CORONARY FLOW RESERVE:
A FUNCTIONAL MEASURE OF STENOSIS SEVERITY

Coronaire doorstromingsreserve:
een funktionele maat voor de ernst van een vernauwing

PROEFSCHRIFT

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CONTENTS

Overview

In 1959 Sones developed selective coronary cineangiography. To date, this technique has remained the only means available for the visualization of the coronary arterial system with such image contrast and resolution, that the presence and severity of coronary stenosis can be determined with sufficient accuracy. Consequently, coronary cineangiography has become the most important tool for clinical decision making, used by the physician caring for patients with coronary artery disease. However, of prime concern has been the relationship between the angiographic severity of the stenosis and the resulting reduction or limitation in coronary blood flow.

The concept of coronary flow reserve has been developed as a means to describe the functional capacity of a coronary artery. Several techniques are currently under development to make the assessment of coronary flow reserve possible in awake humans. This thesis describes a radiographic technique to measure coronary flow reserve, that can be applied during routine diagnostic or interventional cardiac catheterization. Several methodological aspects on which no previous data existed, such as the role of pharmacological coronary vasodilation, radiographic data acquisition and digital data processing as well as application of this technique in several clinical conditions have been studied.

In chapter 1 the anatomy and function of the coronary vasculature are described briefly. The concept of coronary flow reserve as a measure of the functional capacity of a coronary artery is outlined. The various methods of measuring coronary blood flow parameters are discussed with emphasis on radiographic techniques. An essential part of all methods that measure coronary flow reserve is the induction of a maximal coronary hyperemia by pharmacologic means. The value and limitations of the intracoronary administration of papaverine and adenosine for the assessment of flow reserve are described in chapters 2 and 3, and in chapter 4, respectively.

In chapter 5 the methodology of the radiographic assessment of coronary flow reserve is described in detail and a first attempt is made to relate coronary flow reserve to quantitatively determined coronary artery dimensions. Myocardial imaging with thallium-201 during exercise has been shown to be a useful non-invasive method to investigate the physiologic significance of a coronary stenosis. In chapter 6 the results of this technique are compared in 38 patients to measured coronary flow reserve and coronary artery dimensions. In chapter 7 the relationships between quantitatively determined coronary artery dimensions and coronary flow reserve are described in 81 patients. An attempt is made to relate these invasive measurements to "bed-side" cardiology that is angina pectoris and non-invasive evidence of myocardial ischemia.

Since the introduction of percutaneous transluminal coronary angioplasty in 1977, this procedure has gained increasing importance in the treatment of coronary artery obstructions. Successful coronary angioplasty, defined as a residual percentage diameter stenosis of less than 50% results in marked improvement in the clinical condition of the patient, but doubt has remained whether this procedure can restore the coronary flow reserve of atherosclerotic coronary arteries to normal. In chapter 8, a comparison between the radiographically assessed coronary flow reserve and intracoronary blood flow velocity measurements with a Doppler catheter is made in the setting of coronary angioplasty. It is shown that coronary flow reserve as measured by these two techniques is not restored to normal immediately following angioplasty. Nevertheless, 3 to 5 months after angioplasty coronary flow reserve can be normalized in selected patients as is described in chapter 9. In chapter 10 two issues are addressed. First, the intra- and interobserver variability, as well as the short-, medium-, and long-term variability of the radiographic assessment of coronary flow reserve are characterized. Second, the immediate and long-term functional results of coronary angioplasty in 25 patients are described in detail.

This thesis describes the implementation and validation of a radiographic technique that uses selective coronary cineangiography as a means to measure coronary flow reserve during routine cardiac catheterization. With the development of digital catheterization equipment this technique may become a valuable and practical addition to the angiographic delineation of coronary artery dimensions.

CHAPTER 1: INTRODUCTION

1. Anatomy and function of the coronary vasculature

A. Epicardial coronary arteries.

The epicardial coronary arteries originate from ostia in the left and right sinuses of Valsalva. In adult humans, the main left coronary artery is 3,5 to 5,5 mm in diameter (1). It gives rise to two major branches: the left anterior descending artery and the circumflex coronary artery. The diameter of the right coronary artery is 2.5 to 5.0 mm at its origin (1). Like all vessels, epicardial coronary arteries act as conduits, semi-permeable membranes and metabolic units (2). Under normal circumstances they contribute little to the total coronary resistance. However, when coronary flow is increased due to a reduction in the resistance of small vessels, atherosclerotic epicardial arteries may become the dominant contribution to the coronary resistance (see figure 1A). The coronary resistance can then be decreased by dilation of the epicardial artery in response to nitroglycerine or papaverine (3,4). When the left ventricle contracts, blood in the intramural coronary arteries is forced retrograde into the epicardial vessels. As blood flow in the proximal coronary arteries is antegrade throughout systole, the retrograde flow must be masked by dilation of the epicardial vessels which act as a functional capacitance by storing blood and energy during systole (5,6).

B. Intramural coronary vessels.

Intramural coronary vessels penetrate perpendicularly into the myocardium from the epicardial coronary arteries. These arteries and arterioles form a dense vascular network in the wall of the ventricles, and play a dominant role in the regulation of coronary vascular resistance (2). Compressive forces are greater in the subendocardium than in the subepicardium resulting in a lower perfusion pressure in the subendocardial intramural vessels. This is partly compensated for by a greater vascular volume and a lower vascular resistance in the subendocardial myocardium (7).

C. Capillaries.

Capillary density in left and right ventricles is 2 to 5 x 10^3 capillaries/mm^2 and the average capillary diameter is 5 micrometer. The ratio of number of capillaries/musclefiber in adult humans is normally 1:1 (8,9). The capillaries act primarily as semipermeable membranes. Oxygen, electrolytes and nutrients leave and simultaneously CO_2 and metabolites enter the vascular space (2).

D. Coronary veins

The heart has three venous systems (10). The largest one drains primarily the left ventricle and consists of epicardial veins that converge into the coronary sinus. The second system of anterior superficial veins drains mainly the right ventricle. The third system, the Thebesian veins, composed of small venules which enter directly into all four chambers, is quantitatively significant with respect to drainage of the atria, but not of the ventricles. During systole, some venous blood is forced into the coronary sinus and some is stored in the venous system, thereby contributing to the capacitance of the coronary vasculature. Venous tone does not contribute significantly to the total coronary vascular resistance (11).

2. Regulation of coronary blood flow.

Coronary blood flow and myocardial oxygen consumption are closely coupled (12,13). Schwartz et al (14) have shown that if the oxygen requirements of the left ventricle are increased, that within one cardiac cycle vascular resistance decreases and coronary flow rises. Thus, the close coupling between myocardial oxygen consumption and coronary blood flow is adjusted on a beat to beat basis. This relationship is the dominant feature of the coronary blood flow regulation (15). The three major determinants of myocardial oxygen consumption are heart rate, myocardial contractility and wall stress; shortening, activation and basal metabolic requirements are only of minor importance (16). The primary mechanism for increasing oxygen delivery to the myocardium is coronary dilation resulting in increased coronary blood flow (15). In normal circumstances coronary blood flow can increase about fivefold (17,18). During maximal coronary dilation a linear relationship exists between coronary driving pressure and coronary flow (19). When normal coronary vasomotor tone is present, coronary flow remains relatively constant over a wide range of perfusion pressures (20). This is called autoregulation. Drugs which cause maximal relaxation of smooth muscle, such as adenosine, dipyridamole or papaverine abolish autoregulation.

3. The concept of coronary flow reserve.

The concept of coronary flow reserve as a functional measure of stenosis severity was initially proposed by Gould et al (21). Two methodological approaches have been developed to assess the coronary flow reserve of individual coronary arteries in the clinical setting, and the definition of coronary flow reserve is therefore method-dependant. The first approach uses quantitative coronary angiography to determine the pressure flow characteristics of coronary stenoses (22)

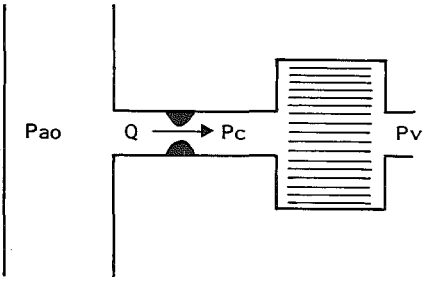

Figure 1A
Schematic of a stenotic coronary artery and distal bed. Pao = aortic pressure, Q = coronary flow, Pc = distal coronary perfussion pressure, Pv = effective coronary back pressure. When coronary flow is increased by reduction of the resistance of the small vessels, the atherosclerotic epicardial artery becomes the dominant contribution to the total coronary resistance.

