throughout the image sequence. The correction is performed in the x–y plane of the local coordinate system, this results in a converging solution. Eq. (6) is changed to include the table translation in the x–y plane:

$$\mathbf{P} = \mathbf{K}\left[\,\mathbf{R}\,\left[\mathbf{t} + \mathbf{R}^{-1}\mathbf{t}_t\right]\,\right]; \tag{21}$$

in which $\mathbf{t}_t$ is the vector:

$$\mathbf{t}_t = \begin{bmatrix} x_t \\ y_t \\ 0 \end{bmatrix} \tag{22}$$

This vector has two parameters x_t and y_t. These parameters represent table motion, which results in an x–y motion in the image plane. The parameters can be solved by minimizing the reprojection error of the catheter-tip in the second image plane using Eq. (9). The method solves the triangulation problem using the direct linear transform. This method is described in detail in Hartley and Zisserman [13].

Fitting

The 3-d model is fitted to each frame in the image sequence from which we want to measure the TFC. The vessel centerline is obtained using the FMM method. The start and end points of the vessel segment are determined by projection of the segments of the 3-d model. Most likely, the projection of the segment will not fit the vessel centerline found by the FMM method. Therefore, the 3-d model is iteratively deformed until the vessel centerline coincides with the projection of the segment. We allow a maximum of 10 iterations of the model deformation to prevent over-fitting when a vessel centerline is incorrectly found due to low or none contrast density.

Annotation

Three dimensional reconstruction from a limited set of projections (Np=2) is a challenging task. Therefore we have created a ground truth dataset using semi automatic annotation

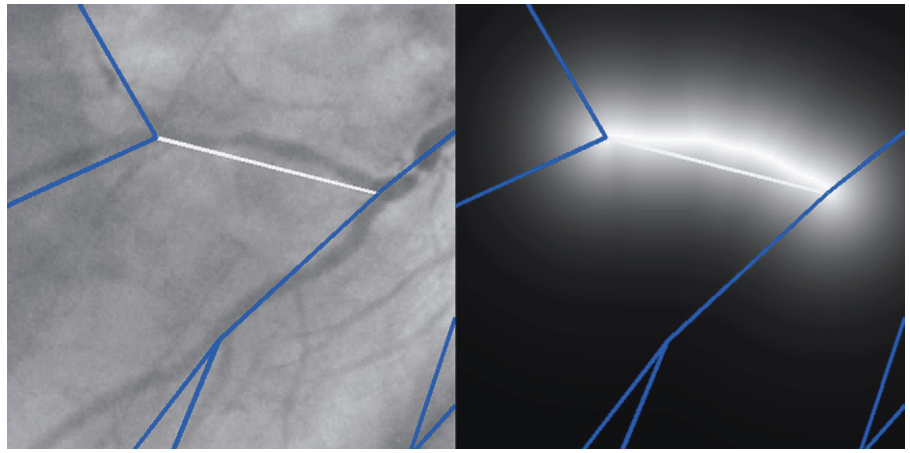

Figure 4 The right image shows the annotation of the vessel segments with a highlight (in white) of the vessel segment currently being traced. The right image shows the euclidean distance map after vessel detection using the FMM method and minimal cost path algorithm. The gradient of the distance map is used as force field in the snake deformation algorithm.

of our dataset. The process of annotating the dataset is based on our flow estimation software as described in ten Brinke et al. [3]. We have discarded image pre-filtering with coherence filters and vessel segmentation algorithms to prevent error accumulation and experimental thresholds.

The user selects an image from the dataset with maximum opacified arteries. Next, the vessel structure is annotated by selecting bifurcations and endpoints. These points are denoted Pi(x, y). Points are interconnected using segments which are stored in a connection matrix Ci,j connecting point Pi with point Pj . It is a redundant matrix, so only the upper triangle is used. All points can be labeled Li, for example 'LAD', 'LCx', 'Cathetertip'. A dataset contains the annotation set S {= P(n), C, L} in which n = [1 . . . N], with N the number of images in the dataset. So each image shares the same labels, interconnections and amount of points, only the locations of the points vary. This allows the creation of a temporal 3-d model using accurate data points. The user can use fast marching assistance for tracing the vessel centerline to make sure that the annotation correctly follows the vessels. All other frames are semi-automatically annotated using template matching.

Contrast flow map analysis

From the DICOM file we obtain 8-bit grayscale images with a size of [512 × 512] pixels. The raw data will be used to construct the contrast flow map, which results in a flow map with the same resolution as the images. Each line in the flow map represtent the contrast agent density along one vessel centerline s = [0 . . . 1], with in the vertical direction the image index n = [1 . . N], see Fig. 5. In this research we will focus on the most clearly visible vessel, which is the LAD. The contrast flow map is analyzed using the following image processing steps: The mean value is removed from the single frame measurements. This mean value Γ_{mean} is the mean from all single measurements in the temporal direction:

$$\Gamma_{mean}(n, s) = \Gamma(n, s) - \frac{1}{N}\sum_{n=0}^{N-1}\Gamma(n, s) \tag{23}$$

for s = [0 . .1]. Next we calculate a threshold using a 256 bins histogram from Γ_{mean} . In general, the maximum peak in the histogram belongs to the contrast agent (dark) values. In practice, we can separate the opacified arteries from the transparent arteries using a threshold consisting of the maximum peak position in the histogram plus the standard deviation of the peak which is empirically set at 1/8 of the total number of bins.

This threshold is then applied to the contrast flow map. A Canny [4] edge detector finds the lines in the contrast flow map. One line (or curve) in the contrast flow map connects the arrival times and vessel positions of the contrast agent. The assumption

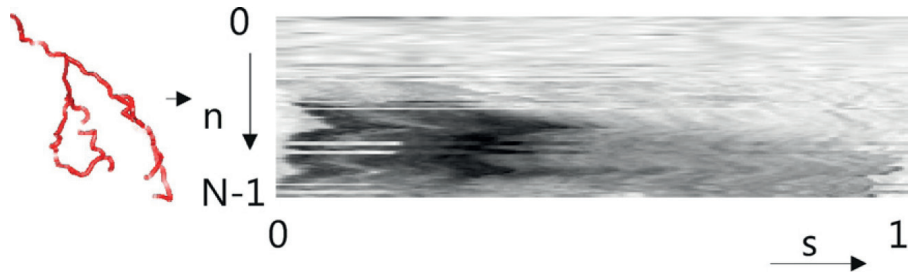

Figure 5 Densitometry is applied on each image. The result is the measurement of the contrast density at the location of the vessels. This information is shown in a flow-map for each vessel. From this the coronary flow velocity can be estimated.

that the contrast agent propagates with a constant velocity through the arteries allows us to use a line fit. The lines are detected using the Hough transform [16]. The slope of the line is related to the contrast flow velocity. All lines that do not have a negative slope are discarded as well as lines with a starting point after 1/2 of the total acquisition time (we assume that the coronary arteries will be fully opacified by the injection of the contrast agent in the first half of the recorded image sequence).

Experiments

Two experiments are conducted: using a static brass model, see Fig. 6, imaged using a Phillips Xper X-ray scanner and with clinical data. Our clinical dataset contains images of interventions with specific TIMI frame counting data and coronary artery length measurements. The coronary artery length is clinically measured using a catheter starting from the left main artery to the apical bifurcation of the LAD. It contains 32 patients (11 female, 21 male) from which two assessments are discarded because they do not contain at least two different projection angles of the left-coronary artery. From the resulting 30 patients a total of 13,096 images have been semi-automatically annotated. The two visually best series are selected for annotation taking into account a large angular distance between the series, allowing to recreate a 3-d model. Note that, in contrast to the catheter measurements, in the measurements of the reconstructed coronary arteries we only measure from the start of the LAD to the apical bifurcation.

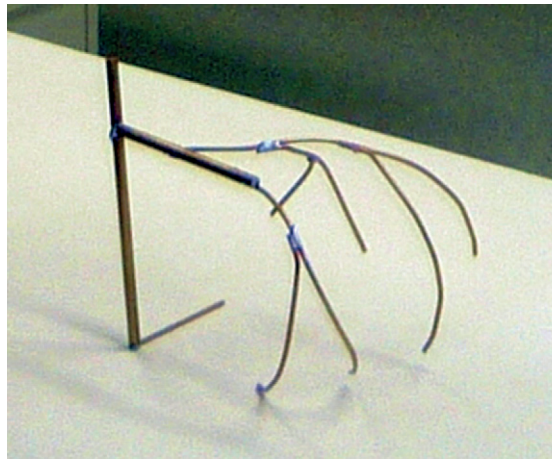

Figure 6 Densitometry is applied on each image. The result is the measurement of the contrast density at the location of the vessels. This information is shown in a flow-map for each vessel. From this the coronary flow velocity can be estimated.

RESULTS

Phantom

We have tested the 3-d modeling algorithm on the brass phantom. A fully automatic reconstruction of the vessel segments based on epipolar line matching was not successful due to the unknown camera calibration parameters. In the literature methods are proposed by e.g. Blondel et al. to address this problem.[2] Since it is not the focus of our research to create reconstruction algorithms we have decided to manually annotate the vessel segments. With the manual annotation and the B-spline algorithm proposed by Fallavollita and Cheriet[9] we were able to create usable models from the 2-d data. Fig. 7 shows the reconstruction of the phantom and Table 1 shows the errors made in the reconstruction. Large variations are visible at the vessel segments which are not clearly visible in both images.

Clinical data

The quality of the coronary models is characterized by the re-projection error. The length of the LAD is known from catheter measurements, so we will compare the LAD length measured from the model with the ground truth of the catheter measurement. The results are displayed in Fig. 9.

Table 1 Baseline and procedure characteristics

Segment	μ_1 [pixels]	σ_1 [pixels]	μ_2 [pixels]	σ_2 [pixels]
1	8	±8	78	±37
2	10	±8	5	±3
3	39	±32	4	±2
4	64	±48	6	±6
5	8	±8	2	±1
6	35	±31	14	±7
7	3	±2	87	±58
8	6	±5	57	±33
9	2	±1	1	±1
10	2	±0	2	±1
11	2	±1	3	±2
12	3	±1	3	±2
13	7	±6	3	±1

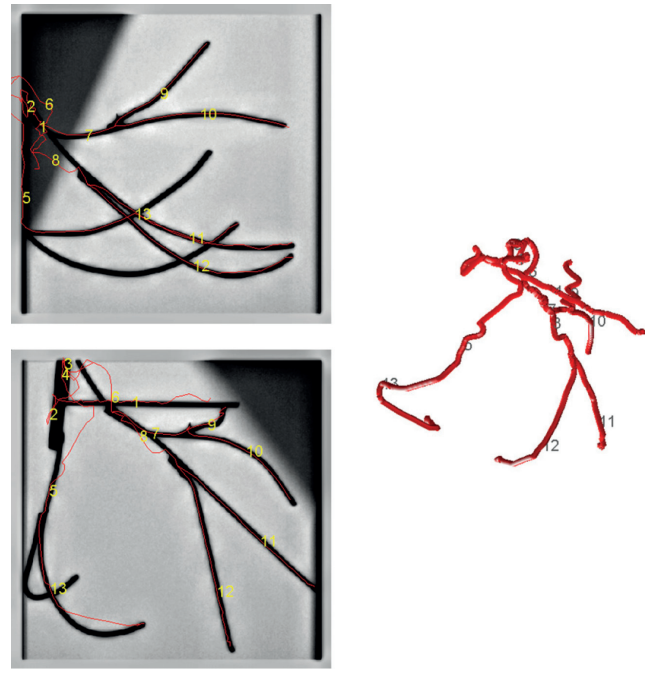

Figure 7 Reconstruction of phantom. See Table 1 for the reconstruction results.

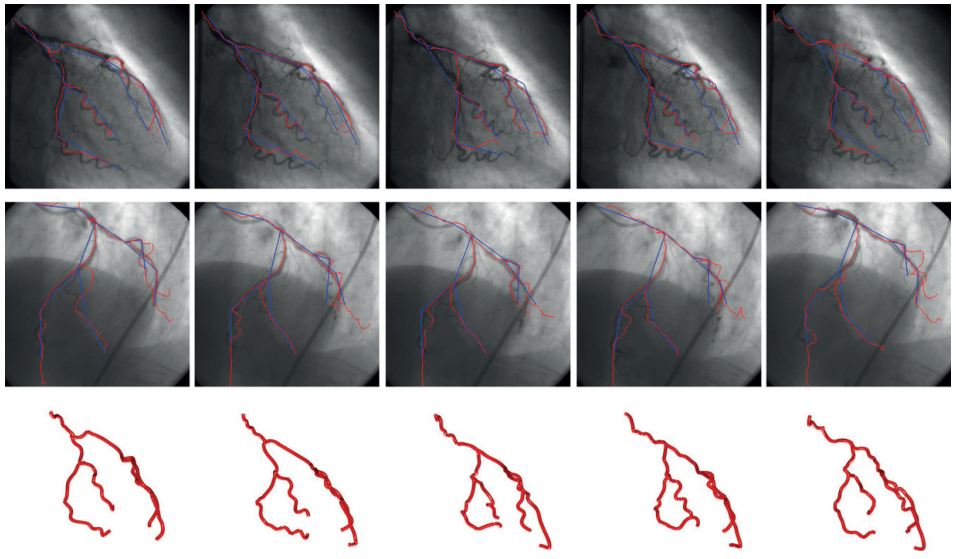

Figure 8 Modeling of the coronary arteries. The first and second row show the two images used in the modeling, the third row shows the generated model. A total of 20 models are created to cover the complete cardiac cycle, only 5 are shown in this figure. (For interpretation of references to color in the text, the reader is referred to the web version of this article.)

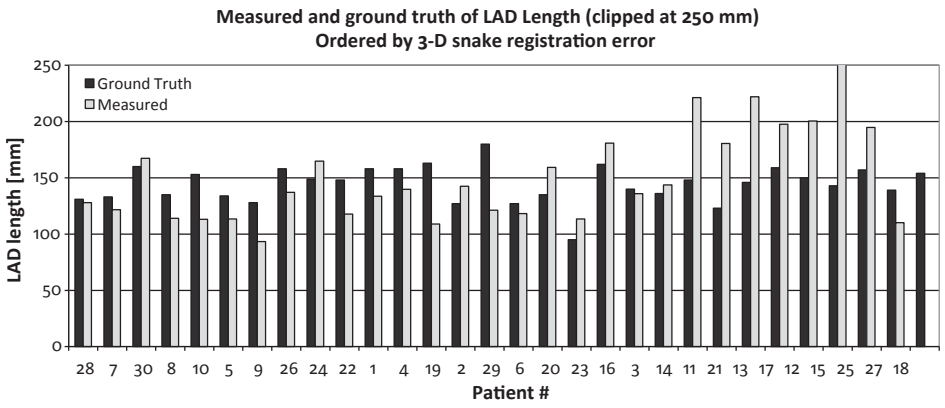

Figure 9 Length of the left anterior descending (LAD) artery. The length calculated from the 3-d model is compared to the length measured with a catheter (ground truth). The patients are ordered by registration error. The registration error is a measure for the accuracy of the LAD length measurement.

Overall results are depicted in Fig. 10(a). The measured TFC correlates with the clinical measurements with r = 0.80 (P<0.0001, 95% CI 0.63–0.89). From 14 of 32 patients we have data of completely opacified coronary arteries during one cardiac cycle from two viewing angles. This data is used to create models covering the complete

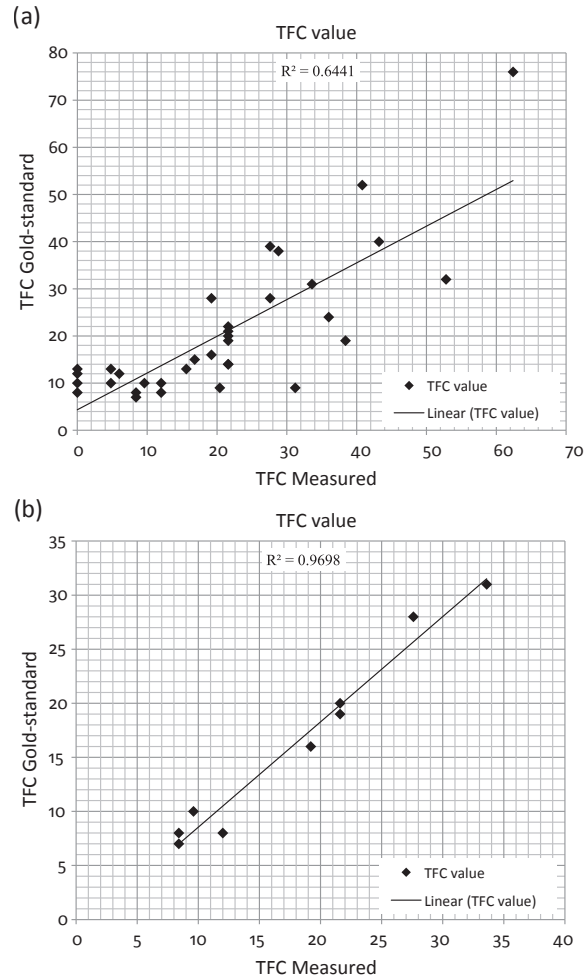

Figure 10 Scatter-plots showing the correlation between the measured (using 3-d modeling and flow measurements) and the ground thruth (measurements performed by a cardiologist). (**a**) Scatter-plot with linear fit of the measured and ground truth TFC values of the 32 patients. (**b**) Scatter-plot with linear fit of the measured and ground truth TFC values of the remaining 9 patients.

cardiac cycle. In Fig. 8 an example of 3-d models created from 5 phases of the cardiac cycle are shown. Retrospective gating is used to select two images for the creation of one 3-d model; the figure shows semi-automatically annotation of the vessels in blue and the 2-d projection of the final model in red. The 2-d projection of the model does not exactly fit the X-ray image, but that is not a main issue because the 3-d model is deformed to fit the X-ray image in a latter phase. From 9 of these 14 patients we were able to obtain a measured TFC within the intra-observer variability range of ± 5 frames. The measured TFC correlates with the clinical measurements with r = 0.98 (P<0.0001, 95% CI 0.92–0.99). See Fig. 10(b).

DISCUSSION

The accuracy of the algorithm depends on clinical and technological limitations. Acquisition of high quality images is limited by the amount of X-ray exposure to the patient and the clinician. Therefore, the clinician tries to minimize the X-ray dose by highly effective usage of the field of view. This results in table motion during the acquisition and a minimum amount of images. Also, toxic effects of contrast agent limit the amount of image acquisition runs. Dose limitation results in lower quality images or incomplete opacification of the coronary structure. Furthermore, the health condition of the patient may limit the usage of the breath hold technique. Moreover, patient arrhythmias during acquisitions may occur spontaneous or due to the injection of contrast agents or vasodilators. Finally, patient dimensions influences the amount of X-ray required and as a result changes the brightness of the images. This may vary at different acquisition angles.

The clinical acquisition problems immediately have an effect on the performance of the analysis software: for 3-d modeling, a calibrated X-ray system is required. System calibration allows epipolar matching and quantized models. Also, the creation of a temporal model requires one completely opacified coronary vessel structure during the whole cardiac cycle. For 3-d modeling it also requires to have this from a minimum of two different angles. Ambiguity still exists, but can be reduced using the B-spline models of the vessel segments. Patient motion like breathing and table motion result in motion artifacts. The results of these motions are inaccurate models. We have minimized these errors by annotating the catheter-tip and applying motion correction by aligning the catheter-tips in both imaging planes.

During an X-ray acquisition, several image enhancements may affect the analysis software. Automatic exposure control, for example, results in an extra variable which should be included in densitometric measurements. This variable, however, is not

updated during the acquisition. Anatomical background structures, like the spinal cord, influence vessel tracing algorithms. Theoretically we can use a background subtraction algorithm, in practice, motion artifacts prevent its application. In this research 3-d modeling is used to compensate for that.

Limitations

The method discussed in this paper can only be used when at least two acquisitions are available with a complete opacification of the coronary arteries during one complete cardiac cycle. The time resolution of the measurements is limited by the frame-rate of the X-ray equipment. In normal acquisitions this frame-rate is 12.5 or 15 frames per second (fps), resulting in respectively 80 ms or 66.7 ms maximum temporal resolution (without interpolation) depending on the acquisition device. Acquisitions with 50 fps are technically no problem, however, clinically not desired because of higher X-ray exposure to patient and clinician.

CONCLUSION

In this paper we have proposed a method towards the automation of TIMI frame counting and, as a result of that, the measurement of coronary flow velocity reserve using standard angiographic X-ray acquisition. It requires a full cardiac cycle of completely opacified coronary arteries from at least two different angular positions recorded with ECG and an additional run for the hyperemic measurement. From 9 patients we were able to obtain a measured TFC within the intra-observer variability range of ± 5 frames. The measured TFC correlates with the clinical measurements with r = 0.98 (P<0.0001, 95% CI 0.92–0.99).

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Chapter 5

Frame Count Reserve

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ABSTRACT

Background

The Doppler wire derived (relative) coronary flow velocity reserve (CVR) that is used to evaluate functional significance of a coronary stenosis, is a method performed only by interventional cardiologists. An angiographic method would be useful in the diagnostic catheterization laboratory. For this purpose we investigated the relation between TIMI frame count reserve (FCR) and CVR.

Methods and Results

In 38 patients (relative) FCR of left anterior descending (LAD) and left circumflex coronary artery (LCx) was calculated using manual, synchronized contrast agent injections, and compared to (relative) CVR. In addition, vessel length was measured with an intracoronary guidewire and frame count flow velocity was calculated and compared to average peak velocity. There was a strong correlation between FCR and CVR (r=0.62, *P*<0.001) and between rFCR and rCVR (r=0.84, *P*<0.001). The LAD was significant longer than the LCx (mean 14.3 ± 1.6 cm versus 11.4 ± 1.8 cm, *P*<0.001) and therefore TIMI frame count (TFC) of LAD was significant higher than of LCx (mean basal 32.5 ± 15.1 versus 23.6 ± 9.1 and hyperemic 12.1 ± 6.6 versus 8.7 ± 3.2, both *P*<0.02). However, all flow velocity measurements and estimations of volume flow were not different for LAD compared to LCx. There were also no differences between mean FCR and CVR of LAD or LCx, of both vessels compared to each other and between mean rFCR and rCVR.

Conclusion

The (relative) frame count reserve can be used to estimate (relative) coronary flow velocity reserve.

INTRODUCTION

To assess functional significance of a coronary stenosis, intracoronary Doppler wire derived coronary flow velocity reserve (CVR) is a well-established method.[1] In absence of coronary stenosis, CVR can also be used to evaluate microvascular function.[2,3] By comparing CVR of a coronary artery with stenosis to CVR of a 'normal' reference vessel, relative coronary flow velocity reserve (rCVR) is calculated. This corrects for influence of microvascular dysfunction.[4,5] CVR > 2.0 and rCVR > 0.65 are considered appropriate cut-off values to defer angioplasty (PCI).[6,7] Because of the need of an intracoronary Doppler wire and dedicated equipment, only an experienced cardiologist in an interventional catheterization laboratory can perform these measurements. In daily practice nevertheless, intermediate coronary stenosis of uncertain significance are often encountered during diagnostic angiography. Therefore an angiographic method to estimate (relative) coronary flow reserve would be very useful.

Some investigators have found good correlation between CVR and (digital subtraction) angiographic estimation of myocardial perfusion,[4,8-11] but these two methods are essentially different. The TIMI frame count (TFC) is an inverted index of coronary flow velocity that correlates with Doppler wire derived average peak velocity (APV),[12] and it can be used 'on line' if angiography is recorded digitally. However, only one study investigated the use of TFC as an estimation of coronary flow velocity reserve.[13]

While TFC is an index of basal flow velocity, during pharmacological induced hyperemia it becomes an index of hyperemic flow velocity. By dividing both counts an estimate of coronary flow velocity reserve is made. This study was done to compare this (relative) 'Frame Count Reserve' (FCR) with (r)CVR. In addition, with the length of the coronary arteries measured with an intracoronary guidewire,[14] 'Frame Count Velocity' (FCV) was calculated and compared to APV determined with the Doppler wire.

METHODS

Patients

In 38 selected patients, referred for diagnostic coronary angiography or PCI for stable angina, (r)FCR and (r)CVR were calculated for both left anterior descending (LAD) and left circumflex coronary artery (LCx). At least one of these two vessels was 'normal' (visually no stenosis > 50%) and all vessels had TIMI 3 flow. In the case of PCI measurements were repeated thereafter. No patient had left main stenosis >30%, history of obstructive pulmonary disease or myocardial infarction in the territory of the

left coronary artery and all patients had sinus rhythm. The Medical Ethics Committee of the hospital of the Free University Amsterdam, The Netherlands, approved the protocol. All patients gave written informed consent.

Procedure

One operator (MS) using 7 French guiding catheters without side-holes (Guidant) and ionic contrast agent (Hexabrix, Guerbet) performed all procedures. At the beginning of the procedure an intravenous bolus of heparin 5000 IU was given. In all but one cases of PCI a stent was implanted; there were no residual stenoses > 30%. More than 5 minutes before angiography (Philips Integris 3000, 25 frames/sec) and Doppler measurements (Cardiometrics) 0.2–0.4 mg intracoronary nitroglycerine was given. Angiography (right anterior oblique with caudal angulation without magnification) was performed by manual injection through the contrast filled guiding catheter, synchronized to an acoustic heart beat signal. It was performed at least 10 minutes after last balloon inflation and 2 minutes after last contrast injection to prevent reactive hyperemia due to ischemia or contrast agent.

Protocol and Calculations

After positioning the Doppler wire in a normal segment of LAD or LCx, as proximal as possible but > 2 cm distal to the culprit lesion if present, basal average peak velocity (APV) was recorded together with blood pressure and heart rate. Angiography was performed for basal TFC of both vessels. Hyperemia was induced by adenosine, 140 μg/kg.min intravenous for at least 3 minutes. Hyperemic APV was recorded and contrast injection for hyperemic TFC was given. The Doppler wire was then repositioned in the ipsilateral vessel with recording of hyperemic APV after which adenosine was stopped. More than 3 minutes later basal APV of this vessel was recorded.

CVR was determined by dividing hyperemic by basal APV. With the digitally numbered frames TFC was calculated as described before.[15] FCR was calculated by dividing basal by hyperemic TFC. Relative CVR and rFCR were determined by the ratio of the reserve of LCx and LAD.

The frames between the last QRS complex and the first frame of the TFC were counted. By dividing this number by 25 (frames/sec) an estimate was made of the beginning of the contrast injection in relation to the phase of the cardiac cycle.

Length of both coronary arteries was measured using the Doppler or regular guidewire, as described by Gibson.[14] The distal end of the guidewire was placed 1-3 mm in the distal landmark, marked outside the proximal end of the guiding catheter, then pulled back until 1-3 mm was still visible outside the distal end of the guiding catheter and marked again. The measured distance between the two marks was used to estimate

the length of the coronary artery from the tip of the guiding catheter to the landmark used for the TFC. By multiplying this length by 25/TFC, Frame Count Velocity (FCV) was calculated.

The diameter of the proximal segment of the coronary artery and the percentage stenosis of the target lesion if present was calculated by QCA as the mean of two orthogonal measurements using the contrast filled catheter as reference diameter. Coronary volume flow was estimated by the equation:

Flow (ml/min) = FCV (cm/sec) × 60 × π × (diameter / 2)²

A coronary vascular resistance index (mm Hg.min/ml) was calculated by dividing mean arterial blood pressure by coronary flow, assuming right atrium pressure was zero.

Statistical Analysis

For statistical analysis Student unpaired *t* test and linear regression analysis (SPSS 9.0) was used. All continuous variables are expressed as mean ± 1 standard deviation with their range. *P* value < 0.05 was considered statistically significant.

RESULTS

In 9 patients both LAD and LCx were normal, in 11 patients there were visually no significant (< 50%) stenosis in LAD and LCx, and in 13 patients either the proximal LAD (8) or proximal LCx (5) had significant stenosis for which angioplasty was thought appropriate. In 5 patients with intermediate (50-70%) lesions PCI was deferred because of CVR > 2.0 and rCVR > 0.65. In two patients the study protocol was terminated early; one because of advanced atrioventricular block during adenosine infusion, and one because of damping of the pressure signal of the guiding catheter during hyperemia. Final analysis consisted of 96 flow velocity reserve measurements performed in 38 patients.

Characteristics

Baseline and procedures characteristics are listed in table 1. In 4 patients the length of LAD (3) and/or LCx (3) was not measured mainly due to severe tortuositas. The majority of patients used β-blockers. The LAD was significant longer by a factor of 1.3 compared to the LCx (mean 14.3 ± 1.6 cm versus 11.4 ± 1.8 cm, *P*<0.001), while there were no differences in diameter of proximal segments (mean 3.2 ± 0.6 mm versus 3.3 ± 0.6 mm) and percentage stenosis of the target lesion. During hyperemia there was significant decrease in blood pressure (mean 100.7 ± 10.8 mm Hg to 93.4 ± 10.4 mm Hg, *P*<0.005) and significant increase in heart rate (mean 67.4 ± 9.0 /min to 76.3 ± 9.9 /min, *P*<0.005).

Table 1 Baseline and procedure characteristics

Variable		Total	Basal	Hyperemic
Patients, n		38	-	-
Age, y		57.9 ± 8.3 34.2 – 73.3	-	-
Sex, % male		68.4	-	-
Risk factors				
Hypertension, %		47.4	-	-
Diabetes mellitus, %		5.3	-	-
Dyslipidemia, %		65.8	-	-
Smoking, %		31.6	-	-
β-blocker use, %		71.1	-	-
LAD (n=35)	diameter, mm	3.2 ± 0.6 2.2 – 4.8	-	-
	length, cm	14.3 ± 1.6 9.5 – 18.0	-	-
	stenosis, %	70.9 ± 11.2	-	-
	(n=7)	59.0 – 90.7	-	-
LCx (n=35)	diameter, mm	3.3 ± 0.6* 2.3 – 4.1	-	-
	length, cm	11.4 ± 1.8† 7.2 – 15.6	-	-
	stenosis, %	68.2 ± 19.3*	-	-
	(n=5)	41.4 – 88.6	-	-
Blood pressure, mm Hg		-	100.7 ± 10.8 76 – 125	93.4 ± 10.4‡ 71 – 115
Heart rate, /min		-	67.4 ± 9.0 42 – 87	76.3 ± 9.9‡ 60 – 101
QRS – first frame, sec		-	0.38 ± 0.09 0.16 – 0.6	0.36 ± 0.08* 0.08 – 0.52

LAD indicates left anterior descending and LCx, left circumflex artery
* *P* = not significant for LCx versus LAD and hyperemic versus basal
† *P* < 0.001 for LCx versus LAD
‡ *P* < 0.005 for hyperemic versus basal

The mean time interval between last QRS complex and first frame included in the TFC was 370 ± 9 msec. The mean difference between basal and hyperemic injection in relation to the cardiac cycle was 0.07 ± 0.06 seconds.

Measurements

The results of 48 paired (both LAD and LCx) measurements are displayed in table 2, consisting of 38 patients with repeated protocol after PCI in 10 cases. The values of FCV, volume flow and resistance index were derived from 44 paired measurements. In 3

Table 2 Baseline and procedure characteristics

Artery	Variable	Basal	Hyperemic	Flow velocity reserve	
LAD (n=48)	TFC	32.5 ± 15.1 10 – 78	12.1 ± 6.6 5 – 45	**FCR:**	**2.9 ± 1.3*** 1.0 – 7.6
	FCV, cm/sec	13.1 ± 5.1 4.5 – 26.7	35.2 ± 11.5 11.3 – 63.5		
	APV, cm/sec	23.3 ± 9.4 5.7 – 41	61.9 ± 24.7 18 – 121	CVR:	2.8 ± 1.0* 1.0 – 5.3
	Flow, ml/min	62.2 ± 33.4 20.1 – 169.3	177.8 ± 94.9 47.4 – 395.1		
	Resistance index, mm Hg.min/ml	2.1 ± 1.1 0.6 – 5.4	0.7 ± 0.4 0.2 – 2.0		
LCx (n=48)	TFC	23.6 ± 9.1‡ 9 – 60	8.7 ± 3.2‡ 4 – 18	**FCR:**	**2.8 ± 1.0*** 1.2 – 5.4
	FCV, cm/sec	12.9 ± 4.1† 6.2 – 23.8	35.3 ± 10.7† 16.5 – 61.9		
	APV, cm/sec	19.3 ± 7.2† 8.3 – 35	51.8 ± 20.1† 26 – 102	**CVR:**	**2.8 ± 0.8*** 1.4 – 4.7
	Flow, ml/min	67.3 ± 32.0† 22.6 – 161.5	187.2 ± 97.0† 45.3 – 478.2		
	Resistance index, mm Hg.min/ml	1.9 ± 0.9† 0.5 – 4.4	0.7 ± 0.4† 0.2 – 2.1		
LAD + LCx (n=96)	FCV, cm/sec	13.0 ± 4.6 4.5 – 26.7	35.2 ± 11.2 11.3 – 63.5	**FCR:**	**2.9 ± 1.2*** 1.0 – 7.6
	APV, cm/sec	20.9 ± 8.7 5.7 – 41	55.6 ± 23.2 18 – 121	**CVR:**	**2.8 ± 0.9*** 1.0 – 5.3
				rFCR:	**1.07 ± 0.51*** 0.37 – 2.90
				rCVR:	**1.07 ± 0.48*** 0.46 – 2.53

LAD indicates left anterior descending; LCx, left circumflex artery; TFC, TIMI frame count; FCV, frame count velocity; APV, average peak velocity; (r)FCR, (relative) frame count reserve and (r)CVR, (relative) coronary flow velocity reserve
* *P* = not significant for (r)FCR versus (r)CVR and LCx versus LAD
† *P* = not significant for LCx versus LAD
‡ *P* < 0.02 for LCx versus LAD

vessels CVR was not measured because the Doppler wire was not repositioned in the non target vessel after PCI. TFC of LAD was significant higher than TFC of LCx (basal 32.5 ± 15.1 versus 23.6 ± 9.1 and hyperemic 12.1 ± 6.6 versus 8.7 ± 3.2, both *P*<0.02), but there were no significant differences in mean basal and hyperemic flow velocity, flow velocity

Table 3 Procedural results, no stenosis > 50%

Artery	Variable	Basal	Hyperemic	Flow velocity reserve
LAD (n=30)	TFC	35.1 ± 17.0 13 – 78	10.3 ± 3.6 5 – 21	**FCR:** **3.4 ± 1.3*** 1.9 – 7.6
	FCV, cm/sec	12.5 ± 5.3 4.5 – 26.7	38.3 ± 10.8 16.9 – 63.5	
	APV, cm/sec	22.3 ± 9.5 5.7 – 38	65.7 ± 22.8 21 – 121	**CVR:** **3.2 ± 0.9*** 1.9 – 5.3
	Flow, ml/min	65.7 ± 35.2 20.1 – 169.3	209.1 ± 95.4 70.4 – 395.1	
	Resistance index, mm Hg.min/ml	2.0 ± 1.1 0.6 – 5.4	0.6 ± 0.4 0.2 – 1.5	
LCx (n=30)	TFC	25.1 ± 9.5‡ 12– 60	8.3 ± 2.7‡ 4 – 14	**FCR:** **3.2 ± 1.0*** 1.5 – 5.4
	FCV, cm/sec	12.7 ± 3.6† 6.2 – 22.1	37.6 ± 10.3† 22.3 – 61.9	
	APV, cm/sec	19.1± 7.4† 8.3 – 35	54.1 ± 21.2† 27 – 102	**CVR:** **2.9 ± 0.7*** 1.9 – 4.7
	Flow, ml/min	71.8 ± 34.4† 27.2 – 161.5	214.3 ± 102.8† 63.2 – 478.2	
	Resistance index, mm Hg.min/ml	1.8 ± 0.9† 0.5 – 3.6	0.6 ± 0.3† 0.2 – 1.6	
LAD + LCx (n=60)	FCV, cm/sec	12.6 ± 4.5 4.6 – 26.7	38.0 ± 10.5 16.9 – 63.5	**FCR:** **3.3 ± 1.1*** 1.5 – 7.6
	APV, cm/sec	20.7 ± 8.6 5.7 – 38	59.9 ± 22.6 21 – 121	**CVR:** **3.1 ± 0.8*** 1.9 – 5.3
				rFCR: **1.12 ± 0.29*** 0.62 – 1.65
				rCVR: **1.11 ± 0.26*** 0.73 – 1.62

LAD indicates left anterior descending; LCx, left circumflex artery; TFC, TIMI frame count; FCV, frame count velocity; APV, average peak velocity; (r)FCR, (relative) frame count reserve and (r)CVR, (relative) coronary flow velocity reserve

* *P* = not significant for (r)FCR versus (r)CVR and LCx versus LAD

† *P* = not significant for LCx versus LAD

‡ *P* < 0.02 for LCx versus LAD

reserve, volume flow and resistance index between both vessels. Mean FCR and rFCR did not differ significantly from mean CVR and rCVR.