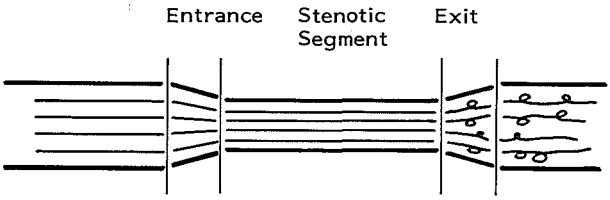

Figure 1B

$$\text{Pressure drop} = \frac{\text{Entrance}}{\text{Effect}} + \frac{\text{Friction}}{\text{Loss}} + \frac{\text{Separation}}{\text{Loss}}$$

$$\text{Pressure drop} = \quad ? \quad + \quad FV \quad + \quad SV^2$$

(see figure 1B). Young et al (23-26) developed fluid dynamic equations that describe the relationship between the pressure distal to a stenosis and the flow. When coronary flow increases the coronary perfusion pressure distal to the stenosis decreases in a nonlinear fashion, according to the equation:

$Pc = Pao - f\,Q - s\,Q^2$,

where Pc = pressure distal to the stenosis, Pao = aortic pressure, f = coefficient of viscous friction, s = coefficient of exit separation and Q = flow (23-26). Viscous friction is mainly dependent on the absolute cross-sectional area of the artery at the site of the stenosis and on the length of the stenotic lesion. Exit separation is mainly dependent on the cross-sectional area at the site of obstruction and on the normal area distal to the stenosis. From the relationship between coronary perfusion pressure and coronary flow under conditions of maximal coronary vasodilation as described by Bache and Schwartz (27), and assuming a resting coronary blood velocity of 15 cm/s, Kirkeeide et al (28) calculated a coronary flow reserve from the quantitative angiographic data. This X-ray predicted flow reserve is schematically shown in figure 2A. The relationship between pressure and flow during maximal coronary vasodilation is represented by the dashed line. The dotted line is the relationship between distal coronary pressure and coronary blood flow. The intersection of these curves is the coronary flow reserve according to Kirkeeide et al. The major advantage of this approach is that it integrates multiple angiographically defined anatomical characteristics of a coronary stenosis into a single parameter. However, the effect of a coronary stenosis on blood flow is a response of an anatomic hemodynamic system in which the stenosis is but one component (28). Therefore, several important factors such as the prevailing perfusion pressure, hypertrophy, collaterals or previous myocardial infarction are not taken into consideration.

The second approach uses the ratio of maximal to resting coronary blood flow as a measure of coronary flow reserve. Temporary occlusion of a coronary artery or potent coronary vasodilation can produce maximal coronary vasodilatation. This results in a hyperemic response characterized by a marked increase in flow which gradually subsides (17,29). Figure 2B is a schematical representation of the approach that is based on the measurement of the ratio of maximal to resting coronary blood flow as a measure of flow reserve, in a format as proposed by Hoffman and Klocke (30,31). Several important complexities of both approaches of coronary flow reserve should be taken into consideration, and some of these are illustrated in figure 2C (30,31). At a constant level of myocardial metabolic demand, coronary flow is maintained constant over a wide range of coronary pressure. This is called autoregulation. When maximal coronary vasodilation is

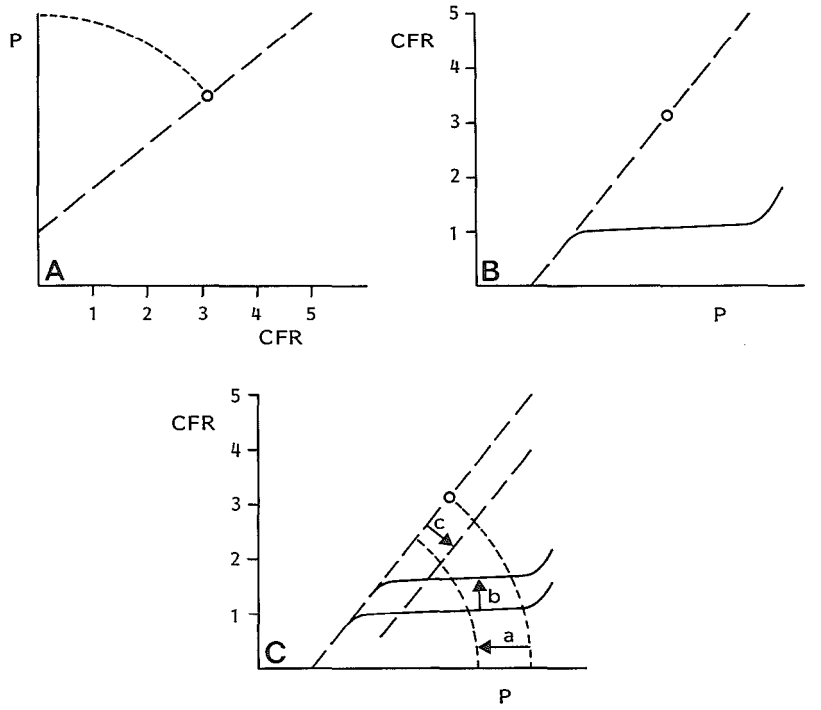

Figure 2
P = coronary perfusion pressure, CFR = coronary flow reserve. The dotted lines represent the calculated distal coronary perfussion pressure as a function of coronary blood flow. The dashed lines describe the relationship between coronary blood flow and perfussion pressure during maximal coronary vasodilation.
In fig 2A the theory of the X-ray predicted CFR as developed by Kirkeeide et al (27) is shown schematically. The open circle represents a CFR of 3.
Fig 2B is a schematical representation of the approach that uses the measurement of the ratio of maximal to resting coronary blood flow as a measure of CFR, in a format as used by Hoffman and Klocke (30,31). At a constant level of metabolic demand, coronary flow is maintained constant over a wide range of perfussion pressure. This is called autoregulation (sollid line) The open circle represents a CFR of 3.
In fig 2C both approaches are combined to show the complexities of the concept of CFR. The open circle still represents a CFR of 3, but small changes in perfussion pressure (A), an increase in resting blood flow (B), or an altered pressure - flow relationship during maximal vasodilation can all result in a substantially lower CFR.

induced by a temporary occlusion of the artery or by pharmocological means, coronary blood flow rises about three fold in this example. However, aside from the presence of the coronary stenosis several other variables influence this ratio of resting and hyperemic coronary flow. These variables can be considered in terms of their effects on coronary pressure, resting coronary blood flow level, and the pressure flow relationship during maximal coronary vasodilation. Coronary perfusion pressure is linearly related to coronary blood flow during maximal vasodilation (19). Therefore, small changes in pressure result in significant changes in flow (A in figure 2C), even in a normal coronary artery. Likewise small dynamic changes in stenosis geometry resulting in changes in distal coronary perfusion pressure can change coronary flow reserve substantially (4). The resting coronary blood flow level varies with metabolic demand (12). An increase in resting flow (B in figure 2C) results in a decrease of the measured flow reserve. The pressure flow relationship during maximal vasodilation varies substantially due to changes in hemodynamic variables. For instance, left ventricular hypertrophy shifts this relationship to the right (C in figure 2C). Several other variables are also important in this regard such as heart rate, contractility, blood viscosity and left ventricular end-diastolic pressure (31).

4. Methods of measuring coronary blood flow and flow reserve

Several methods have been developed to measure coronary blood flow or flow reserve which are not applicable during cardiac catheterization but are useful in the animal laboratory and/or during cardiac surgery, and have contributed enormously to our understanding of coronary pathophysiology. Timed venous collection with a graduated cylinder and a stopwatch is the oldest method of measuring coronary blood flow (32). It is a simple and accurate method of measuring coronary blood flow and is widely used in animal laboratories. The major limitation of this technique is that it can be employed only when the heart is either excised or exposed and this technique is therefore rarely used in humans (33). Electromagnetic flow meters are based on the principle of Faraday's induction law. Perivascular or extracorporal electromagnetic flow probes can measure rapid changes in flow and are used in animal preparations and during cardiac surgery to assess bypass graft flow (34,35). The major limitation is that the coronary artery must be dissected prior to probe placement (36). The microsphere technique is based on the principle that when particles that do not recirculate because of capillary entrapment are injected, their distribution will be proportional to the blood flow, provided that certain criteria are met (37). This technique is the only method that allows accurate measurements of the transmural distribution of myocardial

perfusion, but is only applicable in the animal laboratory (38,39).

Several applications of the three classical principles to measure blood flow in intact animals and man (indicatordilution, first-pass distribution and inert substance washout) have been adapted to the coronary circulation. The indicator-dilution principle as introduced by Stewart (1897) and developed by Hamilton (1931) has been modified for measurements of coronary blood flow during cardiac catheterization. Ganz et al (40) developed a thermodilution method for measuring coronary sinus flow. However, several conditions must be met to obtain valid measurements. The injectate infusion rate must be adequate and sensitive thermistors and an insulated catheter system must be used. If multiple comparable measurements of flow are needed a stable position of the catheter in the cardiac venous system is mandatory. Flow from the anterior left ventricular wall can be measured separately if the catheter is placed in the great cardiac vein (40-42). The main advantages of the technique are that it is simple and relatively inexpensive and allows multiple measurements at short intervals with a frequency response sufficient to measure changes in flow occurring in 2 to 3 s (40). The major disadvantage of the technique is that a stable catheter position can not always be obtained and that small changes in catheter position induce large changes in measured flow and thus pose a difficulty in relating measured flow to a specific myocardial region (43). An other application of this principle was recently developed by Vogel et al (44). They measured absolute coronary blood flow with an angioplasty catheter and electrical impedance measurements induced by a 5% dextrose indicator bolus.

The principle of first-pass distribution was introduced by Sapirstein (45). If a diffusible indicator is infused into the arterial circulation, the concentration of the substance in an organ will depend upon the arterial concentration of the indicator, the organ extraction ratio of the indicator and organ blood flow (45). Thallium-201 scintigraphy is a widely used clinical application of this principle. Relative coronary blood flow can be assessed following the same basic principles with tracers labeled with positron emitters (36). This is a very promising technique that permits accurate and repeated measurements of regional coronary flow in awake humans (46). However, the technique is expensive and the resolution is limited to about 1-2 cm^2 (36).