The results of 30 paired (both LAD and LCx) measurements concerning only coronary arteries without visually significant (<50%) stenosis are listed in table 3, consisting of 20 patients without significant stenosis at baseline and 10 paired measurements after PCI. Again, TFC of LAD was significant higher than TFC of LCx (basal 35.1 ± 17.0 versus 25.1 ± 9.5 and hyperemic 10.3 ± 3.6 versus 8.3 ± 2.7, both *P*<0.02), without significant differences in mean basal and hyperemic flow velocity, flow velocity reserve, volume flow and resistance index between the two vessels. As in the total group, mean FCR and rFCR did not differ significantly from mean CVR and rCVR.

Figure 1 shows the relation between FCR and CVR for all measurements (r=0.62, *P*<0.001), figure 2 the relation between rFCR and rCVR (r=0.84, *P*<0.001). The relation between FCV and APV for basal and hyperemic measurements combined is shown in figure 3 (r=0.75, *P*<0.001).

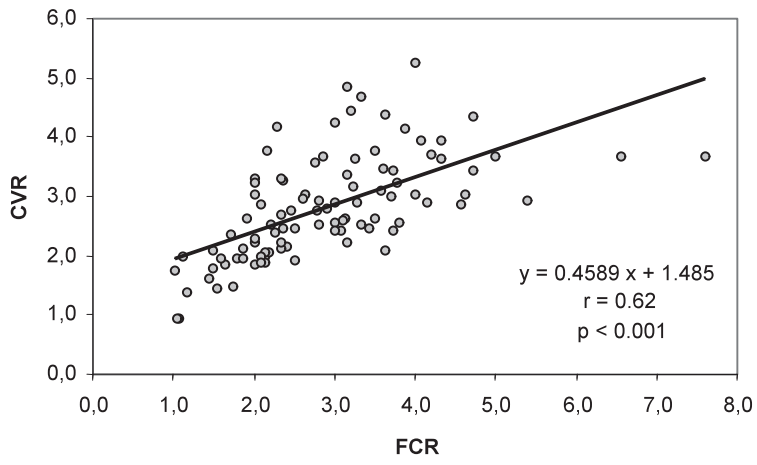

Figure 1 Relation between frame count reserve (FCR) and coronary flow velocity reserve (CVR), n=96 measurements.

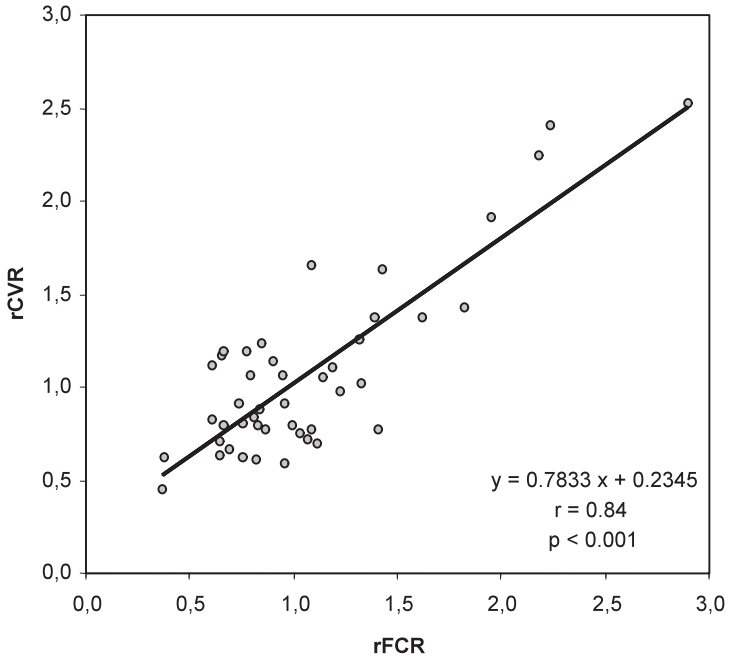

Figure 2 Relation between relative frame count reserve (rFCR) and relative coronary flow velocity reserve (rCVR), n=45 measurements.

DISCUSSION

In this study, the Frame Count Reserve, an angiographic method using TIMI frame count to estimate coronary blood flow velocity reserve, was compared to Doppler wire derived CVR. The results demonstrate strong correlation between (relative) FCR and (relative) CVR. There were no significant differences between mean (r)FCR and mean (r) CVR.

In contrast to normal basal flow velocity, when the coronary artery is usually filled with contrast in more than one complete cycle of the heart (including systole with relative low flow velocity), high coronary flow velocity during hyperemia can cause contrast filling within one diastole (with relative high flow velocity). This will result in an augmented FCR compared to CVR in which peak flow velocity is averaged during diastole as well as systole. This can explain the fact that the correlation of FCR and CVR is not so good in the range of high (>3.0) flow velocity reserve compared to low (<3.0) flow

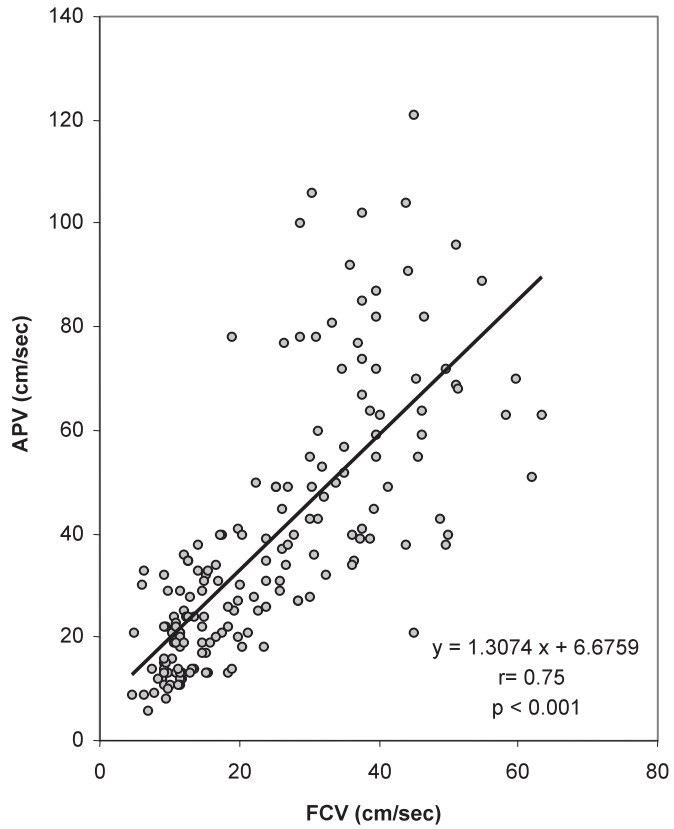

Figure 3 Relation between frame count velocity (FCV) and average peak velocity (APV), n=174 measurements.

velocity reserve, as shown in figure 1. Low heart rate with relative more influence from diastole can contribute to this effect, but in this study population heart rate during hyperemia was higher compared to basal. In addition, the influence of the moment of contrast injection in relation to the cardiac cycle is more important in case of low TFC (high flow velocity and/or relative short vessels) compared to high TFC. Because CVR of 2.0 is used as cut-off value, the less strong correlation of values >3.0 has little clinical implications.

The correlation of rFCR and rCVR is stronger, also in high values as is shown in figure 2, because differences in methods of flow velocity assessment are partially normalized, just like influence of microvascular resistance.

Comparison to previous studies

The findings are in accordance to the study of Manginas et al, the only other study comparing the TIMI frame count method to CVR(13). In this study contrast agent was also injected manually, but adenosine was given intracoronary. However, because of the short half live time of adenosine it is difficult to inject the agent consistently in the maximal hyperemic phase. With intravenous adenosine a steady state of hyperemia can be obtained, making it possible to inject contrast during maximal hyperemia and easier to synchronize injection to the cardiac cycle, resulting in a more accurate hyperemic TFC. As pointed out by Abaci et al, the phase of the cardiac cycle in which the contrast agent is injected has important influence on TFC.[16] In the present study there were only small differences in the timing of contrast injections, beginning at or near the end of the T wave, just before diastole.

The FCR using intracoronary adenosine was measured in a trial evaluating eptifibatide, and it highly correlated with digital subtraction angiographic reserve (r = 0.76, p<0.001).[17] All TFC (but not the ratios) found in the present, European study can only be compared to US studies after been multiplied by a factor of 1.2 to convert to a frame rate of 30/second. To the best of our knowledge this is the first study to measure relative FCR and compare it to relative CVR.

Flow velocity measurements

A comparison between FCV and APV is complex. With the Doppler wire peak blood flow velocity is measured locally, averaged during two cycles of the heart. It has to be converted to a mean velocity, compensating for lower blood flow velocity near the vessel wall. This can be done by multiplying APV by a factor of 0.5,[18] or by using the velocity integral.[19] Because in normal coronary arteries there are no significant differences in proximal and distal flow velocity, further correction should not be necessary.[20] However, segments in which Doppler measurements are performed are not always completely normal because angiography is often not sensitive enough to show diffuse lumen narrowing causing flow velocity acceleration, or a positive remodeled vessel segment with possible influence on flow velocity assessment.[21] In addition, in stenosed arteries, flow velocity can be higher proximal to the lesion compared to distal because of proximal side-branches. This will influence FCV, but not distal APV. Finally, length of the coronary artery measured with the guidewire and thus FCV can be underestimated because the wire takes the shortest way along the curves of the vessel. As discussed above, FCV can be overestimated when flow velocity is so high that contrast filling of the coronary artery takes place only in diastole. Figure 3 shows the good correlation between FCV and APV (r=0.75, *P*<0.001). In this population the ratio of mean APV and FCV was 0.63.

Comparison between LAD and LCx

Basal and hyperemic TFC of LAD were significantly higher compared to LCx (basal 32.5 ± 15.1 versus 23.6 ± 9.1 and hyperemic 12.1 ± 6.6 versus 8.7 ± 3.2, both *P*<0.02). The ratio of TFC of LAD and LCx is 1.4 while the ratio of length of both vessels is 1.3. This is less than the factor of 1.7 used to adjust TFC of LAD to derive the "corrected" TFC because the latter was corrected to mean TFC of both LCx and right coronary artery.[15] In the present study, after adjusting TFC to the specific length of the artery, all basal and hyperemic mean blood flow velocity measurements were equal in both vessels. In addition, there were no significant differences in FCR and CVR of LAD compared to LCX. Because the proximal vessel diameter of both vessels was the same, there were also no differences in mean volume flow and resistance index.

Measurements in non significant diseased vessels

Table 3 shows the results of measurements in coronary arteries with visually no stenosis >50%. Mean "normal" basal FCV of left coronary artery (LCA) is 12.6 ± 4.5 cm/sec and hyperemic 38.0 ± 10.5 cm/sec, without differences between LAD and LCx. With this method estimated volume flow of the LCA is basal 137.5 ± 69.6 ml/min and 423.4 ± 198.2 ml/min during hyperemia. However, above mentioned considerations concerning FCV also apply here. In addition, these results can not be interpreted as completely normal values, because part of these patients had possible microvascular dysfunction (hypertension, dyslipidemia), causing lower hyperemic flow velocity with lower flow velocity reserve. Moreover, in 10 patients measurements were also performed after PCI. Mean basal FCV post angioplasty was borderline significantly higher compared to the total group (15.8 ± 5.2 cm/sec versus 12.6 ± 4.5 cm/sec, *P* = 0.032), causing a (not significant) lower FCR (2.7 ± 1.1 versus 3.3 ± 1.1). This is in accordance with previous studies in which high basal flow velocity after angioplasty and stenting sometimes persisted for more than 10 minutes after the procedure because of persistent low microvascular resistance.[22,23] Finally, a visual stenosis of less than 50% can sometimes unexpectedly prove to be functional significant, and not significant but diffuse epicardial stenosis can cause so much resistance that it impairs flow velocity reserve.

Limitations

All procedures were done by a single operator using manual contrast agent injections. Because timing of injection in relation to the phase of the heart cycle is important,[16] it was synchronized to an acoustic heart beat signal. To do this, a basic sense of rhythm is needed. An alternative is the use of an ECG-triggered mechanical injector, but that was not done in this study because diagnostic coronary angiography is usually performed with manual injections. In addition it has been shown that the impact of the injection rate on the TFC is only minor.[24]

During adenosine infusion there was a limited, but significant drop in blood pressure with an increase in heart rate as has been described by others.[25] Therefore, hyperemic APV and FCV and thus flow velocity reserve were possibly underestimated. All measurements were done in LAD and LCx. It is likely but not certain that these results are applicable to the right coronary artery.

The study population consisted of patients who were asymptomatic or had stable angina. Therefore, results may not be applicable to patients with acute coronary syndromes, for example because flow in 'normal' reference vessels can be impaired.[26,27]

Conclusion

This study shows that the FCR and rFCR can provide a good estimate of CVR and rCVR. This relative simple, fast and inexpensive angiographic method can be used during diagnostic catheterization to assess functional significance of a coronary stenosis and, in absence of coronary stenosis to evaluate microvascular function.

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Chapter 6

High Dose Adenosine for Suboptimal Myocardial Reperfusion After Primary PCI

A randomized placebo-controlled pilot study

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ABSTRACT

Objectives

This study was designed to investigate the influence of high dose intracoronary adenosine on persistent ST-segment elevation after primary percutaneous coronary intervention (PCI).

Background

After successful PCI for acute myocardial infarction 40-50% of patients show persistent ST-segment elevation indicating suboptimal myocardial reperfusion. Adenosine has been studied to ameliorate reperfusion and is frequently used in a variety of doses, but there are no prospective studies to support its use for treatment of suboptimal reperfusion.

Methods

We conducted a blinded, randomized and placebo-controlled study with high dose intracoronary adenosine in 51 patients with <70% ST-segment resolution (STRes) after successful primary PCI. All patients were treated with stents and abciximab.

Results

Immediately after adenosine significantly more patients showed optimal (>70%) STRes compared to placebo (33% versus 9%, *P*<0.05). Mean STRes was higher after adenosine (35.4% versus 23.0%, *P*<0.05). In addition, TIMI frame count was significant lower (15.7 versus 30.2, *P*<0.005), Myocardial Blush Grade was higher (2.7 versus 2.0, *P*<0.05) and resistance index was lower in the adenosine group (0.70 versus 1.31 mm Hg per ml/min, *P*<0.005).

Conclusions

Intracoronary adenosine accelerates recovery of microvascular perfusion in case of persistent ST segment elevation after primary PCI.

INTRODUCTION

In patients with acute myocardial infarction, the most effective way to open the occluded coronary artery is by percutaneous coronary intervention (PCI). However, successfully opening an epicardial vessel does not always fully restore tissue reperfusion because of suboptimal microvascular reflow.[1] This is related to several potential mechanisms, including embolisation of plaque material and thrombus, microvascular spasm, oedema and leukocyte and thrombocyte adhesion.[2,3] Myocardial reperfusion can be assessed by contrast echocardiography[4], magnetic resonance imaging[5,6] and angiography (myocardial blush grade, MBG).[7] In addition, electrocardiography (ST-segment elevation resolution, STRes) is a simple method to quantify the effect of reperfusion therapy and can be used as surrogate endpoint in reperfusion strategies.[8-10]

A number of pharmacological interventions have shown to be effective in the prevention and/or treatment of the so-called no reflow phenomenon and are associated with better reperfusion, in particular abciximab,[11,12] verapamil,[13,14] nicorandil[15-17] and adenosine[18-26]. However, occurrence of no reflow is not easy to predict[27-30] and the majority of primary PCI's results in acceptable microvascular reflow. Therefore most operators are reluctant to take preventive actions.

Adenosine delivered intracoronary can be used in case of no reflow to ameliorate reperfusion based on several reports.[31-33] However, these findings have not been confirmed by randomized studies, in particular in the setting of acute myocardial infarction. In addition, there is a high variability in the dosages used since the optimal dose is unknown. In our experience, intracoronary infusion of adenosine in a dose that is normally used intravenous to get maximal microvascular dilatation for physiological measurements is needed for optimal results. Therefore we conducted this blinded, randomized and placebo-controlled pilot study with high dose intracoronary adenosine in patients with suboptimal reperfusion after primary PCI to assess the effect on ST segment resolution.

METHODS

Patients and PCI procedure

Following successful (defined as TIMI flow grade 2 or 3 without residual dissections or stenosis >30% and no angiographic evidence of embolisation) PCI for acute myocardial infarction, patients with suboptimal reperfusion (<70% STRes with persistent ST-elevation >2 mV in at least one anterior lead and >1 mV in a non-anterior lead) more than 10 minutes after last balloon inflation could be included. Excluded were patients

with hemodynamic instability, prior myocardial infarction or an ECG unsuitable for calculation of STRes (left bundle branch block, paced or severe disturbed rhythm). In addition patients with a history of obstructive pulmonary disease were excluded because of potential side effects of adenosine. All patients received one or more stents, acetylsalicylic acid (450 mg IV), heparin (5000 IU IV), nitroglycerine (0.2 to 0.4 mg intracoronary), abciximab (weight adjusted) and clopidogrel (300 mg loading dose). At the beginning of the procedure all patients had an occluded target vessel (TIMI 0 or 1) and reperfusion moment was defined as the beginning of persistent TIMI 2 or 3 flow. Total occlusion time was the time from the beginning of chest pain to reperfusion moment.

Patients were followed for cardiac events (heart failure, myocardial infarction, re-interventions and death) during the initial hospital stay and at 12 months (telephone interview).

The study was conducted in the hospital of the Free University Amsterdam, the Netherlands. The Medical Ethics Committee approved the protocol. While oral informed consent was given during the primary angioplasty procedure, all patients gave written informed consent after the procedure.

Protocol and Calculations

With continuous 10 lead ECG registration (ST-Guard®, Medtronic) from the beginning of the procedure until approximate 90 minutes after reperfusion on the coronary care unit, ST-segment elevation (60 ms after j-point) was measured on line. STRes (100% minus {ST-elevation $_{\text{after study medication}}$ / ST-elevation $_{\text{before study medication}}$} ×100%) was calculated for the single lead with maximal elevation and for all leads with elevations ($STRes^{\Sigma}$). ST-segment depression in V_1-V_4 was used in case of posterior infarction.

Patients with suboptimal reperfusion were randomized to 60 mg of adenosine (6 mg/ml) or 10 ml NaCl 0.9% infused in 5 to 10 minutes using an intracoronary catheter placed in the target lesion. Patient and operators were blinded for the study medication. In case of inferior infarction first a prophylactic temporary pacemaker was placed in the right ventricle.

Before and at least 2 minutes after infusion of the study medication the blood pressure and heart rate were recorded and coronary angiography (25 frames/s) was performed to assess TIMI frame count {TFC} as described by Gibson[7] and MBG as described by van 't Hof.[34] Quantitative coronary angiography of the proximal segment of the target vessel was performed using the contrast-filled catheter as reference diameter. Coronary flow velocity was calculated by multiplying 25/TFC with the mean length of the target vessel. These lengths were derived from 3 groups of 62 elective angioplasty patients using a guidewire for measurements, a similar method as described

by Gibson (35). The mean length ± SD and range of the left anterior descending was 14.3±1.5 (9.5-18.0) cm, 12.1±1.9 (7.2-16.7) cm for the left circumflex and 11.3±1.3 (8.6-15.5) cm for the right coronary artery, *P*<0.0001for comparison between all vessels. Coronary blood flow was estimated by the following equation: flow (ml/min) = flow velocity (cm/s) × 60 × π × (diameter/2)^2. A coronary vascular resistance index (mm Hg per ml/min) was calculated by dividing mean arterial blood pressure by coronary flow.

Statistical Analysis

For statistical analysis, X^2 and t-test for equality of means analysis (SPSS 9.0) were used. All continuous variables are expressed as mean ± 1 SD with their range. P<0.05 was considered statistically significant. Analysis was performed on basis of intention to treat.

RESULTS

In this study 51 patients were included. Two patients in the placebo group were excluded because of missing ECG data. Randomization resulted in 27 patients receiving high dose adenosine intracoronary and 22 receiving placebo. After randomization 2 patients in the placebo group already had >70% STRes before the study medication was given as is shown in figure 1. One patient in the placebo group with persistent ST-elevation after study medication was treated unblinded with high dose adenosine.

Baseline characteristics are shown in table 1; there were no significant differences between both groups. As shown in figure 1, there were significantly more patients with >70% STRes after adenosine compared to placebo (33% versus 9%, *P*<0.05). In the placebo group no patients with < 70% STRes had >70% STRes after study medication. There were no differences anymore at approximate 90 minutes after reperfusion. (41% of patients had >70% STRes in both groups). Mean STRes was significantly better after adenosine compared to placebo: 35.4% versus 23.0%, *P*<0.05 (figure 2). Table 2 shows the procedure characteristics. After PCI and randomization, patients in the adenosine group had significant less STRes. After infusion of adenosine compared to placebo TFC was lower (15.7 versus 30.2 frames, *P*<0.005), MBG higher (2.7 versus 2.0, *P*<0.005) and resistance index lower (0.70 versus 1.31 mm Hg per ml/min, *P*<0.005). After transfer to the coronary care unit, nearly 90 minutes after reperfusion, a further significant amelioration of STRes had occurred in both groups *(P*<0.05) resulting in similar mean STRes.

There were no differences for STRes measured single lead compared to all leads with ST segment elevation. The maximal CK-Mb was somewhat lower after adenosine

Table 1 Baseline characteristics

Variable	Adenosine	Placebo
Patients, n	27	22
Age, y	67.3 ± 15.6 32 – 88	66.3 ± 11.7 45 – 83
Sex, % male	63.0	70.4
Risk factors		
Hypertension, %	40.7	40.9
Diabetes mellitus, %	3.7	18.2
Dyslipidemia, %	22.2	22.7
Smoking, %	25.9	45.5
Family history of CAD, %	33.3	22.7
ST-elevation, mV		
Single lead	6.7 ± 2.3 1.2 – 12.2	6.7 ± 3.5 1.5 – 15.0
Sum	20.8 ± 8.4 1.2 – 39.4	21.7 ± 9.9 6.5 – 43.2
Culprit artery, %		
LAD	55.6	45.5
RCA	40.7	36.4
LCx	3.7	18.2
Reference diameter QCA, mm	3.8 ± 0.5 3.1 – 4.8	3.8 ± 0.4 3.1 – 4.9
Total occlusion time, min	196 ± 78 84 – 413	249 ± 137 85 – 590

P=not significant for all variables
CAD = coronary artery disease, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery

(268 versus 362 u/l, *P*=0.08). In one patient surgery was required for perforation of the right ventricle caused by the temporary pacemaker lead.

Follow up at 12 months showed no significant differences between both groups. NYHA class was mean 1.4 in the adenosine versus 1.3 in the placebo group, heart failure occurred in 3 respectively 4 patients and there were 2 non-cardiac deaths in the adenosine group and one cardiac death in the placebo group. One patient in the adenosine group suffered subacute stent thrombosis two days after primary PCI and one was lost for follow up.

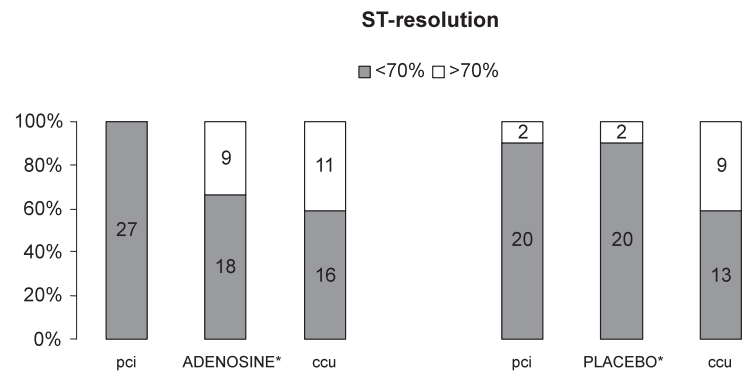

Figure 1 ST segment resolution ■ < 70% and □ > 70%, after PCI, after adenosine or placebo and on the CCU. Numbers in bars are number of patients
*P<0.05 for adenosine versus placebo.

DISCUSSION

This pilot study shows that high dose intracoronary adenosine accelerates recovery of microvascular perfusion in patients with persistent ST-segment elevation after primary PCI. As illustrated in figure 1, significantly more patients had optimal STRes (>70%) immediately after adenosine administration compared to placebo (33% versus 9%, *P*<0.05). However, in the placebo group delayed but significant regression of ST-elevation also occurred. This resulted in equal STRes at 90 minutes after reperfusion. The acceleration of ST segment resolution in the adenosine group compared to placebo is also reflected in mean STRes after study medication, 35.4% versus 23.0%, *P*<0.05 (figure 2).

TFC and MBG were assessed at least 2 minutes after infusion of the study medication assuming potential vasodilating action not to be present anymore. Still, TFC was significant lower (15.7 versus 30.2, P<0.005) and MBG significant higher (2.7 versus 2.0, P<0.005) in the adenosine group. After correction for blood pressure, diameter and length of the vessel, the resistance index was significant lower in the adenosine group (0.70 versus 1.31 mm Hg per ml/min, P<0.005). These angiographic parameters confirm the improved myocardial reperfusion after administration of adenosine. In addition, the lower maximal CK-MB release suggest smaller infarct size with the use of adenosine (268 versus 362 u/l, P=0.08).

Study End Point

The clinical value of ST-segment resolution has been demonstrated,[10] but still it is a surrogate end point for studies concerning reperfusion therapy. Therefore it is uncertain

Table 2 Procedure characteristics

Variable	Adenosine	Placebo
after PCI		
Mean Blood pressure, mm Hg	92.8	94.0
Heart rate, per min	79.1	78.1
TIMI flow grade	2.6	2.6
TIMI frame count	27.3	29.1
MB grade	1.9	1.9
Resistance index, mm Hg per ml/min	1.22 ± 0.91 0.32 – 4.77	1.25 ± 0.75 0.26 – 3.32
ST-elevation, mV		
Single lead	5.1 ± 2.9 1.1 – 11.9	4.1 ± 3.0 1.1 – 13.7
STRes, %	21.1 ± 43.7 * -122.9 – 61.5	38.5 ± 19.9 5.7 – 81.6
Sum	15.4 ± 9.3 1.1 – 40.1	13.3 ± 8.3 2.4 – 33.4
STRes$^{\Sigma}$, %	23.0 ± 39.1 * -99.1 – 62.1	39.4 ± 22.9 -4.6 – 88.0
after study medication		
Time after PCI, min	14 ± 4	11 ± 4
Mean Blood pressure, mm Hg	93.4	96.0
Heart rate, per min	83.2	78.8
TIMI flow grade	2.9	2.7
TIMI frame count	15.7 *	30.2
MB grade	2.7 *	2.0
Resistance index, mm Hg per ml/min	0.70 ± 0.32 * 0.29 – 1.77	1.31 ± 0.87 0.34 – 3.27
ST-elevation single lead, mV	3.4 ± 2.4 0.7 – 9.6	3.2 ± 2.5 0.6 – 12,2
STRes, %	35.4 ± 21.2 * -1.1 – 71.7	23.0 ± 17.5 -32.0 – 45.8
Coronary care unit		
Time after study medication, min	66 ± 34	62 ± 15
Time after reperfusion, min	86 ± 34	85 ± 16
ST-elevation single lead, mV	2.5 ± 1.9 0.3 – 8.5	2.2± 2.0 0.2 – 8.5
Stres, %	51.1 ± 26.8 4.9 – 107.9	52.2 ± 23.6 8.3 – 94.5

**P*<0.05 versus placebo

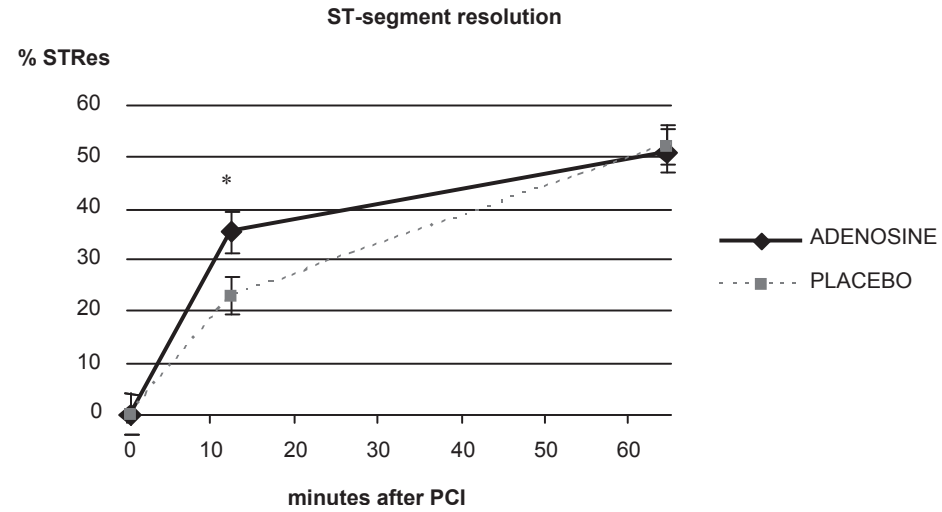

Figure 2 Mean (with standard error) ST segment resolution after adenosine or placebo and on the CCU.
*P<0.05 for adenosine versus placebo immediately after study medication at approximate t=12 minutes.

if the observed acceleration of ST-segment resolution in the present study is of any benefit for patients. However, the aim of primary PCI is to achieve optimal reperfusion as soon as possible. In addition, it has been demonstrated that pharmacological reversal of angiographic no reflow, which is often accompanied by persistent ST-elevation, is associated with lower 30-day mortality.[36] The present pilot trial is too small and was not designed to draw conclusions concerning left ventricular function and clinical course.

Adenosine

How adenosine works is uncertain. It is possible that the strong vasodilating activity of adenosine plays a role, particularly when microvascular spasm occurs. Furthermore it has anti-platelet as well as anti-inflammatory effects, inhibiting adhesion of neutrophils and release of cytokines from mononuclear cells, release of oxygen radicals and limiting cardiomyocyte apoptosis.[37,38] In addition, adenosine can possibly mimic postconditioning.[39]

Safety

There were no serious adverse events during infusion of the study medication. Some patients complained of temporary increase of chest pain, but progressive resolution of ST-elevation was accompanied by less pain. Of course all patients suffered acute

myocardial infarction and most of them had been given strong analgesics. Adenosine is a safe drug to use and has a very short half-life time (less then 10 s). In most patients administration of high dose of adenosine in the right coronary artery causes temporarily loss of atrioventricular conduction. Therefore a pacemaker lead in the right ventricle was used. Right ventricular perforation and tamponade, as happened in one patient can complicate this. Using an intracoronary guidewire for pacing could avoid this risk.

Comparison With Previous Studies

To our knowledge this is the first randomized and placebo controlled study of high dose intracoronary adenosine given to patients with persistent ST segment elevation (STRes <70%) after successful PCI with stenting for acute myocardial infarction.

Several studies investigated the benefits of preventive use of adenosine during and after reperfusion therapy for acute myocardial infarction. Claeys et al showed that compared to a historical cohort group,[21] adenosine 60-90 µg/min intracoronary for 20 min during primary PCI in 79 patients, resulted in better STRes and less infarct expansion. However, in 84% of patients in the adenosine group a glycoprotein 2b3a inhibitor was used versus only 45% in the control group (P<0.0001). In addition, 26% of patients in the control group did not receive a stent versus 4 % in the adenosine group (P<0.0001). In the randomized and placebo controlled AMISTAD trials,[22,23] IV adenosine 70 µg/kg per min for 3 hours during and after reperfusion therapy was found to reduce anterior infarct size. Because the majority of the 2354 patients (100% in AMISTAD 1 and 60% in AMISTAD 2) were treated with thrombolysis, the state of epicardial reperfusion was mostly unknown and this may have influenced the results. This limitation also applies to the placebo controlled ATTACC study,[25] in which 608 patients treated with thrombolysis were randomized to IV adenosine 10µg/kg per minute for 6 hours. This very low dose adenosine did not resulted in better left ventricular function, the primary end point. Marzilli et al found in 54 patients better angiographic flow, ventricular function and clinical course after 4 mg of adenosine in 1 minute intracoronary distal to the occlusion, just before mechanical reperfusion compared to placebo.[18] However, only in 15% and 19% (P=NS) of patients stents were used. Re-occlusion and restenosis, possibly subclinical, could have been of influence. In a study of Petronio et al 90 patients were randomized to abciximab, adenosine 4 mg intracoronary and a control group.[24] All patients underwent PCI with stenting. Adenosine improved angiographic measurements but not left ventricular remodelling, the primary endpoint, as did abciximab. In a retrospective study of Assali et al 51 patients with myocardial infarction received 24-48 µg adenosine before and after each balloon inflation.[19] Angiographic assessed no-reflow was seen in 5.9% of the adenosine group versus 28.6% in a control group. However, the incidence of no reflow in the control group is high and the decision to give adenosine

was at the discretion of the operator on unknown grounds, so definitive conclusions could not be drawn.