The method of inert-substance washout was developed by Kety and Schmidt (47) for measuring cerebral blood flow. A modification of this technique can be used in the coronary circulation (48). A major advantage of this technique is that it can be used in humans to measure flow per gram of tissue in the left ventricle. Grines et al (49) developed an application of this method that measures absolute regional coronary blood

flow. Hydrogen saturated saline is infused into a coronary artery. The hydrogen is detected during washout in the pulmonary artery by means of the voltage response of a platium-tipped electrode and volume flow is calculated according to the Kety-Schmidt principle (47). This technique is potentially easily applicable during coronary angioplasty (50). The major disadvantages seem that subselective cannulation of the coronary arteries is necessary and that volume flows above normal are substantially underestimated (49).

Recently, Doppler methods have been developed that allow the assessment of coronary flow and/or flow reserve of individual coronary arteries. Ultrasonic flow meters measure phasic and mean coronary blood flow velocity using the Doppler effect. A piezoelectric crystal for the emission and detection of ultrasonic sound waves can be mounted in a suction cup, and placed on epicardial coronary vessels at the time of cardiac surgery (17). A piezoelectric crystal can also be mounted on the tip of an angiography catheter or on an angioplasty balloon catheter (51,52), to assess coronary blood flow velocity and vasodilatory reserve during diagnostic or interventional catheterization. Currently, ultrasonic probes provide the only available means of assessing phasic coronary blood flow velocity in the coronary arteries in awake humans. The principal disadvantages of the technique are that absolute flow cannot be determined without knowledge of the angle between blood column and crystal and the cross-sectional area of the coronary artery (36), and that the introduction of a Doppler catheter into a coronary artery is not without risk (51).

Radiographic techniques

Selective coronary angiography is the standard means for obtaining anatomic information and is the most important tool for clinical decision making used by the physician caring for patients with coronary artery disease. Several approaches have been developed to assess coronary blood flow with radiographic techniques during cardiac catheterization and coronary angiography (53). Rutishauser et al (54) measured the density of contrast medium at two sequential locations in a proximal coronary artery to measure the transit time. After determination of the volume of the arterial segment between the two points, volume flow can be calculated. Spiller et al (55) reported good correlations between a similar approach using contrast wave-front transit time for diastolic and systolic coronary blood flow and data obtained by electromagnetic flow meters. The major limitation of this approach is that it cannot be applied to branching and/or circuitous arterial segments which are often present in the coronary arterial system of humans, and that multiple radiographic projections must be used if the arterial segment cannot be positioned parallel to

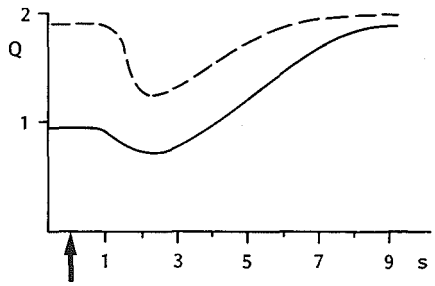

Figure 3A
Sequence of events following injection of radiographic contrast in a coronary artery during baseline (——) and already hyperemic (—-) coronary blood flow, as described by Hodgson et al (59) and Cusma et al (61). Q = volume flow, the arrow marks the timing of the contrast injections.

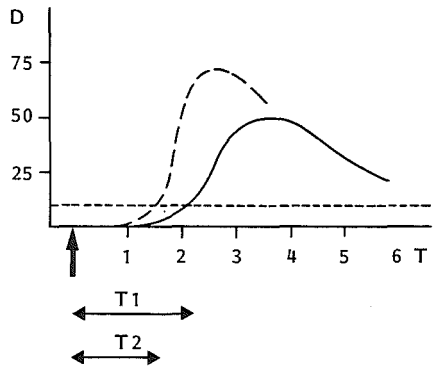

Figure 3B
In the myocardial region of interest a baseline (——) and hyperemic (—-) time-density curve can be generated with the use of digital subtraction of selected end-diastolic cineframes. After application of a fixed density threshold a myocardial contrast appearance time can be measured a baseline (T1) and hyperemia (T2). The maximal contrast density is also measured at baseline (D1) and hyperemia (D2). Coronary flow reserve (CFR) can then be calculated according to the equation:

$$CFR = \frac{Q(\text{—-})}{Q(\text{——})} = \frac{D_2}{T_2} : \frac{D_1}{T_1} = 2$$

the plane of the image intensifier. An indicator dilution video densitometric method was developed by Foerster et al (56) and was recently validated by Nissen et al (57). However, subselective injection of contrast medium is necessary and streaming or reflux of the contrast medium must be prevented.

The fundamental problem with all radiographic techniques is that contrast media cannot be used to measure coronary blood flow by the traditional methodological approaches (53). An essential prerequisite of indicator dilution (Stewart-Hamilton), inert substance washout (Kety-Schmidt), or first-pass distribution (Sapirstein) techniques is that the indicator substance does not affect the flow being measured. Unfortunately, radiographic contrast media have substantial vascular effects (49), although nonionic media may disturb blood flow less than ionic agents (53). Hodgson et al (59) studied the effects of a bolus injection of contrast medium on baseline and hyperemic coronary blood flow. They found that the ratio of baseline to hyperemic flow is approximately constant during the first five seconds after contrast injection. This is illustrated in figure 3A. Using ECG gated power injection of a contrast agent at a rate that is presumed to be sufficiently rapid to achieve complete replacement of blood with contrast, a mask mode subtraction technique was developed that determines myocardial time-density curves before and during coronary vasodilation before the vascular effects of the contrast medium disturb the ratio between resting and hyperemic coronary blood flow. This approach has been validated in the animal laboratory by Hodgson et al (60) and Cusma et al (61), and is illustrated in figure 3B. The major advantage of this technique is that it can be performed during routine cardiac catheterization, without increasing the risk to the patient (18,53,62). Although at present coronary flow reserve can only be assessed in a two dimensional projection of the myocardium, developments towards three dimensional reconstruction from biplane angiographic views are in progress (63).

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CHAPTER 2: PAPAVERINE: THE IDEAL CORONARY VASODILATOR FOR INVESTIGATING CORONARY FLOW RESERVE? A STUDY OF TIMING, MAGNITUDE, REPRODUCIBILITY AND SAFETY OF THE CORONARY HYPEREMIC RESPONSE AFTER INTRACORONARY PAPAVERINE.

Summary

A potent, short-acting vasodilator that induces a maximal hyperemic response of the coronary vascular bed is needed to determine coronary flow reserve. In 12 patients, we measured coronary sinus blood flow by thermodilution over a period of 2 min during which a bolus of 10 mg papaverine was given into the left main coronary artery. This was repeated after 5 min to assess the reproducibility of the changes. The maximal hyperemic response lasted from 24 till 37 sec after papaverine administration. There was no significant difference between the two consecutive hyperemic responses.(Student's t-test for paired observations).The mean difference between first and second hyperemic responses at 30 sec was 7.0% (SD ± 6.2%).

In conclusion, 10 mg of intracoronary papaverine is a short-lasting and reproducible means of inducing a maximal hyperemic response in the coronary vascular bed and therefore appears to be the ideal agent for investigating coronary flow reserve.

Introduction

The concept of coronary flow reserve is essential in understanding the physiological significance of obstructive coronary artery disease (1,2). The recent development of methods such as digital subtraction cine angiography or subselective coronary artery blood flow velocity measurements using a Doppler catheter have made the assessment of regional coronary flow possible during routine cardiac catheterization (3,4). Coronary reactive hyperemia defined as the ratio of maximal coronary blood flow to resting flow can be used as a measurement of coronary flow reserve. In order to detect a limitation in coronary flow reserve due to an obstruction in a major epicardial coronary artery, measurements should be obtained when distal coronary resistance has been minimized by dilating this arteriolar bed pharmacologically (1). Since the advent of interventional catheterization, multiple assessment of coronary flow reserve is mandatory, for instance to evaluate the effect of an intervention or to assess coronary flow reserve in different myocardial regions (3). Long-acting vasodilators, such as dipyridamol not only make multiple assessments of the hyperemic response impossible but may also give undesirable side effects such as a long-lasting endo-epicardial redistribution of coronary blood flow with a concomitant increase in oxygen consumption (5), thereby inducing

ischemia and angina pectoris.

Therefore, a potent short-acting vasodilator that will induce a maximal hyperemic response is needed to facilitate an accurate and reproducible means of determinating coronary flow reserve. When digital subtraction cine-angiography is used to measure coronary flow reserve, angiograms during maximal hyperemia must be compared with baseline angiograms. Timing of the peak hyperemic effect is then of crucial importance. We studied reproducibility, timing and duration of the coronary hyperemic response after intracoronary papaverine by measuring coronary sinus blood flow with thermodilution.

Patients and methods

Twelve patients who underwent cardiac catheterization and coronary angiography for clinical indications, were studied after informed consent was obtained. The patients were studied without sedation, following overnight fasting. All medication was withheld on the day of the catheterization. A thermodilution catheter (Webster laboratories) was introduced after percutaneous puncture of the femoral vein or after cutdown of a right antecubital vein and positioned in the coronary sinus. Catheter position was verified by contrast injection. Coronary sinus blood flow was measured according to the thermodilution technique by infusing saline 50 ml/min with a Medrad mark IV infusion pump. The temperature of the coronary sinus blood was measured at 25/sec from which flow was calculated (ml/min) and averaged for 5 sec intervals (see fig 1a and 1b). In each patient a stable position of the catheter was assured by fluoroscopy and a stable baseline measurement was recorded. Thereafter the coronary catheter was inserted after percutaneous puncture of the femoral artery or after cutdown of the brachial artery. The tip was positioned into the ostium of the left main coronary artery under fluoroscopy. Coronary sinus blood flow was measured continuously over 2 min during which a bolus of 10 mg papaverine was given into the left main coronary artery, to record the timing and magnitude of the coronary hyperemic response. This was repeated after 5 min to assess reproducibility of the changes. Reproducibility was assessed by comparing for first and second injections of papaverine the ratio of coronary sinus blood flow 30 sec after intracoronary papaverine to baseline flow.