Compared to these reports, the adenosine dose used in the present study is much higher: 60 mg in 5 to 10 minutes intracoronary, which means for a patient of 75 kg 80 to 160µg/kg per minute. The AMISTAD 2 study showed that the beneficial effect of 70 µg/kg per minute intravenous adenosine was not found with a lower dose of 50 µg/kg per minute.[23] For physiological measurements like the fractional flow reserve, generally not used in patients with acute myocardial infarction, the intravenous dose of adenosine is 140 µg/kg per minute.

Limitations

Besides limitations concerning sample size and primary end point previously discussed, this study was done in a selected group of patients with strict ECG and procedural criteria. They were all patients with persistent ST-segment elevation despite successful PCI, with normal QRS complex and without hemodynamic instability. In addition patients with angiographic evidence of distal embolisation were excluded. This may also explain the relative low incidence of adverse events in both groups.

Estimation of infarct size is less accurate using maximal enzyme release compared to measuring the area under the enzyme release curve. In addition, with adenosine it is possible that kinetics of enzyme release changes, making it more difficult to find the nadir of the curve. Maximal enzyme release is also dependent on the size of the risk area, not assessed in this study.

Although not statistically different, the patients in the adenosine group had a shorter total occlusion time compared to the placebo group (196 versus 249 minutes, P=ns) and were less likely to have diabetes mellitus. In addition, although patients were randomized, STRes after PCI but before study medication was less in the adenosine group compared to placebo (21.1% versus 38.5%, P<0.05). This could have been of influence on the results of the present study.

Conclusion

In patients with suboptimal microvascular reperfusion after primary PCI, high dose intracoronary adenosine accelerates ST-segment resolution and ameliorates angiographic parameters of coronary reflow, indicating improved myocardial reperfusion. The results of this pilot study have to be confirmed by larger studies with assessment of infarct size or salvage index, left ventricular function and clinical end points.

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Chapter 7

Early Versus Late ST-Segment Resolution and Clinical Outcomes After Percutaneous Coronary Intervention for Acute Myocardial Infarction

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ABSTRACT

Background

Absence of complete ST-segment resolution (STR) after percutaneous coronary intervention (PCI) for ST-segment-elevation myocardial infarction (STEMI) is a determinant of mortality. Traditionally, STR is determined on the coronary care unit (CCU) 60 to 90 minutes after the initiation of reperfusion therapy. We studied the prognostic value of STR immediately after PCI.

Methods

We analysed 223 consecutive patients with STEMI and successful PCI. Continuous ECG data were collected during PCI and at 30 minutes after arrival on the CCU (mean time 81±17 minutes after reflow of the culprit artery). Patients were divided into three groups: patients with complete STR immediately after PCI ('early'), patients with complete and persistent STR at 30 minutes on the CCU, but not immediately after PCI ('late') and patients without STR. One-year follow-up was obtained for death and rehospitalisation for major adverse cardiac events. Cox proportional hazards regression was used to evaluate the association between STR and outcome.

Results

Early STR occurred in 115 (52%) and late STR in 43 (19%) patients. Patients with early or late STR had a lower incidence of one-year cardiac death than those without STR (1.9 vs. 9.2%; p=0.02). In contrast, rehospitalization occurred more frequently in patients with early or late STR (20.3 vs. 6.2%; p=0.009). As compared with patients without STR, early and late STR had a similar prognostic value (hazard ratios [95% confidence interval] for cardiac death 0.40 [0.08-2.03] and 0.25 [0.03-2.08]).

Conclusions

We found no (major) change in prognostic value of STR during the 0 to 90 minutes time window after PCI.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) restores epicardial coronary flow in the vast majority of patients with acute ST-segment elevation myocardial infarction (STEMI). However, despite successful primary PCI, a substantial number of patients show signs of suboptimal myocardial reperfusion, manifested by persistent ST-segment elevation and incomplete ST-segment elevation resolution (STR). Absent or incomplete STR after PCI is a strong predictor for impaired left ventricular function and adverse clinical outcomes.[1-8]

After fibrinolysis for STEMI, the electrocardiogram (ECG) for measuring STR is usually taken 60 to 90 minutes after onset of therapy.[9-11] After primary PCI, the first ECG that is suitable for evaluation of STR is usually done on the coronary care unit (CCU). In previous studies, the timing of the ECG after primary PCI for determination of STR is highly variable. It ranges from the time of arrival on the CCU, approximately 30 minutes after PCI, to another 30 minutes or even several hours later.[1-7] Earlier studies showed that STR at 30 minutes after PCI correlated better with other markers of myocardial perfusion than STR at 60 to 90 minutes.[12,13]

However, the optimal time to measure STR after primary PCI is unknown. In addition, in case of suboptimal myocardial reperfusion, therapeutic options have to be considered as soon as possible, preferably during the PCI procedure.

Therefore, in the present study we used continuous ten-lead ST monitoring,[14,15] and measured STR at the end of the PCI procedure (early STR) and compared it with STR measured at 30 minutes after arrival on the CCU (late STR). We evaluated the predictive value of early versus late STR for (cardiac) death and rehospitalization for major adverse cardiac events (MACE) at one year.

METHODS

Patients

The study population consisted of consecutive patients with STEMI (>1 mm ST-segment elevation in ≥2 limb leads or >2 mm ST-segment elevation in ≥2 precordial leads, in case of posterior myocardial infarction >2 mm ST-segment depression in ≥2 precordial leads) admitted for primary PCI at the department of cardiology of the VU University Medical Centre in Amsterdam, the Netherlands. Patients were included after successful PCI, defined as sustained patency of the occluded epicardial coronary artery with TIMI flow grade ≥2, within six hours after symptom onset. Patients were excluded in case of a history of myocardial infarction in the same vascular territory, if continuous ECG

registration failed or if the ECG could not be used to measure STR (left bundle branch block, pacemaker or ventricular rhythm). In addition, patients who already showed reperfusion at the start of the PCI procedure, defined as resolved symptoms with complete STR, were excluded.

All patients received acetylsalicylic acid (450 mg IV) and heparin (5000 IU IV) before the procedure. Administration of abciximab or intracoronary adenosine was left to the discretion of the operator. After the procedure all patients received clopidogrel 75 mg daily with a loading dose of 300 mg orally. In 216 (97%) of patients in the study population, one or more coronary stents were implanted.

ST-segment resolution

During and after the procedure, patients were monitored with a continuous ten-lead ECG registration (ST-Guard®, Medtronic, Santa Rosa). An ECG was derived and stored every minute. Automated ST-segment deviation (μV) was measured on line for each single lead at 60 ms after the J point. Percentage STR (100% minus (ST elevation after PCI/ST elevation before PCI) × 100%) was calculated for the single lead with maximal elevation. ST-segment depression in leads V1 to V4 was used in case of posterior infarction.[16]

STR was determined based on the ECG at the beginning and the end of the PCI procedure and at 30 minutes after arrival on the CCU (mean time 81±17 minutes after reflow of the culprit artery). Complete STR was defined as >70% STR or <70% without residual ST-segment elevation (<1 mm in non-anterior leads and <2 mm in anterior leads), while no STR was defined as <70% STR with residual ST-segment elevation.[6] Patients were divided into three groups according to the presence or absence of STR: complete and persistent STR immediately after PCI, ('early'), complete and persistent STR at 30 minutes on the CCU, but not immediately after PCI ('late') and no or incomplete STR at 90 min after PCI ('without').

Endpoint definition

One-year follow-up data were collected on (cardiac) death and rehospitalization for MACE, defined as nonfatal infarction, unstable angina or re-revascularisation. We contacted patients by telephone, the patient's general practitioner, as well as the referring physician to obtain information on these events. The primary endpoint was cardiac death, which was defined as death that could directly be related to loss of heart function. Secondary endpoints were all-cause death, and hospitalisation for MACE.

Statistical analyses

Statistical analysis was performed with SPSS 15.0 (SPSS, Inc, Chicago, Illinois). Categorical variables are summarised as numbers and percentages and continuous variables are presented as mean values ± one standard deviation (SD). Differences in baseline characteristics according to STR classification were studied by X^2 or Fisher's exact tests (categorical data) and analysis of variance (ANOVA) and Mann-Whitney tests (continuous data).

The incidence of study endpoints over time was studied according to the method of Kaplan-Meier, and differences in the incidence according to the STR classification were evaluated by log-rank tests. The association between STR and study endpoints was further analysed by Cox proportional hazard regression. We obtained crude, unadjusted hazard ratios (HR), and HRs that were adjusted for age and infarct localisation. HRs are reported together with their 95% confidence intervals (CI). All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

RESULTS

Between January 2003 and April 2004, 223 patients met the inclusion criteria. A total of 115 (52%) patients had early STR, and another 43 (19%) had late STR. Hence, STR at 30 minutes after arrival on the CCU was obtained in 71% of patients. There were differences in baseline clinical and procedural characteristics between patients with early and late STR: patients with late STR were older and TIMI flow post-PCI was worst in these patients. Larger differences were found in the baseline profile between those with and without STR. Patients without STR were older, more often had the culprit lesion in the left anterior descending artery and TIMI flow grade 3 after PCI was (considerably) more often obtained in patients with (early) STR than in those without (table 1). The event-free survival curves according to presence or absence of STR show that more patients died in the group without STR from cardiac causes (figure 1, p=0.049) as well as from overall causes (figure 2, p=0.03). Figure 3 shows that rehospitalization occurred more frequently in the early STR group (figure 3, p=0.02).

During one-year follow-up, 15 patients died and 36 were rehospitalized for MACE. As table 2 demonstrates, patients with early or late STR had a significantly lower incidence of one-year cardiac death than those without STR (1.9 vs. 9.2% events; p=0.02). Although no difference in cardiac mortality was found between the three groups (p=0.06), total mortality was higher in the group without STR (13.8 vs. 3.8%; p=0.02). As compared with patients without STR, early and late STR had a similar prognostic value (HRs for cardiac death 0.40 [0.08-2.03] and 0.25 [0.03-2.08]) (table 3).

Table 1 Baseline and procedural characteristics

Variable	Early STR	Late STR	Without STR	p value
Patients, n (%)	115 (51.6)	43 (19.3)	65 (29.2)	
Age, years	60.8±13.2	65.5±12.7	65.6±14.2	0.03
Male sex, n (%)	80 (70)	28 (65)	46 (71)	0.81
Culprit artery, n (%) - LAD	36 (31)	18 (42)	38 (58)	<0.01
- LCx	21 (18)	4 (9)	6 (9)	
- RCA	58 (50)	21 (49)	21 (32)	
Post PCI TIMI 3 flow, n (%)	111 (97)	37 (86)	47 (72)	<0.01
Medication				
- Abciximab, n (%)	77 (67)	24 (56)	44 (68)	0.37
- Adenosine, n (%)	28 (24)	12 (28)	14 (22)	0.75
ST elevation, µV				
- Pre PCI*	323 (190; 541)	424 (249; 649)	463 (320; 722)	<0.01
- Post PCI*	78 (9; 136)	224 (122; 302)	302 (224; 449)	<0.01
- CCU*	58 (9; 97)	92 (58; 161)	273 (181; 351)	<0.01

Continuous data are expressed as mean ± standard deviation. Categorical data are expressed as percentage. P values indicate the difference between the three groups. * Data are expressed as the median and interquartile range because of skewed distribution. STR=ST-segment resolution. LAD=left anterior descending coronary artery, LCx=left circumflex coronary artery, RCA=right coronary artery, PCI=percutaneous coronary intervention, CCU=coronary care unit.

Early and late STR was associated with an increased risk of rehospitalization for MACE (table 2; p=0.009). After adjustment for age and infarct localisation, the HR for rehospitalization for early STR was 3.76 (1.29 to 11.02) and for late STR 2.19 (0.62 to 7.78) (table 3).

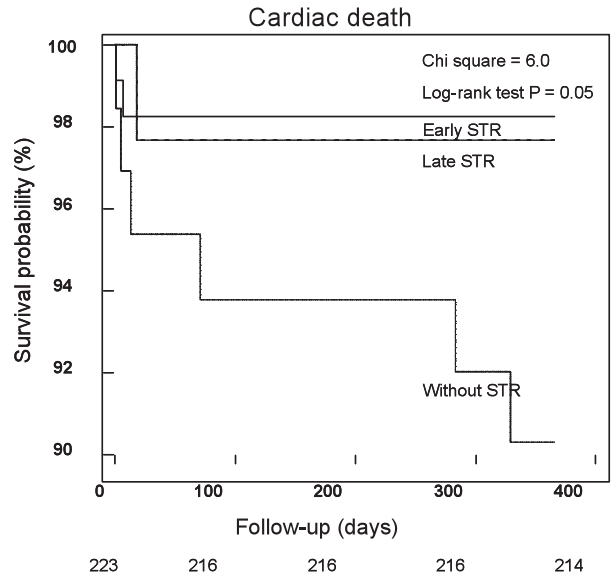

Figure 1 Event-free survival curve according to ST-segment resolution (STR) classification.

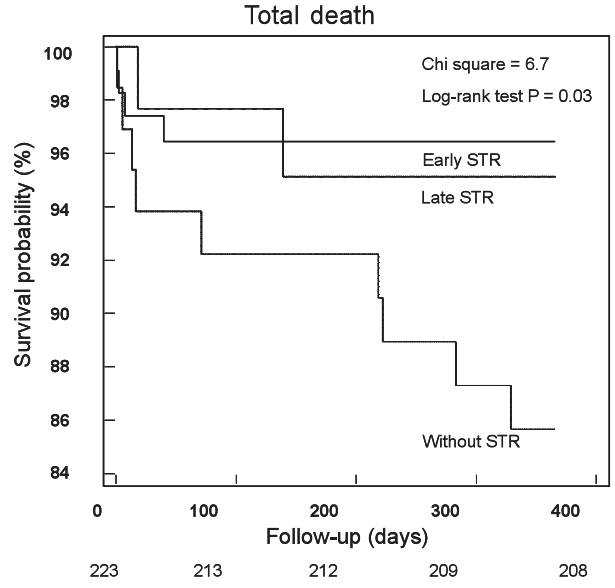

Figure 2 Event-free survival curve according to ST-segment resolution (STR) classification until the occurrence of death of any cause.

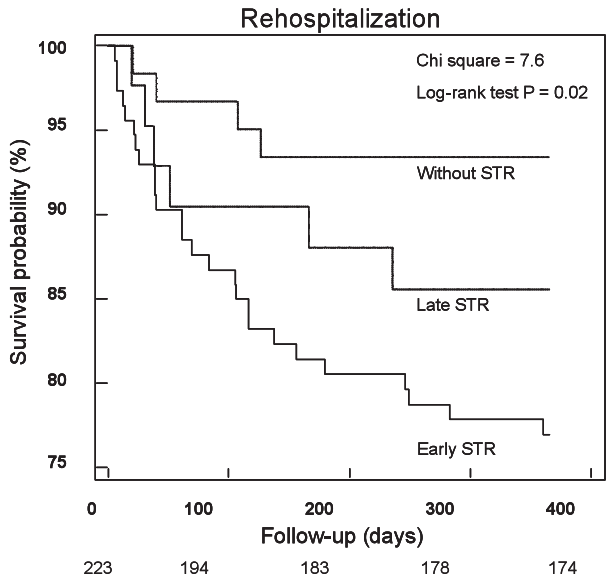

Figure 3 Event-free survival curve according to ST-segment resolution (STR) classification until the occurrence of rehospitalisation.

Table 2 Early ST resolution and clinical endpoints

	Early STR n=115	Late STR n=43	Early + late STR n=158	Without STR n=65	P value
Cardiac mortality, (%)	2 (1.7)	1 (2.3)	3 (1.9)	6 (9.2)	0.02
Non cardiac mortality (%)	2 (1.7)	1 (2.3)	3 (1.9)	3 (4.6)	0.36
Total mortality (%)	4 (3.5)	2 (4.7)	6 (3.8)	9 (13.8)	0.02
Rehospitalisation (%)	26 (22.6)	6 (14.0)	32 (20.3)	4 (6.2)	0.009
- Nonfatal infarction	3 (2.6)	1 (2.3)	4 (2.5)	0	0.56
- Unstable angina	9 (7.8)	0	9 (5.7)	0	0.04
- Revascularisation	18 (15.7)	5 (11.6)	23 (14.6)	4 (6.2)	0.08
- PCI	11 (9.6)	1 (2.3)	12 (7.6)	1 (1.5)	0.12
- CABG	11 (9.6)	4 (9.3)	15 (9.5)	3 (4.6)	0.22
- TVR	10 (8.7)	4 (9.3)	14 (8.9)	4 (6.2)	0.50
Total MACE	26 (22.6)	7 (16.3)	33 (20.9)	10 (15.4)	0.34

Data are expressed as numbers (%). P values indicate the difference between early + late STR versus without STR. STR=ST-segment resolution, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, TVR=target vessel revascularisation, MACE=major adverse cardiac event.