The spontaneous variations of all 5 sec intervals of the baseline flows were used to calculate the standard deviation of the mean baseline flow expressed in percentage. This standard deviation was used to define the duration of the plateau phase of the maximal hyperemic response. Systemic arterial pressure and heart rate were recorded continuously. Thereafter, the diagnostic study was completed.

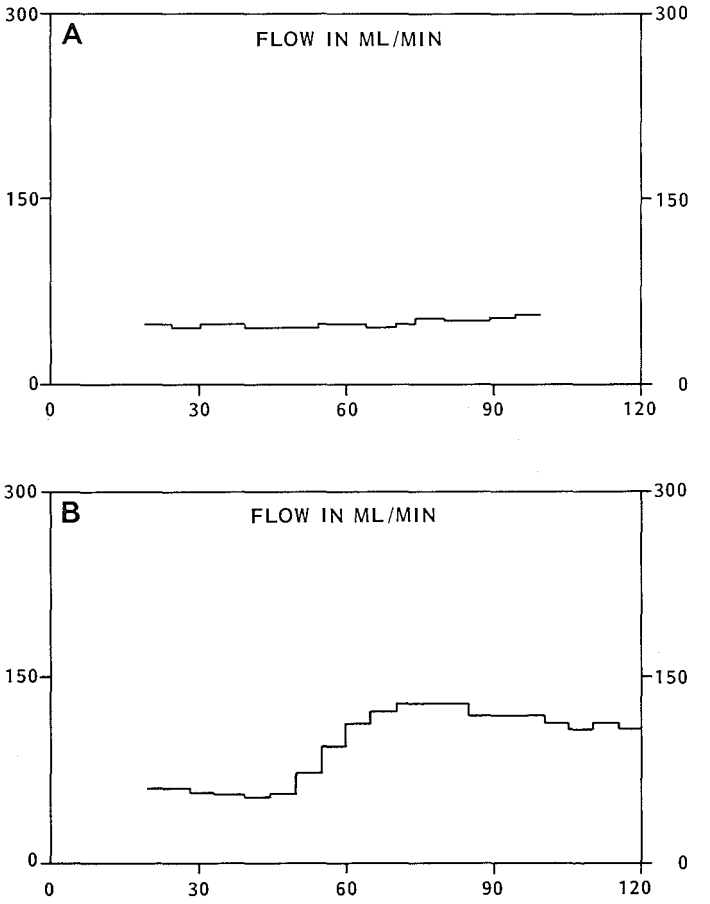

Figure 1
Coronary sinus blood flow measurement with thermodilution.
a. Stable baseline recording.
b. Recording during a 10 mg bolus injection of papaverine into the left main coronary artery.

Table I: Patient characteristics.

Pat	age	sex	CAG	LVEF
1	55	m	0	44%
2	64	m	0	59%
3	60	m	1	64%
4	57	f	0	66%
5	63	m	2	65%
6	67	m	2	50%
7	59	m	1	67%
8	62	f	1	76%
9	48	m	3	66%
10	61	m	3	65%
11	61	m	1	70%
12	52	m	0	66%

Abbreviations: CAG = coronary arteriogram, number of vessels with lesions of more than 50%; LVEF = left ventricular ejection fraction.

Results:

Patient characteristics

The patient characteristics are shown in table I. The mean age of the patients was 57.4 years (range 48-67), 10 were male, 2 female. Four patients had no angiographic significant coronary artery disease (greater than 50% diameter stenosis), 4 patients had one-vessel disease, 2 patients had two-vessel disease and 2 patients had three vessel disease. The mean left ventricular ejection fraction was 67% (range 44 - 76%).

Timing of the coronary hyperemic response

The average plateau phase of the maximal hyperemic response was reached after 24 sec and lasted up to 37 sec after the intracoronary injection of papaverine (fig 2). The peak effect of individual intracoronary injections was reached after a mean time of 31.3 sec, (standard deviation ± 3.4 sec). Peak hyperemia following each individual papaverine injection (n = 24) was within the defined plateau-phase of the maximal hyperemic response.

Magnitude of the coronary hyperemic response

The mean baseline coronary sinus blood flow was 105.7 (range 71 - 175) ml/min before the first papaverine injection and rose to a mean peak value of 194.4 (range 130 - 325) ml/min. The mean baseline coronary sinus blood flow was 109.6 (range 69 - 180) ml/min immediately before the second papa-

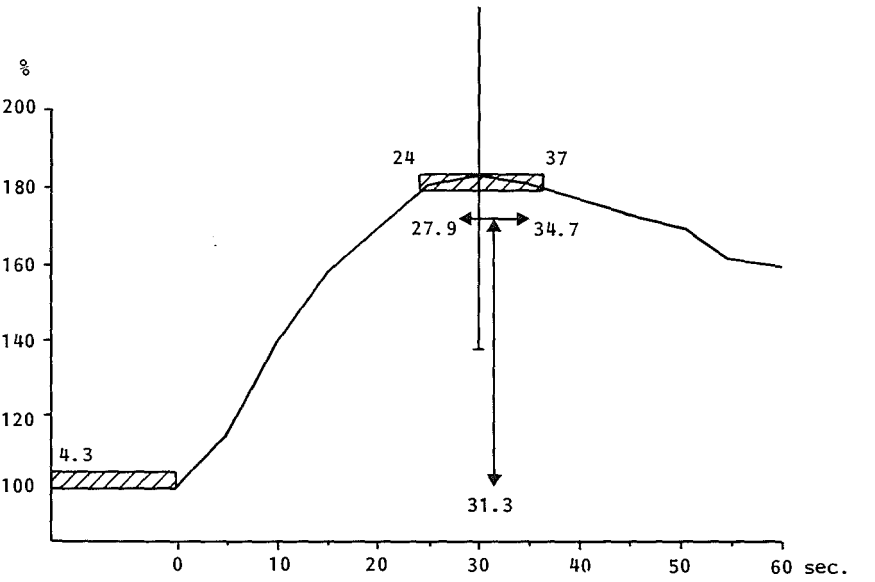

Figure 2
Timing of the average coronary hyperemic response of all 24 papaverine injections. The shaded area is 1 SD calculated from the spontaneous variations in the baseline recordings. The plateau phase of the hyperemic response lasted from 24 till 37 sec after the intracoronary injection of papaverine. The peak effect of the injections was reached after a mean time of 31.3 sec, (standard deviation $\pm$ 3.4 sec).

Table 2: Reproducibility of changes in coronary sinus blood flow after intracoronary papaverine.

Pat	first pap injection				second pap injection				
	Ao1	A	B	C	Ao2	D	E	F	G
1	90	102	173	1.70	92	106	174	1.64	3.5
2	103	71	132	1.86	105	75	126	1.68	9.7
3	91	91	181	1.99	85	83	153	1.84	7.5
4	106	78	219	2.81	107	79	223	2.82	0.3
5	83	94	159	1.69	79	95	177	1.86	10.0
6	82	117	174	1.49	83	119	184	1.55	4.0
7	89	110	335	3.05	90	164	398	2.43	20.3
8	106	90	144	1.60	104	115	185	1.61	0.6
9	105	175	252	1.44	101	180	251	1.39	3.5
10	96	99	140	1.41	98	69	97	1.41	0.0
11	82	86	130	1.51	82	76	130	1.71	13.2
12	110	155	294	1.90	106	154	259	1.68	11.6

Abbreviations: Pat = patient; pap = papaverine; Ao1 = mean aortic pressure during the first papaverine injection; A = baseline measurement; B = measurement 30 sec after intracoronary pap; C = ratio of B/A; Ao2 = mean aortic pressure during the second papaverine injection; D = second baseline measurement; E = measurement 30 sec after intracoronary pap; F = ratio of E/D; G = difference between C and F in percentage, calculated as (C-F)/C. Mean difference: 7.0% with a standard deviation of 6.2%.

verine injection and rose to a mean peak value of 196.1 (range 97 - 398) ml/min. In figure 3a the percentage increase in coronary sinus blood flow (mean and standard deviation) is shown after all papaverine injections (n=24). Coronary vascular resistance was calculated as systemic arterial pressure divided by coronary sinus blood flow and is shown in figure 3d.