Table 3 Hazard ratios for cardiac and total mortality and rehospitalisation according to STR

	Cases/ subjects	Hazard ratio (CI)	
		Model 1*	Model 2*
Cardiac mortality			
- Without STR	6/65	1 (reference)	1 (reference)
- Early STR	2/115	0.25 (0.05-1.28)	0.40 (0.08-2.03)
- Late STR	1/43	0.27 (0.03-2.22)	0.25 (0.03-2.08)
Total mortality			
- Without STR	9/65	1 (reference)	1 (reference)
- Early STR	4/115	0.36 (0.11-1.20)	0.53 (0.16-1.76)
- Late STR	2/43	0.37 (0.08-1.72)	0.34 (0.07-1.59)
Rehospitalisation			
- Without STR	4/65	1 (reference)	1 (reference)
- Early STR	26/115	4.17 (1.45-12.05)	3.76 (1.29-11.02)
- Late STR	6/43	2.27 (0.64-8.04)	2.19 (0.62-7.78)

* Model 1 adjusted for age; model 2 adjusted for age and infarct localisation (anterior versus non-anterior).
STR=ST-segment resolution.

DISCUSSION

Immediately after the percutaneous intervention, approximately half of the patients had complete and sustained resolution of the ST segment, whereas about two thirds of the patients had complete STR at 30 minutes after arrival on the CCU. Our data suggested that, within this time window, there is no major change in prognostic value of early versus late STR with respect to all-cause mortality, cardiac mortality, or rehospitalization for adverse cardiac events during one-year follow-up.

This improvement of STR over time after reperfusion, from 54% early STR to 71% late STR, is caused by a gradual, spontaneous recovery of the ST segment. This finding is consistent with earlier studies[17-20] and has important consequences, in particular in considering additional therapies in persistent ST-segment elevation after PCI. Currently, additional therapies, such as vasodilators, glycoprotein IIb/IIIa receptor antagonists or an intra-aortic balloon pump, are mainly applied in case of no reflow.[21,22] However, even though angiographic evidence of reflow may be present, absence of STR is a negative prognostic marker and must be considered as a guide to initiate additive, above-

mentioned, therapies as well. Studies investigating the effect of pharmacological or mechanical therapies to optimise myocardial reperfusion should take spontaneous late STR into account in nearly half of the patients with persistent ST elevation directly after PCI.

As shown in table 1, patients with late STR and without STR had more single lead ST-segment elevation before PCI compared with patients with early STR (424 µV, 463 µV and 323 µV respectively, p<0.01). A possible explanation is that more ST-segment elevation pre-PCI reflects more intense myocardial ischemia, for example due to distal embolization, causing less STR after restoring blood flow in the epicardial coronary vessel. In addition, more ST-segment elevation before reperfusion can reflect more irreversible myocardial cell damage, for instance due to a lack of collateral blood supply or less preconditioning, with less myocardial tissue rescue and less STR after reperfusion.

One-year survival free from cardiac death was not significantly different in patients with early STR compared with late STR, but in patients without STR, cardiac death was significantly higher. This is unexpected considering the fact that persistent ST-segment elevation after PCI is thought to reflect ongoing myocardial cell damage and thus should be associated with larger final infarct size, lower left ventricular ejection fraction and higher mortality. It is possible that persistent ST-segment elevation after successful PCI is not equal to longer ischemic time or that the time between early and late STR in our study was not long enough to find a significant difference. Moreover, our study may be too small to detect small but clinically relevant differences. Future studies are needed to investigate the effect of delayed recovery of the ST segment after primary PCI on microvascular reperfusion, no reflow area and infarct size.

Another finding in this study was a significantly higher incidence of rehospitalization in the early and late STR group compared with patients without STR (20.3 vs. 6.2%, p=0.009) caused by a higher incidence of nonfatal myocardial infarction, unstable angina and revascularisation. Bainey et al. also found a higher likelihood for recurrent acute myocardial infarction and unstable angina[23] as well as De Lemos et al. who reported that more STR was associated with higher rates of recurrent myocardial infarcts.[24] We can hypothesise that STR after primary PCI is associated with more extensive residual myocardial viability. Restenosis or re-occlusion (stent thrombosis) of these target vessels may therefore lead to more symptoms and rehospitalization compared with target vessels without myocardial viability in its territory. However, there was no significant difference between the incidence of target vessel revascularisation in patients with STR compared with those without STR (8.9 vs. 6.2%, p=0.50) that would have supported this hypothesis. In addition, unknown confounding factors could have contributed to the association of no-STR after primary PCI with less rehospitalization, for instance differences in certain patient baseline and therapeutic characteristics.

In the one-year results of the Horizons-AMI study, MACE (defined as death, re-infarction, ischemia-driven target vessel revascularisation and stroke) was 10.2 to 12.9%[25] compared with 15.4 to 22.6% in our study. Non-target vessel revascularisations could partly explain these differences, but it is unknown how many of our patients had ischemic-driven target vessel revascularisation. However, in our study period, only the target vessel was treated by primary PCI using bare metal stents and staged PCI procedures were only performed in case of clearly demonstrated ischemia by nuclear tests, which was rarely the case.

Study limitations

Our study population consisted of relatively low-risk STEMI patients, because high-risk patients (e.g. shock, respiratory failure, previous myocardial infarction and failed PCI) were excluded. This may have caused an underestimation of the incidence of cardiac death and MACE in STEMI patients in the general cardiology clinic. In addition, patients with persistent conduction or rhythm disturbances could not be used for determination of STR. Data concerning blood pressure, heart frequency, myocardial infarct size (cardiac enzyme release) and left ventricular function were not available so that we could not correct for all known confounders. We can therefore not exclude a residual bias in the effect estimates (HRs). The number of patients we studied was relatively small. Consequently, clinically relevant associations between STR status and patient outcome might have been missed due to this relatively small sample size resulting in few events during follow-up. Therefore, we warrant further large sample studies to conform our data.

Conclusions

We found no (major) change in the prognostic value of STR during the 0 to 90 minutes time window after PCI for one-year follow-up on cardiac death and MACE. Therefore, for initiation of additional therapy in case of suboptimal myocardial reperfusion after primary PCI, STR determined at the end of the procedure is a useful guide.

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Chapter 8

Aspiration of Embolized Thrombus During Primary Percutaneous Coronary Intervention

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ABSTRACT

During percutaneous coronary intervention for acute myocardial infarction, distal embolization of thrombus and plaque material often occurs, despite the use of thrombectomy and aspiration catheters. Large embolized thrombi can cause occlusion of distal coronary vessels for which angioplasty most often leads to no more than poor results. We describe the successful use of an aspiration catheter to treat distally embolized thrombus, to optimize coronary reperfusion therapy and improve salvage of myocardial tissue. We discuss the manifestation and incidence of distal embolization and show its clinical relevance.

INTRODUCTION

Although primary percutaneous coronary intervention (PCI) for acute myocardial infraction is very effective in restoring epicardial patency, myocardial salvage is often limited by embolization of thrombus and atherosclerotic material with occlusion of distal vessels. Small particles cause microvascular obstruction, visible on the coronary angiogram as an absence of myocardial blush. Embolization of large thrombus can cause occlusion of distal branches and is seen on the angiogram as an abrupt cut-off or a filling defect. Embolization can occur before or during PCI; it is related to more extensive myocardial infarction and higher mortality.[1]

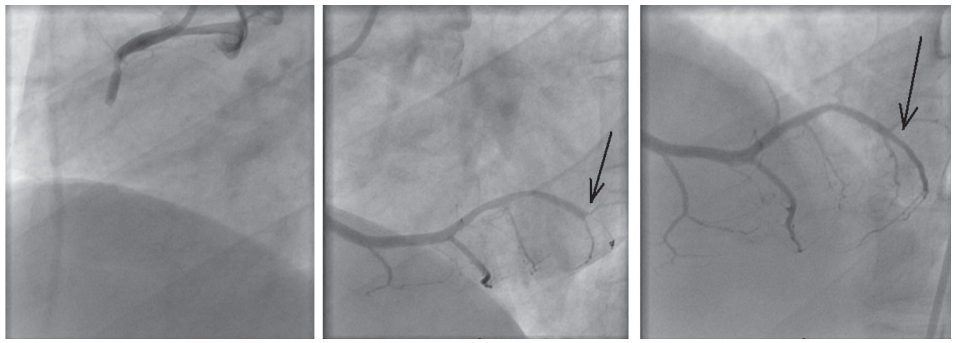
A recent study showed the benefit of systematically planned use of manual thrombus aspiration as initial step (after passage of a guidewire) in the interventional approach of acute myocardial infarction, resulting in more optimal myocardial perfusion and improved clinical outcomes.[2,3] One possible explanation is that by removing thrombus, the risk of distal embolization during balloon angioplasty or stent implantation is reduced. However, even with the use of thrombectomy and aspiration catheters, distal embolization still may occur.

In the present report, we describe and discuss three cases of primary PCI in which, despite the successful initial use of an aspiration catheter, embolization of large thrombus occurred, causing occlusion of distal vessels. They were successfully treated with an additional distal thrombus aspiration.

CASES

Case 1

The patient, a 44 years old male with a history of smoking, was admitted with acute myocardial infarction of the inferior wall. The pain-to-PCI (PtP) time was 60 minutes. In the ambulance he was treated with acetylsalicylic acid (ASA) 450 mg IV, clopidogrel 600 mg orally and heparin 5000 EH IV. The angiogram showed a normal left coronary artery (LCA) and a proximally occluded right coronary artery (RCA) (figure 1a). The patient received 25 mg/kg bolus of abciximab intracoronary. After guidewire positioning, there was some restoration of coronary flow, showing a distal occlusion of a postero-lateral (RPL) branch (figure 1b). With a 6 French compatible Export Aspiration Catheter (Medtronic, Santa Rosa), red thrombus was aspirated from the culprit lesion with subsequent successful aspiration of a large red thrombus out of the ostium of the RPL that normalized coronary flow (figure 1c). A stent was placed in the proximal lesion. The maximal creatinine phosphokinase release (CPK_{max}) was 773 U/l (normal <200 U/l) and recovery was uneventful.



1a 1b 1c

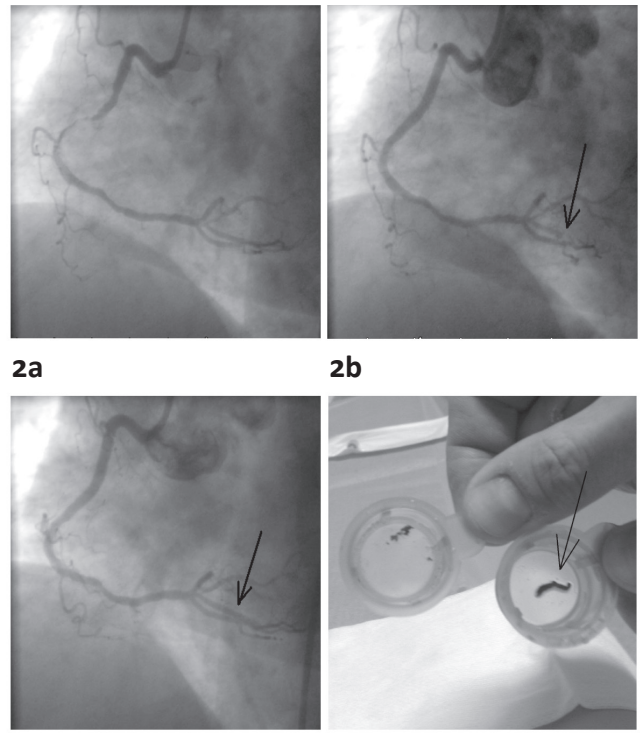
Figure 1 Acute inferior wall myocardial infarction caused by occlusion of the right coronary artery (**a**). After aspiration of thrombus out of the proximal lesion, coronary flow is partly restored with an occluded postero-lateral branch (arrow) in which the guidewire is visible (**b**). After distal thrombus aspiration, flow in the postero-lateral branch (arrow) is restored (**c**).

Case 2

The patient was a 69 years old, non-smoking woman with a history of diabetes, hypertension and cerebral bleeding one year before. She was presented with an acute myocardial infarction of the inferior wall. The PtP time was 150 minutes. She received ASA 450 mg IV and heparin 5000 EH IV and was transferred for primary PCI. The LCA was normal while the RCA showed a severe lesion with TIMI 2 flow (figure 2a). She did not receive abciximab because of her history of cerebral bleeding. After aspiration of a small amount of red thrombus, the first RPL was occluded by an embolism (figure 2b). However, the aspiration catheter could not be pushed into the distal RCA. After a stent was implanted to treat the proximal lesion, the aspiration catheter could then be placed easily in the RPL with aspiration of the embolized thrombus and recovery of flow (figure 2c). The red thrombus turned out to be larger than expected (figure 2d). Clopidogrel was started with a loading dose of 600 mg. CPK_{max} was 523 U/l and the patient recovered uneventfully.

Case 3

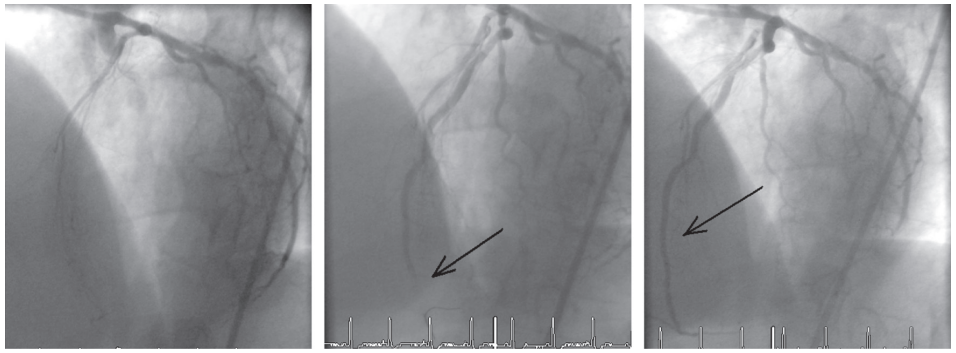
The patient was a 47 years old non-smoking male with an acute anterior wall myocardial infarction. The PtP time was 4 hours. He received ASA 450 mg IV, clopidogrel 600 mg orally and heparin 5000 EH IV and was transferred for primary PCI. He had three vessel disease with an occluded proximal left anterior descending (LAD) artery (figure 3a). An



2a 2b 2c 2d

Figure 2 Acute inferior wall myocardial infarction caused by a subtotal stenosis in right coronary artery, three distal branches are visible (**a**). After stent implantation in the culprit lesion, there is persistent occlusion of a postero-lateral branch (arrow) (**b**). After distal thrombus aspiration, the flow in the postero-lateral branch is normalized (**c**). The thrombi that were aspirated from the culprit lesion were small (left), but a large thrombus was aspirated out of the postero-lateral branch (arrow) (**d**).

intracoronary bolus of abciximab 0.25 mg/kg was given. A red thrombus could be aspirated with recovery of flow through the proximal LAD but with persistent occlusion of the distal LAD (figure 3b). With the aspiration catheter we could easily retrieve two large red thrombi out of the distal LAD, after which coronary flow was normalized (figure 3c). In the culprit lesion a stent was implanted. CPK_{max} was 1430 U/l and recovery was uneventfully.



3a 3b 3c

Figure 3 Acute anterior wall myocardial infarction caused by an occluded proximal left anterior descending coronary artery (LAD) (**a**). After thrombus aspiration out of the proximal lesion, the distal LAD is occluded (arrow) (**b**). After distal thrombus aspiration, flow in the distal LAD is restored (**c**).

DISCUSSION

The presented cases show the feasibility and safety of the use of an aspiration catheter during PCI for acute myocardial infarction, for the treatment of distal coronary embolization of large thrombi. Patency and function of distal vessels were successfully restored which limited the extent of myocardial infarction. With this technique it was avoided to perform additional distal balloon angioplasty with the risk of further fragmentation of thrombus and embolization more distally.

Embolization of thrombus

In all cases, aspirated material consisted macroscopically of large red thrombi. Therefore, pharmacologic intervention other than thrombolysis could probably not have resulted in restoration of flow in the occluded distal vessels. Embolization of smaller thrombi and atheromatous material will lodge more distally in vessels, to small for contemporary aspiration devices.

In our experience, in the majority of patients with large distal embolism, the culprit vessel was the RCA. Compared to the LAD and left circumflex artery, the RCA generally appears to contain more thrombus in case of an acute coronary syndrome. Possible explanations are a relatively bigger diameter, often with atherosclerotic dilatation with low coronary flow velocity and more flow turbulence. In addition, a big vessel can have

a high plaque load that, in case of rupture or erosion, can cause more severe platelet activation and thrombus formation.

In a recent study with a new thrombectomy device in 109 patients with an acute myocardial infarction, the incidence of distal embolism was already 8.3% before PCI even started.[4] However, in case of a totally occluded proximal coronary artery, possible distal embolization cannot be seen. Therefore, the incidence may probably be underestimated. It is unknown, whether pharmacological pre-treatment, for instance with thrombolytics or platelet glycoprotein IIb/IIIa inhibitors, can prevent embolism.

Embolization of thrombus can also occur during the passage of the guidewire through the culprit lesion. The only way of possible prevention is the use of a proximal occlusion device before wire passage. Aspiration catheters and distal protection devices themselves can cause embolization and this risk is dependant on the crossing profile and performance. In addition, the way these devices are handled by the operator is of influence on the risk of thrombus embolization. Finally, in lesions with high thrombus load, undersized balloon angioplasty and adapted stent implantation techniques can lower the risk of distal embolization caused by PCI.

It is remarkable that thrombus migration during PCI often takes place along the guidewire. A possible explanation is that the thrombus is truly guided by the wire. Alternatively, the thrombus preferably flows into the most straightforward vessel with the biggest diameter, the same vessel in which the guidewire preferably finds its way. It is advisable to maintain guidewire position in the distal vessel during the procedure to make aspiration of distal thrombus embolism as easy and successful as possible.