Reproducibility of the coronary hyperemic response

In figure 4 the percentage increase in coronary sinus blood flow after the first papaverine injection is plotted versus the percentage increase in coronary sinus blood flow after the second papaverine injection; linear regression showed an r-value of 0.92. There was no significant difference (Student's t-test for paired observations) in magnitude or timing of the hyperemic response between first and second injections or in baseline coronary sinus blood flows. The responses of individual patients to first and second injections are shown in figure 5. The difference between the first and the second hyperemic response, 30 sec after papaverine

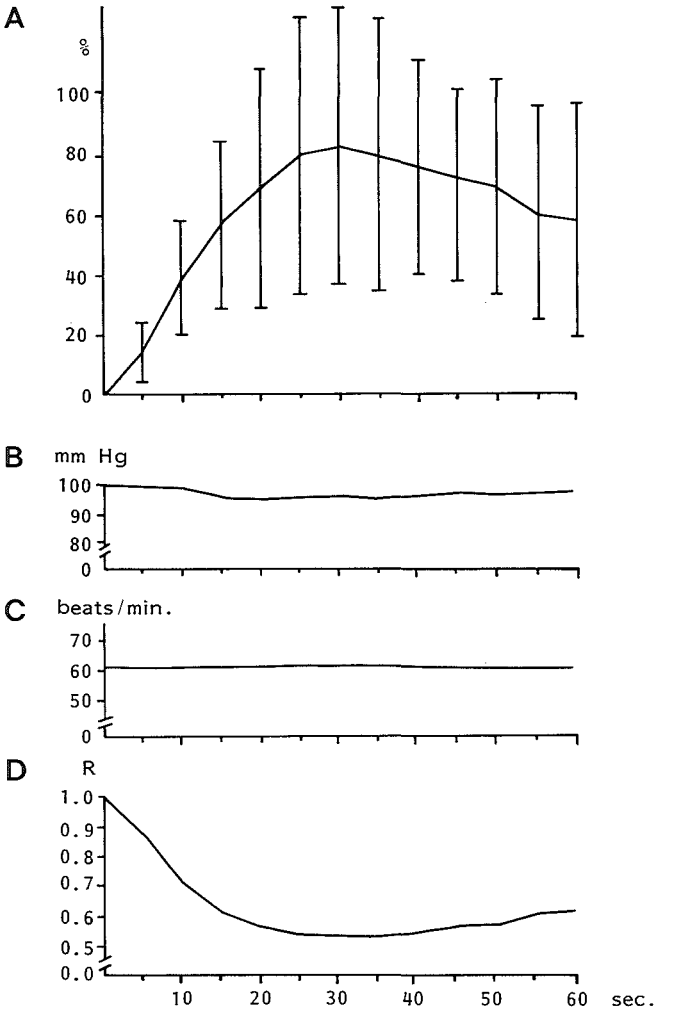

Figure 3
a. Percentage increase in coronary sinus blood flow (mean and standard deviation).
b. Mean arterial pressure.
c. Heart rate.
d. Coronary vascular resistance calculated as systemic pressure divided by coronary sinus blood flow.

injection was calculated as a percentage of the coronary sinus blood flow (see Table 2). The average difference was 7.0% with a SD of 6.2%.

Safety

There was no significant effect of the intracoronary given papaverine on either systemic arterial pressure or heart rate (fig 3b and c). No patient reported angina pectoris despite striking changes in the repolarization phase of the surface electrocardiogram (6) and no complications occurred during the procedure.

Discussion

Visual interpretation of the coronary angiogram is a poor means of predicting the physiological importance of obstructive coronary artery disease (7). Computer-based quantitative analysis of the coronary angiogram has solved, in sofar as currently possible, the problems of high interobserver and intraobserver variability and makes calculation possible of hydrodynamic parameters of the coronary artery lesion that are correlated with translesional pressure gradient and thallium perfusion scintigraphy (8-11). Even so, the relation between the quantitatively analysed coronary artery lesion and its hydrodynamic repercussion is not fully understood and methods that assess the limitation in coronary flow reserve due to an obstructive lesion are therefore needed. Various ways to study coronary flow reserve have been described (1-4,12). Induction of a hyperemic response is an essential part of all these methods. The recent description of a digital angiographic technique to measure relative coronary blood flow makes assessment of coronary flow reserve during routine cardiac catheterization possible (4). A safe, reproducible way of inducing a maximal hyperemic response is therefore all the more imperative (2).

Assessment of coronary hyperemic response with thermodilution measurements of coronary sinus blood flow.

A wide range of values for the coronary flow reserve of normal coronary arteries is reported, depending on the vasodilator used and the measuring technique (3,12-16). The carefully validated studies with a Doppler-catheter suggest that the maximal coronary blood flow of a normal coronary artery is 4 to 6 times resting flow (3). The thermodilution measurements of coronary sinus blood flow have shown the highest flow increment reported in the literature as hyperemic flow 3 times resting flow, which was indeed observed in some of our patients (17). With thermodilution, Foult et al studied the coronary hyperemic response following a coronary angiogram

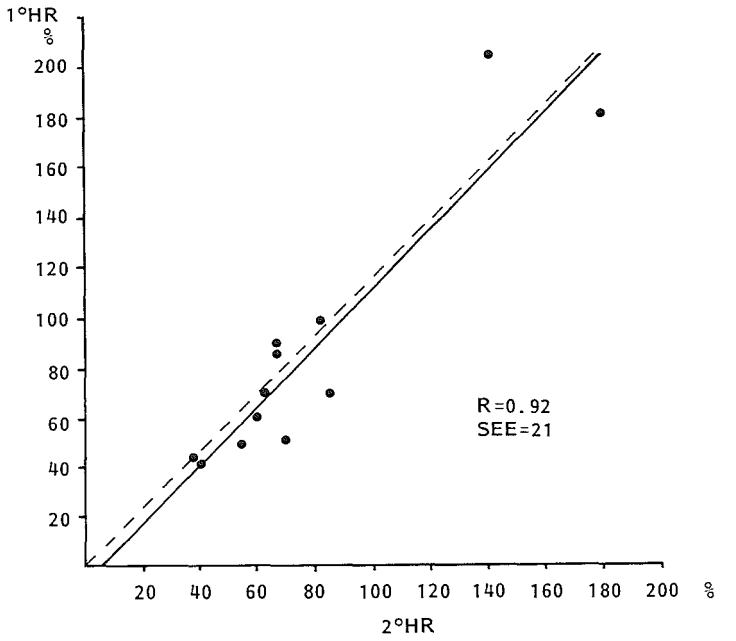

Figure 4
Reproducibility of the coronary hyperemic response after intracoronary papaverine.
1°HR = first hyperemic response, 2°HR = second hyperemic response.

with a hyperosmolar ionic contrast medium and measured a ratio of maximal flow to resting flow of only 2, for patients with normal coronary arteries. However, there was a significant relation between the coronary hyperemic response and the extent of the coronary artery disease (15). Our results (compare table 1 and 2) show a similar trend. Since we were not specifically interested in the absolute changes in flow but especially in timing and reproducibility of the flow changes, we felt that thermodilution, which gives continuous recordings and is easy to repeat, was in this particular instance an adequate technique of investigation. The frequency response of the measurement is sufficient to measure changes in flow which occur within 2 to 3 sec(1,18,19).

Vasodilator agents

The most widespread used vasodilator agents are dipyridamol and hyperosmolar ionic contrast media(1,3-5,7). An intravenous infusion of dipyridamol in adequate dosage results in a maximal coronary vasodilation, but its use has several disadvantages (16). First, its long-lasting effect makes repeated assessment of the hyperemic response of a coronary vascular bed or assessment of different coronary vascular beds during the same procedure impossible (3). Second, the long-lasting endo-epicardial redistribution of coronary blood flow in conjunction with an increase in myocardial oxygen consumption (5) may induce ischemia which can only be terminated by the intravenous administration of aminophylline (16). Hyperosmolar ionic contrast media do not produce maximal arteriolar vasodilation (2,6,13). Bookstein and Higgins have shown in dogs that the coronary hyperemic response after a bolus injection into a coronary artery of adenosine-triphosphate or papaverine is of the same magnitude as after a 15 sec occlusion of the coronary artery (6). Hodgson and Williams compared in human beings, the coronary hyperemia induced by a hyperosmolar ionic contrast medium with papaverine and observed a twofold greater hyperemic response after papaverine (13).

The exact dosis of intracoronary papaverine needed to produce maximal coronary vasodilation has recently been established (14). Wilson and White compared the coronary hyperemic response after 4,8,12 and 16 mg intracoronary papaverine and reported a maximal hyperemic response after 8 mg in most coronary arteries and after 12 mg in all coronary arteries. Papaverine at this dosage (8-12 mg) produced a response equal to intravenous infusion of dipyridamol in a dosage of 0.56 to 0.84 mg/kg. The coronary blood flow velocity after papaverine and dipyridamol was 4.8 times resting coronary blood flow velocity (14).

In conclusion, this study shows that reproducibility of the coronary hyperemic response after intracoronary papaverine is excellent. Timing of the peak effect is crucial if a

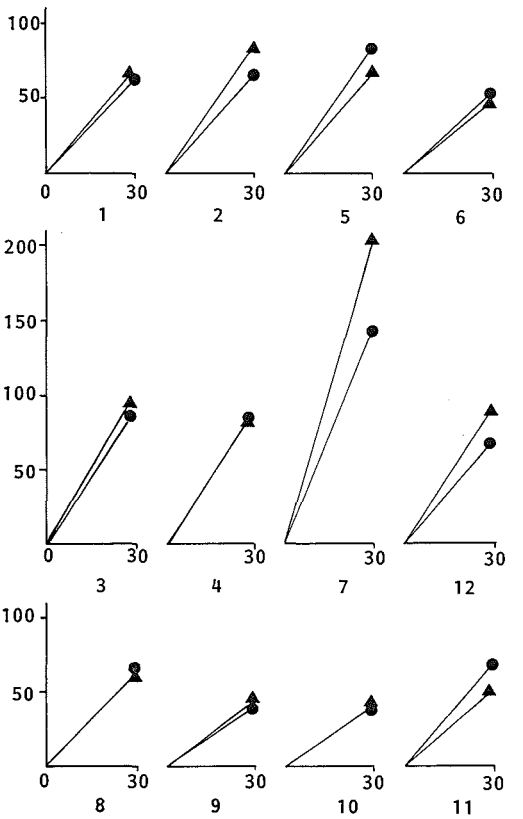

Figure 5
Responses of individual patients to first (▲) and second (●) injections of papaverine. Numbers 1-12 correspond to patients 1-12 in table 1 and 2. The ordinates present percentage increase of coronary sinus blood flow. On the abscissas: 0 = before papaverine injection, 30 = 30 sec after papaverine injection.

digital angiographic technique is to be used because angiograms during maximal hyperemia have to be compared with baseline angiograms. We measured the time interval after intracoronary papaverine during which hyperemia is maximal, and showed the practical feasibility of making an angiogram during maximal arteriolar vasodilation. The effect of the intracoronary papaverine disappears completely within 5 min so that multiple assessments of coronary flow reserve can be undertaken during the same procedure.

Conclusions

Ten mg intracoronary papaverine is a safe and reproducible means of inducing a strong hyperemic response in the coronary circulation with a peak effect lasting from 24 till 37 sec and a duration of action less than 5 min, and therefore seems an ideal agent for investigating coronary flow reserve.

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CHAPTER 3: DOES INTRACORONARY PAPAVERINE DILATE EPICARDIAL CORONARY ARTERIES? IMPLICATIONS FOR THE ASSESSMENT OF CORONARY FLOW RESERVE.

Summary

Intracoronary papaverine is used as a means to induce a strong and short-lasting hyperemia in several recently developed methods to measure coronary flow reserve. Changes in stenosis geometry due to papaverine would influence the measured coronary flow reserve. Therefore, we investigated the influence of intracoronary papaverine on stenosis geometry with quantitative analysis of the coronary angiogram and assessed the influence of papaverine on pressure-flow characteristics of the stenosis and coronary flow reserve. The cross-sectional area (mean ± SD) of the stenoses increased 18 ± 7% after papaverine. The normal proximal and distal parts of the coronary artery dilated 5 ± 2% after papaverine. This results in a decrease of the calculated pressure drop over the stenosis varying from 20 to 30%. Coronary flow reserve of a flow-limiting epicardial stenosis is overestimated by 16% when papaverine is used to induce hyperemia. These papaverine induced changes can nevertheless be circumvented by maximal vasodilation of the major epicardial coronary artery with 3 mg intracoronary isosorbidedinitrate prior to the investigation of the coronary flow reserve with papaverine.

Introduction

Recently several methods have been developed to measure coronary flow reserve (1,2) and to calculate pressure-flow characteristics of a coronary stenosis (3). Induction of a maximal coronary hyperemia is an essential part of these methods. Intracoronary papaverine induces a short-lasting, reproducible and maximal hyperemic response in the coronary circulation, so this agent has been proposed as an ideal vasodilator for these investigations (4,5). Changes in geometry of epicardial stenoses from intracoronary administration of papaverine would influence the viscous (Poiseuille) and turbulent resistance and consequently alter the pressure-flow characteristics of the coronary stenoses, and the measured coronary flow reserve (6). The goal of the present investigation was to assess the influence of intracoronary papaverine on coronary arterial dimensions and pressure-flow characteristics and to establish whether prior intracoronary administration of a vasodilator of the epicardial coronary artery (isosorbidedinitrate) could prevent these papaverine induced alterations.

Patients and Methods

Coronary angiography was performed in 11 patients as part of an ongoing study of restenosis after percutaneous transluminal coronary angioplasty. Selection of these patients was based on the occurrence of restenosis to some extent. Informed consent was obtained for the additional investigation. All patients were studied without premedication, but their standard postangioplasty medical treatment consisting of aspirin 500 mg/day, and nifedipine 60 mg/day was continued. No patient received oral or intravenous nitrates. No patient had clinical evidence for vasospastic angina.

Angiographic procedure

Coronary angiography was performed with the Judkins technique. The angiographic projection was selected such that the stenosis, and the proximal and distal parts of the coronary artery were clearly visible and were parallel to the image intensifier. Hand-injections were made at a rate and volume sufficient to cause back-flow of the contrast agent into the aorta. Therefore, essentially all blood in the epicardial coronary arteries was replaced by contrast agent. Iopamidol, a nonionic agent was injected at 37°C. At this temperature it has a viscosity of 9.4 cP, the osmolality is 0.796 osm/kg and the iodine content is 370 mg/ml. For this investigation 30 to 40 ml of this agent was used per patient. Consequently, the maximal change in blood viscosity induced by this procedure is only 2%. Therefore blood viscosity was assumed to be constant. A total of four angiograms were obtained in the selected angiographic view. First, a baseline angiogram was made. A second angiogram was performed 30 sec after a bolus injection of 12.5 mg papaverine into the coronary artery. After a pause of 5 min, 3 mg intracoronary isosorbidedinitrate was administered and 30 sec later a third angiogram was performed. Finally, immediately following this third angiogram, 12.5 mg papaverine was given intracoronary and the last angiogram of the study was made 30 sec later.

Quantitative coronary cineangiography

The procedures for the quantitative assessment of coronary arterial dimensions from 35 mm cinefilm have been implemented on the computer-based Cardiovascular Angiography Analysis System (CAAS) and have been described extensively (7,8). For the assessment of the absolute and relative dimensions of selected coronary segments with the CAAS, the boundaries of a selected coronary segment are detected automatically from optically magnified and video-digitized regions of interest of an end-diastolic cineframe. Calibration of the diameter data in absolute values (mm) is achieved by detecting

the boundaries of a section of the contrast catheter and comparing the computed mean diameter in pixels with the known size in millimeters. Each catheter is measured individually with a micrometer to determine its true size (9). To correct the contour positions of the arterial and catheter segments for the pincushion distortion of the image intensifier, a correction vector is computed for each pixel based on a computer-processed cineframe of a centimeter grid placed against the input screen of the image intensifier (8).
The procedure for contour detection requires the user to indicate a number of center positions with the writing tablet from the proximal to the distal end of the selected arterial segment such that the straight lines connecting these points are within the artery. The contours of the vessel are detected on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions. From the detected contours the diameter function is determined in absolute millimeters.

Since the functional significance of a stenosis is also related to the expected normal cross-sectional area of the vessel at the point of the obstruction, we use a computer estimation of the original arterial dimensions at the site of the obstruction to define the reference region (interpolated reference). A representative example with the detected contours and the reconstructed reference contours is shown in figure 1. The computed reference diameter function allows for tapering of the vessel. The interpolated percentage area stenosis (AS) is then computed by comparing the squared minimal diameter value at the obstruction with the squared value of the reference diameter function at this position, thereby assuming circular cross-section:

$$AS = \left(1 - (\text{minimal diameter}/\text{reference diameter})^2\right) \times 100\%.$$

The estimation of the length of the obstruction is made on the basis of a curvature analysis of the diameter function.

The pressure-drop (PD) over the stenosis for coronary flows of 1,2,3,4 and 5 ml/sec is calculated using the following hemodynamic equation:

$$PD = (25.1uL/MLCA^2)\,Q + d/0.266\,(1/MLCA - 1/NA)^2\,Q^2$$

or $PD = fQ + sQ^2$
where u = blood viscosity, L = stenosis length, NA = normal cross-sectional area, MLCA = minimal luminal cross-sectional area, Q = volume flow, d = blood density, f = coefficient of viscous resistance (Poiseuille), and s = coefficient of turbulent resistance or exit separation (3,10,11).

Table 1: Clinical characteristics (n = 11).

Mean age (range)	: 57 (41-71)
Sex	: 9 male, 2 female
0	: 1
1	: 8
2	: 2
LVEF more than 50%	: 11

0, 1 and 2 = the number of vessels per patient with an area stenosis in excess of 50%, LVEF = left ventricular ejection fraction.

Statistical methods:

Comparisons between data were carried out with the Student's t-test for paired observations.

Results

The clinical characteristics of the patients are shown in table 1. The mean age of the 11 patients was 57 years (range 41-71 year). Nine patients were male. Eight patients had single vessel disease, two patients had two-vessel disease and one patient had no significant coronary artery disease (area stenosis in excess of 50%). All patients had a normal left ventricular ejection fraction. Eleven discrete proximal stenoses were analyzed quantitatively (table 2). When compared to the baseline measurements 12.5 mg papaverine given intracoronary induced a 5 ± 2% increase in cross-sectional area of the normal proximal and distal part of the coronary artery and this resulted in an 5 ± 2% increase in interpolated reference area. The cross-sectional area of the stenoses increased from 2.0 ± 1.1 mm^2 to 2.3 ± 0.9 mm^2 after intracoronary papaverine (18 ± 7% increase). After the first papaverine injection percentage area stenoses decreased from 72 ± 11% to 69 ± 10% because of the increase in absolute terms in stenosis area. After isosorbidedinitrate the proximal and distal parts of the coronary artery dilated respectively by 10 ± 4 and 10 ± 3%. The increase of the stenosis area after isosorbidedinitrate was of the same magnitude as after papaverine. Since isosorbidedinitrate changed the stenosis area and the interpolated reference area to the same extent, the relative percentage area stenosis was comparable to baseline (72 ± 11% versus 71 ± 10%). Given after isosorbidedinitrate intracoronary papaverine induced no changes in proximal and distal cross-sectional area, cross-sectional stenosis area, or relative percentage area stenosis.