Aspiration catheter

In the reported cases, we used the Medtronic Export Aspiration Catheter to aspirate the embolized thrombus in the distal vessels, but its use is limited to arteries that have at least a diameter of 1.5 to 2 mm. In addition, in markedly tortuous and stenosed or calcified coronary arteries it may be difficult or impossible to push the aspiration catheter as distally as required. Aspiration catheters with a smaller outer lumen diameter can potentially be used is smaller distal vessels, but a smaller inner lumen diameter makes them less useful for aspirating large thrombi. The use of an aspiration catheter in distal, relatively small vessels has the risk of damaging the endothelium and even the vessel wall. However, this risk is lower than with the use of balloon dilatations.

Incidence of coronary embolism

In an early study of patients undergoing primary angioplasty without implantation of stents or the use of platelet glycoprotein IIb/IIIa inhibitors, the incidence of distal embolization is reported to be 15.2 %.[1] In a recent meta-analysis of more contemporary

studies it was reported that the incidence of embolization with the use of distal protection devices was not significant better compared to the control group (6.3% versus 7.3%).[5] In contrast, in a meta-analysis of studies using thrombectomy and aspiration catheters, the incidence of distal embolization was significantly lower than in the control group (7.9% versus 19.5%, $p<0.00001$).[6] However, the combined spontaneous and PCI-related incidence of distal embolism in a recent multicentre thrombectomy device study was as high as 17.6%.[4] Thus, despite the use of these catheters in primary PCI, many patients show signs of embolization in distal vessels. Novel devices and/or a different use of existing devices to prevent distal embolization are being investigated.[7, 8] In the mean time, optimal treatment of thrombus embolization is required.

CONCLUSION

Distal coronary embolization during primary PCI continues to occur in a substantial part of patients, thereby limiting myocardial salvage. Some of these patients can be successfully treated with aspiration of large embolized thrombi.

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Chapter 9

Summery, Conclusions, and Future Perspective

SUMMARY OF THE THESIS

Chapter 1

Coronary angiography is primarily used to demonstrate or exclude obstructive coronary artery disease. In daily clinical practice, coronary angiography is also applied to evaluate coronary flow by use of the TIMI flow grade classification or the TIMI frame count (TFC) method. Although the measurement of TFC (i.e. the time required to fill the coronary artery with dye) clearly goes beyond the assessment of the TIMI flow grade, it still is a quite basic method that can be refined by adapting TFC measurements to the patients' individual coronary anatomies. In fact, coronary flow velocity (cm/min) can be calculated from the TFC data in combination with information on the length of the coronary artery of interest. The addition of coronary lumen area data even permits the calculation of coronary flow (ml/min).

The function of the coronary arteries is to supply a sufficient amount of blood to the myocardium in order to assure cardiac function without ischemia. This applies to resting conditions but in particular to physical exercise, when coronary flow must be increased to levels that are at least twice as high as at rest. The degree by which coronary blood flow can be increased under such circumstances is called coronary flow reserve. Microvascular resistance, influenced by myocardial metabolic demand, regulates coronary flow, while the capacity of the epicardial coronary arteries mainly depends on flow velocity (NO-regulated). During coronary angiography, the administration of adenosine can simulate exercise conditions, as it induces maximal myocardial hyperemia. At the same time, the subtending epicardial coronary artery needs to be maximally dilated, which is achieved by the intracoronary administration of nitroglycerin. In this way, during angiographic assessment, a state of maximum coronary flow and minimum epicardial coronary resistance can be achieved. The hyperemic-to-basal ratios of angiography-derived indices (TFC, flow velocity, volume flow, and vascular resistance) reflect coronary flow reserve.

Chapter 2

The evaluation of coronary flow during coronary angiography may be influenced by dye injection, which is often manually performed. Previous studies have shown that injection rates had little impact on coronary flow velocity. In this chapter, we investigated the impact of dye injections on intracoronary pressure measurements with a pressure guide wire. The rise in intracoronary pressure during dye injection was found to be small, even in coronary segments that are located just distal to the coronary ostium (6.7 ± 4.9% of the mean arterial pressure). Our conclusion is that in coronary arteries without a significant stenosis, coronary angiography causes only a slight increase in intracoronary

pressure. The limited impact of dye injection on intracoronary blood pressure confirms the value of coronary angiography for the assessment of coronary flow velocity.

Chapter 3

The corrected TFC is originally an index of coronary flow velocity that is derived by correcting TFC only for a longer left anterior descending (LAD) as compared to the left circumflex (LCx) and right coronary (RCA) arteries. Correcting for the mean length of all three coronary arteries in question results in even further refinement of the index that is then called frame count velocity (FCV). To perform such correction, we determined the distance from the coronary ostium to a distal landmark in 119 coronary arteries by use of a guide wire. The mean length of the LAD, LCx and RCA differed significantly (14.5 ± 1.6 cm, 12.8 ± 1.9 cm and 11.3 ± 1.4 cm, respectively; p<0.001 for all comparisons). As a result, the FCV was significantly higher in the RCA than in LAD and LCx (23.0 ± 7.9 cm/sec vs. 17.6 ± 7.4 cm/sec and 16.4 ± 6.3 cm/sec, respectively; p<0.001). We conclude that the FCV, derived from TFC and mean coronary artery length data, is a more accurate estimate of coronary flow velocity as compared to TFC alone.

Chapter 4

In this chapter, we present a three-dimensional (3D) and 4D coronary model that is used for measurement of vessel length that can be used for automated assessment of TFC, which we compared to conventional TFC measurements. In fact, the length of coronary arteries as measured with an intracoronary guide wire can be underestimated because the guide wire tends to take the inner curves of the vasculature and stretch the vessel. The use of a coronary angiography-based 3-D model prevents such underestimation. In addition, automated assessment can make TFC more objective, reproducible, and online applicable. Data obtained from measurements in nine patients showed a good correlation between automated and conventional TFC measurements (r=0.98, p<0.0001). Moreover, measurements of basal and hyperemic TFC with this 4D model enable the automated assessment of angiographic flow velocity reserve.

Chapter 5

We introduced the frame count reserve (FCR) as the ratio of the hyperemic to basal TFC. In this chapter, we describe a comparison of the angiography derived FCR and relative FCR (rFCR) with intracoronary Doppler wire derived coronary flow velocity reserve (CVR) and relative CVR (rCVR) measurements in the LAD and LCx in 38 patients. In addition, we assessed flow velocity, volume flow, and coronary resistance index in the LAD and compared it to corresponding measurements in the LCX. FCR and CVR as well as rFCR and rCVR showed strong correlations (r=0.62, p<0.001, and r=0.84, p<0.001;

respectively). The LAD was significantly longer than the LCx (14.3 ± 1.6 cm vs. 11.4 ± 1.8 cm, p<0.001); therefore, the TFC of the LAD was significant greater than that of the LCx (basal 32.5 ± 15.1 vs. 23.6 ± 9.1, and hyperemic 12.1 ± 6.6 vs. 8.7 ± 3.2, p<0.02 for both). However, mean flow velocity measurements and estimations of volume flow did not differ between LAD and LCx. There was also no significant difference between mean FCR and CVR (and in addition no difference between LAD and LCx) and between mean rFCR and rCVR. In conclusion, the FCR shows a good correlation with the CVR and can be used as a simple method that allows evaluation of coronary function in any cardiac catheterization laboratory.

Chapter 6

After successful restoration of epicardial flow by primary PCI for acute ST segment elevation myocardial infarction (STEMI), 40-50% of patients do not have an optimal myocardial perfusion, which is reflected in a persistence of ST segment elevation on the electrocardiogram (ECG). In the study presented in this chapter, patients with STEMI and persistent ST segment elevation in spite of a successful primary PCI, were randomized to high dose (60 mg) intracoronary adenosine or placebo. Besides the ST segment resolution (STR), angiographic parameters of coronary function (TFC, myocardial blush, and an index for coronary resistance using FCV) were assessed. Immediately after the administration of adenosine, significantly more patients showed an optimal STR (STR >70%) compared to placebo (33% versus 9%, p<0.05). In addition, early mean STR was significantly higher after adenosine (35.4% vs. 23.0%, p<0.05). Late ST segment resolution at 90 minutes after PCI, however, did not differ between groups. In the adenosine group, the TFC was significantly lower (15.7 vs. 30.2, p<0.005), the myocardial blush grade was higher (2.7 vs. 2.0, p<0.05), and the resistance index was lower (0.70 vs. 1.31 mmHg per ml/min, p<0.005). We conclude that in patients with persistent ST segment elevation immediately after otherwise successful primary PCI, high dose adenosine can accelerate angiographic and ECG signs of myocardial reperfusion.

Chapter 7

Assessment of the STR is often used to evaluate myocardial perfusion after primary PCI for STEMI. STR has been assessed early (immediately after PCI) and – more traditionally – later (after 60–90 minutes). However, the optimal timing is unknown. We therefore compared in 223 primary PCI patients with early, late, or no STR the 1-year clinical outcome: mortality and rehospitalization for adverse cardiac events. Early STR occurred in 115 (52%) and late STR in 43 (19%) patients. Patients with early or late STR had a lower incidence of cardiac death than patients with no STR (1.9% versus 9.2%; p=0.02). In

contrast, rehospitalization occurred more frequently in patients with early or late STR (20.3% versus 6.2%; p=0.009). As compared with patients without STR, early and late STR had a similar prognostic value for death (hazard ratio [95%CI] 0.40 [0.08-2.03] and 0.25 [0.03-2.08], respectively). We conclude that in this relatively small and low risk group of patients with STEMI, there was no (major) change in prognostic value of STR during the 0–90 minutes time window following primary PCI.

Chapter 8

Embolization of a thrombus into a distal segment of the epicardial coronary artery is frequently seen during primary PCI for STEMI. Treatment of such emboli with balloon angioplasty is generally not very successful. We describe three cases, in which we were able to aspirate embolized thrombi with subsequent improvement of myocardial perfusion, thereby probably limiting infarct size. Using this approach, we could also avoid additional distal balloon dilatations with the inherent risk of further fragmentation and distal embolization of thrombi. We conclude that the presented cases show the feasibility of manual, catheter-based thrombus aspiration during primary PCI for the treatment of large, distally embolized thrombi.

CONCLUSIONS

Coronary angiography has the potential to determine coronary function in addition to merely showing coronary anatomy. In this thesis, we describe several facets of angiographic evaluation of coronary flow velocity and function. Measurement of the length of the coronary vessels by means of a guide wire or a 3D angiography-based computer model permits calculation of coronary flow velocity, volume flow, and coronary resistance. In addition, the frame count reserve (FCR), an angiographic method that does not require use of an intracoronary guide wire, can be used as an estimate of coronary flow reserve. This can be performed in an automated way by use of a 4D model, based on coronary angiography. In the setting of primary PCI for STEMI, auxiliary therapeutic options may help to optimize coronary flow. As shown in this thesis, the administration of adenosine and the aspiration of distally embolized thrombi are methods that should be considered to improve coronary flow after primary PCI. To assess myocardial reperfusion in such patients, ST segment resolution on the ECG early after PCI may be used.

FUTURE PERSPECTIVE

For the evaluation of the functional significance of an intermediate coronary stenosis, the pressure guide wire-based method of measuring Fractional Flow Reserve (FFR) is increasingly applied. Angiography-based assessment of FCR, as presented in this thesis, could be complementary to FFR. If the FCR is truly normal (e.g. greater than 3), the presence of a significant stenosis is very unlikely and measurement of the FFR might be omitted. On the contrary, if the FCR is abnormal further evaluation with FFR is needed. Such approach could reduce the number of costly FFR procedures in clinical practice and may further reduce the (relatively low) risk of complications related to the FFR examination. In addition, the ratio of maximal angiographic coronary flow velocity and hyperemic blood pressure drop over an intermediate lesion might provide more accurate information on its functional significance than use of the FFR measurement only. Nevertheless, large-scale clinical studies with a long-term follow-up are required to answer the question, whether use of FCR measurements for clinical decision-making might be useful.

In the absence of obstructive epicardial coronary artery lesions, coronary micro-vascular function can be assessed by measuring FCR and (in particular) minimal coronary resistance (MCR), a parameter that takes into account perfusion pressure. This approach might be useful especially in patients suspected of microvascular dysfunction as a cause of myocardial ischemia. Moreover, it might be of future interest in the setting of acute myocardial infarction as an instrument to guide treatment that aims at optimization of myocardial reperfusion. Before such application may be considered, extensive research is required to determine reference values for FCR and MCR in various groups of patients such as: (1) patients without (angiographic) signs of coronary atherosclerosis; (2) patients without significant coronary stenoses; (3) patients with arterial hypertension (with/without left ventricular hypertrophy); (4) patients with diabetes mellitus; (5) patients with acute myocardial infarction; (6) patients with chronic myocardial infarction.

Computer software for automated measurement of TFC, based on 3D or 4D coronary models that are derived from 2D coronary angiography, is still not applicable in routine cardiac catheterization laboratories. Nevertheless, such approaches are realizable and expected to evolve. While computed tomography-based assessment of the coronary vasculature has a great potential to further evolve into an important diagnostic technique, invasive coronary angiography remains mandatory for patients who require PCI. In addition, rotational coronary angiography holds promises for the future to generate 3D coronary models “online” in the cardiac catheterization laboratory. Such 3D models allow determining vessel length and TFC as well as coronary vessel distribution to the myocardium and area at risk in the setting of acute STEMI. The latter

is an important baseline characteristic for all studies that focus on improvement of myocardial reperfusion.

Although clinical studies with administration of adenosine in the setting of STEMI provided conflicting data, we advise to consider administration of a high intracoronary dose of adenosine (1–60 mg) in patients with signs of suboptimal myocardial reperfusion following primary PCI (i.e. if ST segment elevation persists on the electrocardiogram or if coronary angiography shows no reflow and/or limited myocardial blush). When there is no flow or slow flow in the culprit coronary vessel, adenosine should be administered through an intracoronary catheter (e.g. an infusion or aspiration catheter) that is placed in or distal to the culprit lesion. Nevertheless, so far there are no data to support prophylactic administration of adenosine.

In primary PCI for STEMI, incomplete ST segment resolution directly after the procedure indicates an inferior prognosis, which may encourage physicians to use adjunctive therapies to ameliorate myocardial reperfusion. Besides maximum inhibition of platelet aggregation and optimization of the hemodynamic status of the patient, the administration of a high dose of adenosine may be considered as a treatment option.
In STEMI patients with distal embolization of fragments of a thrombus, manual aspiration with dedicated coronary aspiration catheters should be considered. Contemporary aspiration catheters can reach distal coronary segments with a two millimeter-sized lumen. So far, operators should counterbalance in each individual case and anatomical situation the potential advantage of improving reperfusion in a (potentially small) myocardial territory versus the risk of complications, such as a coronary dissection or perforation. Nevertheless, it is expected that the arsenal of aspiration catheters will increase, including catheters with a smaller outer diameter and optimized handling to allow the aspiration of fragments of thrombus from the very distal coronary segments.

SAMENVATTING, CONCLUSIES EN TOEKOMST PERSPECTIEVEN

Hoofdstuk 1

Coronair angiografie wordt voornamelijk gebruikt om vernauwingen in de kransslagaderen aan te tonen of uit te sluiten. In de dagelijkse praktijk wordt het ook gebruikt om de mate van bloedstroom te beoordelen door middel van de 'TIMI flow grade' classificatie of de 'TIMI frame count' (TFC) methode. Hoewel de TFC meting (het aantal filmbeeldjes, ofwel de tijd die nodig is om het gehele coronaire bloedvat met contrast te vullen) een stuk nauwkeuriger is dan de 'TIMI flow grade', kunnen deze metingen verder verbeterd worden door ze te corrigeren voor de verschillen in de anatomie van de kransslagaderen. In feite kan de bloedstroomsnelheid (in cm per minuut) in de bloedvaten berekend worden uit de TFC en de lengte van het betreffende bloedvat. Wanneer vervolgens de doorsnede van het bloedvat gemeten wordt kan de bloedstroom (in ml per minuut) berekend worden.

De kransslagaderen moeten voldoende bloed kunnen laten stromen naar de hartspier zodat deze kan blijven functioneren zonder zuurstoftekort. Dit geldt voor de rusttoestand, maar vooral tijdens inspanningen moet de doorbloeding minstens twee maal zo veel worden. De verhouding tussen de bloedstroom bij inspanning en in rust noemen we de coronaire flow reserve. De weerstand in de kleine bloedvaatjes, die onder invloed staan van de stofwisselingsbehoefte van de hartspier, regelt de bloedstroom door de kransslagaderen, terwijl de capaciteit van de grote bloedvaten van het hart (door middel van NO) afhankelijk is van de bloedstroomsnelheid. Tijdens angiografie kan door middel van toediening van de stof adenosine de doorbloeding maximaal toenemen (hyperaemie), alsof er sprake is van lichamelijke inspanning. Tevens kunnen de grote kransslagaderen maximaal verwijd worden door toediening van nitroglycerine in het betreffende bloedvat. Op deze wijze kan coronair angiografie worden gedaan terwijl sprake is van een maximale bloedstroom bij minimale weerstand in de bloedvaten. De verhouding tussen de hyperaemische en basale metingen (van TFC, stroomsnelheid, volume bloedstroom en vaatweerstand) geven de coronaire flow reserve weer.