The hemodynamic consequences of these vasodilator induced

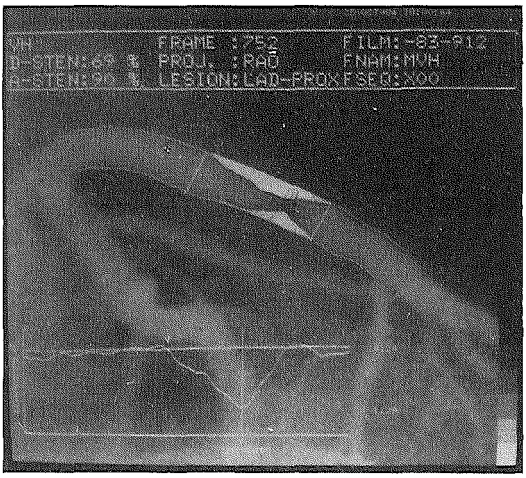

Figure 1
Detected contours for a representative stenosis of the left anterior descending coronary artery. The normal size of the artery over the obstruction has been estimated by the interpolated method.
The diameter function is shown on the bottom.

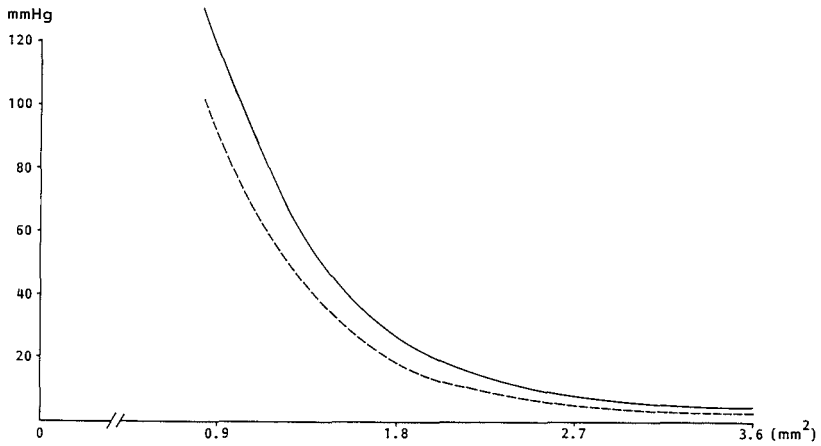

Figure 2
Relation between the pressure drop over the stenosis at a coronary flow of 5 ml/sec at baseline (——) and after papaverine (----) as a function of baseline stenosis severity.

Table 2: Changes in stenosis geometry after coronary vasodilatation (n =11)

	cross-sectional area (mm^2)			stenosis area	
Angio	proximal	interp. ref.	distal	mm^2	%
1°					
baseline	8.3±3.1	7.2±2.8	6.0±2.9	2.0±1.1	72±11
2°					
pap	8.7±3.1	7.6±3.0	6.3±2.9	2.3±0.9	69±10
% change compared to 1° angio	5±2*	5±2*	5±2*	18±7*	4±3*
3°					
ISDN	9.6±3.5	8.4±3.3	7.0±3.2	2.4±1.0	71±10
% change compared to 1° angio	16±7*	17±7*	17±6*	20±8*	2±2NS
% change compared to 2° angio	10±4*	11±4*	10±3*	3±2NS	3±2NS
ISDN + papa	9.6±3.2	8.3±3.1	6.9±3.0	2.3±1.0	72±11
% change compared to 3° angio	0±1NS	0±2NS	0±2NS	-3±2NS	1±2NS

Results are expressed as mean ± SD, * = p less than 0.05, interp.ref. = interpolated reference, pap = papaverine, ISDN = isosorbidedinitrate, ic = intracoronary, NS = not significant, angio = angiogram.

changes in coronary arterial dimensions are characterized by the alterations in viscous (Poiseuille) resistance and separation resistance as well as the consequent change in pressure drop over the stenosis. Therefore, we calculated the viscous and separation coefficient and the resulting pressure drop over the stenosis for a physiological range of coronary blood flows (table 3). The magnitude of the resulting change in pressure drop over the stenosis was critically dependent on the baseline severity of the coronary stenosis. The patient with the most severe (86%) percentage area stenosis and the patient with the mildest (48%) percentage area stenosis are shown in table 4 as examples of this phenomenon. The relation between the pressure drop over the stenosis at a coronary flow of 5 ml/sec at baseline and after papaverine as a function of baseline stenosis severity is shown in figure 2. The reduction in pressure drop from papaverine ranged from 20-30%. The rela-

tive contribution of the viscous and separation resistance to the pressure drop over the stenosis is a function of the coronary blood flow. With coronary blood flows of 1-2 ml/sec the viscous resistance is the dominant factor whereas with higher coronary blood flows (4-5 ml/sec) viscous and separation resistances are quantitatively comparable (see fig.3). After both papaverine and isosorbidedinitrate this relation remained essentially unchanged.

The total resistance over a coronary stenosis depends mainly on three geometric factors: cross-sectional area of the stenosis, normal area of the coronary artery, and length of the stenotic lesion. The length of the stenotic lesions (mean ± SD: 7.1 ± 1.9 mm) did not change significantly after papaverine and/or isosorbidedinitrate. The vasodilator induced reduction of the viscous resistance is due to the increase in cross-sectional area of the stenosis. The vasodilator induced changes in separation resistance are related to both the increase in normal distal area of the coronary artery and the increase in cross-sectional area of the stenosis (table 5). The increase in normal distal area of the coronary artery results in an augmention of the separation resistance. The increase in cross-sectional area of the stenosis results in a decrease of the separation resistance. This latter change is of greater magnitude, so the alteration in separation resistance stems predominantly from the increase in absolute stenosis area.

Discussion

The variability in quantitative measurements of various parameters of coronary arterial segments is reported in a previous paper from our laboratory (7). The mean difference between obstruction diameters of the stenoses from repeated angiographic studies is 0.0 with a standard deviation of the difference of 0.22 (mm). Therefore, this system of quantitative analysis allows for a reliable assessment of even very small changes in coronary artery dimensions due to interventions such as administration of vasodilating agents. Papaverine is an attractive vasodilator for studies of the coronary circulation in human beings, since it induces a maximal fall in coronary vascular resistance, has few side effects and has a duration of action less than 2 min (4). The exact dose of intracoronary papaverine needed to induce a maximal coronary vasodilation has recently been established. Wilson and White (5) compared the coronary hyperemic response after 4, 8, 12 and 16 mg intracoronary papaverine and reported a maximal hyperemic response after 8 or 12 mg.

However, using papaverine Gould and Kelley (6) described important changes in stenosis geometry in dogs and consequently important alterations in pressure-flow characteristics of the stenosis. Wilson and White (5) studied in human beings the

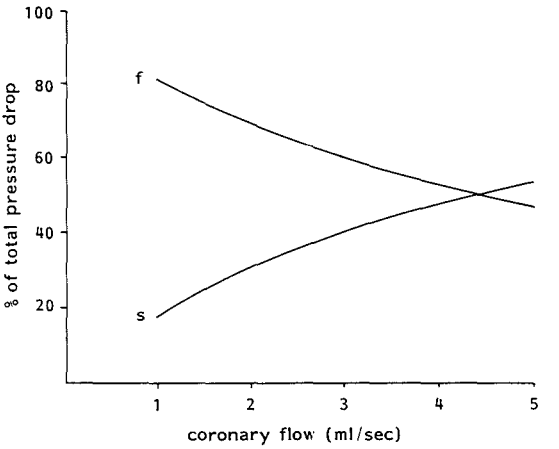

Figure 3.
Contribution to the stenosis resistance of viscous and separation resistances as a function of coronary blood flow.

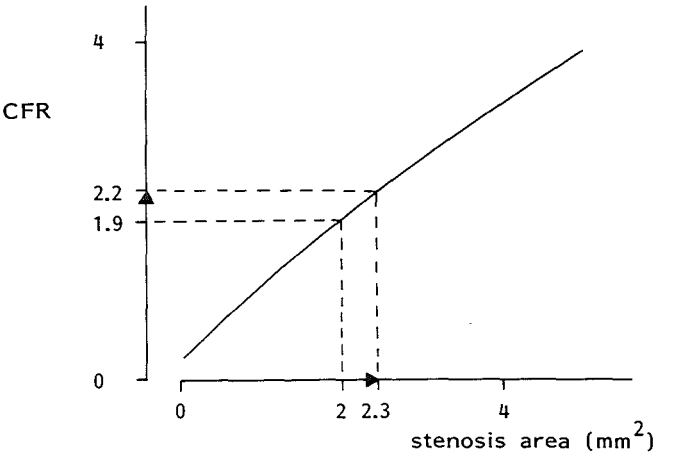

Figure 4
Influence of intracoronary papaverine on coronary flow reserve (CFR) as a result of the change in stenosis area. The relation between CFR and stenosis area was established in a previous study from our laboratory.
Papaverine induced an increase (mean value of 11 patients) in stenosis area from 2.0 to 2.3 mm^2 which corresponds to an increase in CFR from 1.9 to 2.2.