Hoofdstuk 2

De beoordeling van de bloedstroom tijdens angiografie van de kransslagaderen wordt beïnvloed door de toediening van contrast dat meestal met de hand in de bloedvaten wordt gespoten. Eerdere studies lieten zien dat de snelheid waarmee contrast wordt ingespoten weinig invloed heeft op de bloedstroomsnelheid. In het onderzoek van dit hoofdstuk hebben wij door middel van een intracoronaire drukdraad gemeten wat de invloed is van een contrastinjectie op de bloeddruk in een kransslagader. De toename in

bloeddruk tijdens angiografie bleek laag te zijn, zelfs in het begin van het bloedvat gemiddeld slechts 6.7 ± 4.9%. Wij concluderen dat in kransslagaderen zonder belangrijke vernauwingen door de angiografie zelf maar een geringe toename ontstaat in de bloeddruk. Daarmee wordt bevestigd dat coronaire angiografie goed gebruikt kan worden voor meting van de bloedstroomsnelheid.

Hoofdstuk 3

De 'corrected TFC' is oorspronkelijk een index voor de bloedstroomsnelheid in de kransslagaderen waarbij de TFC wordt gecorrigeerd voor de grotere lengte van de ramus descendens anterior (left anterior descending, LAD) in vergelijking met de ramus circumflexus (left circumflex, LCx) en de rechter kransslagader (right coronary artery, RCA). Deze index kan verder verbeterd worden door correctie voor de gemiddelde lengte van alle drie de bloedvaten; deze index noemen wij de 'frame count velocity' (FCV). Hiervoor hebben wij door middel van een voerdraad in 119 kransslagaderen de afstand gemeten tussen het begin en het (voor de TFC gebruikte meetpunt aan het) einde van een bloedvat. De gemiddelde lengte van de LAD, LCx and RCA verschilde significant (14.5 ± 1.6 cm, 12.8 ± 1.9 cm and 11.3 ± 1.4 cm, respectievelijk; p<0.001 voor alle vergelijkingen). De FCV bleek hiermee significant hoger in the RCA dan in de LAD en de LCx (23.0 ± 7.9 cm/sec vs. 17.6 ± 7.4 cm/sec and 16.4 ± 6.3 cm/sec, respectievelijk; p<0.001). Onze conclusie is dat de FCV, berekend uit de TFC en de gemiddelde lengte van de kransslagaderen een betere meting is van de bloedstroomsnelheid dan alleen de TFC.

Hoofdstuk 4

In dit hoofdstuk bespreken wij een driedimensionaal (3D) en 4D coronair model om de lengte van de kransslagaderen te bepalen waarmee de TFC automatisch vastgesteld kan worden. Deze hebben we vergeleken met conventionele TFC metingen. In feite kan de lengte van de bloedvaten gemeten door middel van een voerdraad onderschat worden omdat deze draad de binnenbochten neemt en tevens de bloedvaten kan strekken. Deze onderschatting kan voorkómen worden door gebruik te maken van een 3D model dat gebaseerd is op het coronair angiogram. Daarnaast kan een automatische meting van de TFC objectiever, beter reproduceerbaar en online beschikbaar zijn. Meetgegevens van de automatische en conventionele TFC bepaling bij negen patiënten toonde een goede correlatie (r=0.98, p<0.0001). Met het 4D coronaire model is het mogelijk door middel van basale en hyperaemische metingen een automatische bepaling van de angiografische coronaire stroomsnelheid reserve (CVR) te verrichten.

Hoofdstuk 5

Wij introduceren hier de 'frame count reserve' (FCR) als de verhouding tussen de hyperaemische en de basale TFC. In dit hoofdstuk vergelijken wij deze angiografische FCR en relatieve FCR (rFCR) met de door middel van een Doppler voerdraad gemeten CVR en relatieve CVR (rCVR) in de LAD en LCx bij 38 patiënten. Daarnaast hebben wij de stroomsnelheden, de bloedstroom en een index voor de coronaire weerstand bepaald in de LAD en de LCx en deze met elkaar vergeleken. Zowel de FCR en CVR als de rFCR en rCVR toonden goede correlaties (r=0.62, p<0.001, en r=0.84, p<0.001; respectievelijk). De LAD was significant langer dan de LCx (14.3 ± 1.6 cm vs. 11.4 ± 1.8 cm, p<0.001); hierdoor was de TFC van de LAD significant hoger dan die van de LCx (basaal 32.5 ± 15.1 vs. 23.6 ± 9.1, and hyperaemisch 12.1 ± 6.6 vs. 8.7 ± 3.2, p<0.02 voor beide). Echter, gemiddelde stroomsnelheden en schattingen van bloedstroom in de LAD en LCx waren niet verschillend. Er waren ook geen verschillen tussen de gemiddelde FCR en CVR (en evenmin in de LAD in vergelijking met de LCx) en tussen de gemiddelde rFCR en rCVR. Concluderend blijkt de FCR goed te correleren met de CVR en kan daarom gebruikt als een simpele methode om de coronaire functie vast te stellen in willekeurig welke hartkatheterisatiekamer.

Hoofdstuk 6

Na geslaagd herstel van de bloedstroom in de grote kransslagaderen door middel van een primaire dotterbehandeling (PCI) bij patiënten met een acuut ST segment elevatie hartinfarct (STEMI), heeft 40-50% van de patiënten geen optimale hartspier doorbloeding, zoals vast te stellen is door persisterende ST segment elevatie op het elektrocardiogram (ECG). In het onderzoek van dit hoofdstuk werden patiënten met een STEMI en persisterende ST segment elevaties ondanks een geslaagde primaire PCI gerandomiseerd naar intracoronaire toediening van een hoge dosering (60 mg) adenosine of placebo. Naast ST segment resolutie (STR) werden angiografische parameters van coronaire functie (TFC, myocardiale blush en een index voor coronaire vaatweerstand met gebruik van de FCV) bepaald. Aansluitend aan de toediening van adenosine bleken significant meer patiënten optimale (>70%) STR te hebben in vergelijking met de placebo groep (33% versus 9%, p<0.05). Tevens was de vroege gemiddelde STR significant hoger na toediening van adenosine (35.4% vs. 23.0%, p<0.05). Late STR (90 minuten na PCI) echter was niet verschillend meer tussen beide groepen. In de adenosine groep bleek de TFC lager (15.7 vs. 30.2, p<0.005), de myocardiale blush grade hoger (2.7 vs. 2.0, p<0.05), en de vaatweerstand index lager (0.70 vs. 1.31 mmHg per ml/min, p<0.005). Concluderend kan een hoge dosis adenosine bij patiënten met persisterende ST segment elevatie aansluitend aan een overigens geslaagde primaire PCI, de angiografische en elektrocardiografische tekenen van myocardiale reperfusie versnellen.

Hoofdstuk 7

Bepaling van STR wordt vaak gedaan om de myocardiale doorbloeding na een primaire PCI wegens STEMI te beoordelen. STR wordt vroeg bepaald (direct na PCI) of, van oorsprong, pas later (na 60-90 minuten). Echter, het optimale tijdstip is onbekend. Daarom hebben wij bij 223 primaire PCI patiënten met vroege, late of geen STR de 1-jaars klinische uitkomsten met elkaar vergeleken, te weten mortaliteit en heropname in een ziekenhuis wegens hartproblemen. Vroege STR trad op bij 115 (52%) en late STR bij 43 (19%) patiënten. Patiënten met vroege of late STR hadden een lagere incidentie van cardiaal overlijden dan patiënten zonder STR (1.9% versus 9.2%; p=0.02). Daar stond tegenover dat heropname vaker voorkwam bij patiënten met vroege of late STR (20.3% versus 6.2%; p=0.009). In vergelijking met patiënten zonder STR waren vroege of late STR gelijke voorspellers voor overlijden (relatief risico [95%CI] 0.40 [0.08-2.03] and 0.25 [0.03-2.08], respectievelijk). Concluderend was er in deze relatief kleine en laag risico groep patiënten met een STEMI geen (groot) verschil in de voorspellende waarde van de STR in het tijdsbeloop van 0 tot 90 minuten na een primaire PCI.

Hoofdstuk 8

Embolisatie van een bloedstolsel naar de stroomafwaarts gelegen delen van de kransslagaderen wordt vaak gezien tijdens een primaire PCI wegens een STEMI. Behandeling van zulke embolieën met een dotterballon is meestal weinig succesvol. Wij beschrijven drie patiënten waarbij het mogelijk was om geëmboliseerde stolsels weg te zuigen waardoor de doorbloeding van de hartspier werd verbeterd en de grootte van het hartinfarct waarschijnlijk werd beperkt. Door deze techniek te gebruiken was het niet nodig ballondilataties te verrichten met het inherente risico van verdere fragmentatie en embolisatie van het stolsel. Wij concluderen uit deze voorbeelden dat het goed mogelijk is tijdens een primaire PCI grotere, naar stroomafwaarts geëmboliseerde stolsels met een handbediende katheter weg te zuigen.

CONCLUSIES

Coronair angiografie biedt de mogelijkheid om naast het afbeelden van de anatomie ook de coronaire functie te beoordelen. In deze thesis beschrijven wij verschillende aspecten van de angiografische beoordeling van de bloedstroomsnelheid in de kransslagaderen en de coronaire functie. Door middel van meting van de lengte van een bloedvat met behulp van een voerdraad of op basis van een 3D computer model gebaseerd op het angiogram, kunnen bloedstroomsnelheid, de bloedstroom en de vaatweerstand van de kransslagaderen berekend worden. Tevens kan met de FCR, een angiografische methode waarbij geen gebruik gemaakt hoeft te worden van een voerdraad in de slagaderen van het hart, een schatting gemaakt worden van de coronaire flow reserve. Dit kan ook op een automatische manier gebeuren met gebruik van een 4D model gebaseerd op het coronair angiogram.

Bij een primaire PCI wegens STEMI kunnen aanvullende therapeutische opties de coronaire bloedstroom verbeteren. Zoals in deze thesis beschreven wordt zijn de toediening van adenosine en het wegzuigen van geëmboliseerde stolsels behandelingen die overwogen moeten worden om tijdens primaire PCI de bloedstroom door de kransslagaderen te verbeteren. Om het herstel van de doorbloeding van de hartspier vast te stellen kan de ST segment resolutie op het ECG dat gemaakt wordt aansluitend aan een primaire PCI gebruikt worden.

TOEKOMST PERSPECTIEVEN

Om de functionele betekenis te bepalen van een vernauwing in een kransslagader waarvan de ernst onzeker is, wordt in toenemende mate gebruik gemaakt van een voerdraad waarmee de bloeddruk in de slagader en de fractionele flow reserve (FFR) gemeten kan worden. Angiografische bepaling van de FCR, zoals in deze thesis besproken wordt, kan complementair aan deze FFR zijn. Wanneer een FCR volledig normaal is (bijvoorbeeld meer dan 3), dan is de aanwezigheid van een ernstige vernauwing in de betreffende kransslagader onwaarschijnlijk en kan meting van de FFR achterwege blijven. Daartegenover staat dat wanneer een FCR te laag is, verdere evaluatie met FFR overwogen moet worden. Deze benadering kan het aantal kostbare FFR procedures in de dagelijkse praktijk beperkt houden en het (relatief weinig) vóórkomen van complicaties gerelateerd aan de FFR meting verder verminderen. Tevens kan de verhouding van de angiografisch bepaalde maximale bloedstroomsnelheid en de hyperaemische bloeddrukdaling over een vernauwing van onzekere ernst betere informatie geven over de functionele betekenis ervan dan FFR alleen. Maar eerst zijn

grote klinische studies met lange termijn vervolg nodig om de vraag te beantwoorden of FCR meting waarde kan hebben in de klinische besluitvorming.

Wanneer er geen vernauwingen zijn in de grote kransslagaderen, kan de microvasculaire functie bepaald worden door middel van de FCR en (met name) de minimale coronaire vaatweerstand (MCR), een parameter die rekening houdt met de perfusie druk. Deze benadering kan helpen bij patiënten met een verdenking op microvasculaire disfunctie als oorzaak van myocardiale ischaemie. Ook kan de FCR bij patiënten met een acuut hartinfarct gebruikt gaan worden om vast te stellen of aanvullende behandelingen nodig zijn om het herstel van de doorbloeding van de hartspier te optimaliseren. Daarvoor zal het nodig zijn om op basis van uitgebreid onderzoek eerst referentie waarden vast te stellen voor FCR en MCR bij verschillende groepen patiënten, zoals: (1) patiënten zonder (angiografische) tekenen van kransslagaderafwijkingen; (2) patiënten zonder significante vernauwingen; (3) patiënten met arteriële hypertensie (met of zonder hypertrofie van de linker kamer); (4) patiënten met diabetes mellitus; (5) patiënten met een acuut hartinfarct; (6) patiënten met een oud hartinfarct.

Computer software voor automatische bepaling van de TFC door middel van 3D en 4D coronaire modellen, op basis van 2D coronaire angiografieën, is nog niet beschikbaar voor de hartkatheterisatiemaker. Desalniettemin bestaan er nu al mogelijkheden en die zullen naar verwachting verder uitbreiden. Hoewel de CT-scan reeds veel diagnostische mogelijkheden heeft wat betreft de coronaire bloedvaten, en daarin verder ontwikkeld zal worden, blijft invasieve coronaire angiografie noodzakelijk voor patiënten die (mogelijk) een dotterbehandeling moeten ondergaan. Tevens komen er in de toekomst wellicht mogelijkheden om door middel van 'rotational coronary angiography' 3D coronaire modellen 'on-line' in de hartkatheterisatiekamer te maken. Met dergelijke 3D modellen kan niet alleen de lengte en de TFC van de bloedvaten bepaald worden, maar ook de ruimtelijke verdeling van de kransslagaderen en de grootte van het bedreigde stroomgebied van het hart bij een patiënt met een acuut infarct. Dit laatste is een belangrijke uitgangswaarde voor alle studies die gericht zijn op verbetering van het herstel van de doorbloeding van de hartspier.

Hoewel klinische studies met toediening van adenosine in het kader van een STEMI tegenstrijdige resultaten laten zien, adviseren wij te overwegen een hoge dosis (1 – 60 mg) intracoronaire adenosine te geven aan patiënten met tekenen van suboptimaal herstel van de doorbloeding van de hartspier tijdens een primaire PCI (persisterende ST segment elevatie op het ECG, 'no reflow' en/of verminderde myocardiale blush). Wanneer de bloedstroomsnelheid doorheen het betreffende bloedvat laag of afwezig is, dan dient de adenosine door een intracoronaire katheter gegeven te worden die in of voorbij de behandelde vernauwing ligt. Niettemin zijn er tot nu toe geen studies die de profylactische toediening van adenosine ondersteunen.

Tijdens primaire PCI wegens een STEMI kan incomplete ST segment resolutie direct na de procedure op een slechtere prognose wijzen, waardoor behandelend artsen attent moeten zijn op eventuele aanvullende therapieën om het herstel in doorbloeding van het hart te verbeteren. Naast maximale remming van de aggregatie van bloedplaatjes en optimaliseren van de haemodynamische toestand van de patiënt, kan toediening van een hoge dosering adenosine een optie zijn.

In STEMI patiënten waarbij bloedstolsels stroomafwaarts zijn geëmboliseerd dient overwogen te worden deze met behulp van manuele aspiratie katheters te verwijderen. Moderne katheters kunnen daarvoor in bloedvaten met een binnen diameter van slechts 2 mm opgevoerd worden. Steeds zullen de eventuele voordelen van herstel van doorbloeding van een (mogelijk beperkt) stroomgebied van de hartspier bij elke patiënt en elke anatomie opnieuw afgewogen moeten worden tegen het risico op complicaties als dissectie of perforatie van het bloedvat. Desondanks zal het arsenaal aan aspiratie katheters verder uitbreiden, ondermeer met katheters met een kleinere buiten diameter en verbeterde gebruikseigenschappen zodat ook stolsels uit dieper gelegen bloedvaatjes weggezogen kunnen worden.

Chapter 10

Publicatielijst

Dankwoord

Curriculum Vitae

PUBLICATIELIJST

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CURRICULUM VITAE

Martin Gerrit Stoel werd op 16 augustus 1959 geboren in Den Haag. Op het Gymnasium Haganum behaalde hij in 1978 zijn diploma waarna hij de daarop volgende vier jaar zou worden uitgeloot voor de studie geneeskunde. Na een jaar de opleiding tot verpleegkundige te hebben gevolgd in het Rode Kruis ziekenhuis te Den Haag ging hij naar de Rijksuniversiteit Gent in België om daar in 1982 het equivalent van het kandidaatsdiploma geneeskunde te behalen. De studie werd vervolgens aan de Rijksuniversiteit Leiden in 1988 afgerond.
Na gedurende 2 jaar een functie als arts-assistent neurologie en interne geneeskunde te hebben vervuld, volgde hij van 1990 tot 1996 de opleiding tot cardioloog in het Leyenburg (nu: Haga) ziekenhuis te Den Haag (opleiders: dr. C.M. Sparling en dr. G.A. van der Kley). Nadien was hij aldaar een jaar werkzaam als chef de kliniek.
Van 1997 tot 2005 was hij interventiecardioloog in het VU medisch centrum te Amsterdam. Bij prof. dr. C. A. Visser en later bij prof. dr. F. Zijlstra werd een begin gemaakt aan het onderzoek dat ging leiden tot dit proefschrift.
Vanaf 2005 is hij werkzaam in de maatschap cardiologie in het Thorax Centrum Twente van het Medisch Spectrum Twente in Enschede met als aandachtsgebieden ondermeer coronaire dotterbehandelingen, percutane implantatie van aorta biokleppen en nierarterie ablaties. De afgelopen jaren werd aldaar bij prof. dr. C. von Birgelen het proefschrift verder vorm en vooral inhoud gegeven.
Martin Stoel is sinds 1992 getrouwd met Karolien Versteeg; samen hebben zij 2 prachtige dochters, Vera (1994) en Nina (1997).