Table 3: Hemodynamic effects of altered stenosis geometry after vasodilation.

	baseline	pap	ISDN	ISDN + pap
f	1.88	1.38	1.31	1.38
s	0.42	0.29	0.28	0.30
PD1	2	2	2	2
2	5	4	4	4
3	9	7	7	7
4	14	10	10	11
5	20	14	14	15

pap = intracoronary papaverine; ISDN = intracoronary isosorbidedinitrate; PD = $fQ + sQ^2$, PD = pressure drop (mmHg) over the stenosis for coronary flows of 1,2,3,4, and 5 ml/sec; Q = flow in ml/sec; f = viscous coefficient (mmHg/ml per sec); s = separation coefficient ($mmHg/ml^2$ per sec^2). Results are mean values from 11 patients.

Table 4: Hemodynamic effects of altered stenosis geometry after vasodilation. A = patient with a 48% area stenosis; B = patient with a 86% area stenosis. Abbreviations as in table 3.

		baseline	pap	ISDN	ISDN + pap
A	f	0.58	0.45	0.44	0.45
	s	0.05	0.04	0.04	0.04
	PD5	4	3	3	3
B	f	9.3	7.1	7.0	7.1
	s	3.4	2.7	2.7	2.7
	PD5	130	102	104	103

Table 5: Hemodynamic effects of altered stenosis geometry after vasodilation. Relative contributions to the change in separation coefficient of the vasodilator induced increases in stenosis cross-sectional area (StA) and normal distal area (NDA).

	baseline	pap	ISDN	ISDN + pap
	($mmHg/ml^2$ per sec^2)	%	%	%
StA	0.42	- 40	- 45	- 40
NDA	0.42	+ 5	+ 14	+ 12
StA + NDA	0.42	- 31	- 33	- 29

impact of papaverine on coronary arterial dimensions and concluded that papaverine induced no significant alterations. In a previous study from our laboratory we reported that papaverine had a small but significant effect on stenosis geometry (1). However the patients of Wilson and White and the patients in our previous study were all treated with nitrates during the investigational procedure.

The ideal vasodilator should dilate exclusively the resistance vessels without affecting the geometry of the flow limiting stenosis in the epicardial coronary artery. Unfortunately as is indicated by our results, intracoronary papaverine influences both resistance vessel and epicardial coronary artery. The hyperemia induced by intracoronary papaverine cannot be solely attributed to a fall in arteriolar resistance but is partially due to changes in epicardial stenoses geometry. In other words, the methodological approaches using this drug affect the investigated phenomenon, namely the pressure-flow relationship of the flow limiting stenoses. In a previous study (1) from our laboratory we established the relation between coronary flow reserve and the stenosis area in patients with single vessel coronary artery disease. An increase in stenosis area from 2.0 to 2.3 mm^2 would correspond to an increase in coronary flow reserve from 1.9 to 2.2, that is, an 16% increase and therefore overestimation of the real coronary flow reserve (see fig. 4).

In accordance with our findings, Gould and Kelley (6) found important changes in stenoses geometry from papaverine in dogs. However, there are some qualitative differences between their results and ours, probably because of the different nature of the human coronary atherosclerotic lesion and stenoses produced by external constriction of normal coronary arteries in dogs. In our material the most significant change in stenosis geometry was the increase in cross-sectional stenosis area; in their material the change in cross-sectional area of the "normal" parts of the coronary artery was the predominant factor in the papaverine induced changes in pressure-flow relationship. The predominance of viscous resistance over separation resistance at "resting" coronary flows was similar in our patients and their material. However, at high coronary flows the separation resistance contributed about four times more to the pressure drop over the stenosis than the viscous resistance in the study of Gould and Kelley, whereas in our material, viscous and separation resistances were equally important at higher coronary flows. In these dogs, an isolated increase in "normal" areas without change in the externally constricted vessel lumen further augments the separation loss of pressure whereas the viscous resistance remains unchanged. In human atherosclerotic coronary artery lesions both separation and viscous resistance are significantly changed, because the human atherosclerotic coronary artery lesion still has a capability of dilating.

This is in accordance with the findings of Brown et al, who documented a significant increase in stenosis area and decrease in stenosis resistance after nitroglycerin in human atherosclerotic coronary arteries (12).

There are two potential mechanisms for this papaverine induced response. As reported by Holtz et al, drugs that cause coronary dilatation can be classified according to their mode of action (13). Some drugs have a direct effect on the arterial vasculature, for instance nitroglycerine and isosorbide dinitrate. On the other hand, adenosine and dipyridamol induce a flow-dependent, endothelium-mediated indirect effect by which even small variations in coronary blood flow may induce substantial alterations in coronary artery dimensions. The relative importance of these two mechanisms in the papaverine induced changes in stenosis geometry remain to be established.

Conclusion

In human beings with atherosclerotic coronary artery lesions, intracoronary papaverine induces significant increases in cross-sectional stenosis area and in normal proximal and distal areas of the coronary artery. As a consequence of these geometric changes, the viscous and separation resistance as well as the resulting pressure drop over the stenosis decrease considerably. The papaverine induced alterations in stenosis geometry and pressure-flow relationship are a serious methodological problem, since the magnitude of the changes is sufficient to influence measurements of coronary blood flow velocity or regional coronary flow reserve significantly. These papaverine induced changes can nevertheless be circumvented by maximal vasodilation of the major epicardial coronary arteries with 3 mg intracoronary isosorbidedinitrate prior to the investigation of the coronary flow reserve with papaverine.

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CHAPTER 4: VALUE AND LIMITATIONS OF INTRACORONARY ADENOSINE FOR THE ASSESSMENT OF CORONARY FLOW RESERVE.

Summary

An ideal coronary vasodilator for studying coronary flow reserve should rapidly produce a maximal hyperemic response, be short acting to permit repeated measurements and not alter systemic hemodynamics. We measured with a Doppler tip balloon catheter, in 12 patients before and/or after percutaneous transluminal coronary angioplasty the hyperemic response following 12.5 mg intracoronary papaverine and following gradually incremental bolus injections of intracoronary adenosine, starting from 0.05 mg until a maximal hyperemic response or side effects. The mean dose (± SD) of adenosine needed to produce maximal hyperemia was 0.23 (± 0.20 mg). Coronary blood flow velocity after adenosine increased to 1.6 ± 0.3 times resting coronary blood flow velocity, comparable in magnitude to the hyperemia following intracoronary papaverine.

The time from injection to peak effect after adenosine was 7.4 (SD± 2.2) s and after papaverine 26 (SD ± 7) s. Adenosine resulted in a bradyarrythmia in 3 patients. Intracoronary adenosine is a potent and very short acting vasodilator for studying coronary flow reserve but side effects and unpredictability of the dosage needed to produce maximal hyperemia, may limit its applicability.

Introduction

The concept of coronary flow reserve which is defined as the ratio of maximal coronary blood flow to resting flow is essential in understanding the physiological significance of coronary artery obstructions (1,2). The recent development of methods such as digital subtraction cineangiography or subselective coronary blood flow velocity measurements using a Doppler catheter have made the assessment of regional coronary blood flow possible during cardiac catheterization (3-5). In order to detect a limitation in coronary flow reserve due to an obstruction in a major epicardial coronary artery, measurements should be obtained when distal coronary resistance has been minimized by dilating the arteriolar bed pharmacologically (1). In order to evaluate the effect of an intervention, such as dilatation of an epicardial vessel, it is necessary to perform repeated measurements of coronary flow reserve (3,6,7). This can only be achieved by using a potent short-acting vasodilator that will induce a transient maximal hyperemic response. Intracoronary papaverine has been proposed as the ideal coronary vasodilator for studies of the coronary circulation (6,7). Intracoronary papaverine in a dosage of 8

to 12 mg induces a strong and reproducible hyperemia with a peak effect after 30 s and a total duration of action of less than 2 to 3 minutes. However, recent reports (8,9) suggest that papaverine may precipitate with certain radiographic contrast agents, and thus potentially cause serious complications. Adenosine has historically been described as the physiological vasodilator in the coronary circulation, although its definitive role has not yet been established. (12-14). Adenosine produces maximal coronary vasodilation when given intravenously, but intravenous administration results in profound alterations of heart rate and arterial pressure (15).

Therefore, we compared the coronary hyperemic response after gradually incremental doses of intracoronary adenosine (until maximal hyperemia or side effects) with the coronary hyperemic response after 12.5 mg intracoronary papaverine in 12 patients.

Patients and methods

Twelve patients who underwent elective coronary angioplasty for stable angina pectoris were studied after informed consent was obtained. An angioplasty guiding catheter (8 Fr, Angiomedics) was placed into the ostium of the left or right coronary artery. Coronary angiography was performed with Iopamidol a non-ionic contrast agent. A long guide wire was passed across the stenotic lesion to be dilated. An angioplasty balloon catheter with an end-mounted Doppler crystal was advanced over the guide wire, into the coronary artery (16). The studies with the two vasodilators were only performed when a reliable Doppler signal (3,17) was obtained and the clinical condition of the patients permitted the additional investigation (absence of signs of ischemia such as chest pain or ST-T segment abnormalities, in the presence of stable systemic hemodynamics). In 3 patients the investigation was performed before the dilatation of the coronary stenosis, in 6 patients after the dilatation and in 3 patients measurements were obtained before and after the angioplasty.

After recording of a stable baseline coronary blood flow velocity, a bolus injection of 12.5 mg papaverine was given through the guiding catheter and the subsequent hyperemic response was recorded. When the coronary blood flow velocity had returned to the baseline level, the procedure was repeated using increasing doses of adenosine starting with of 0.05 mg, until either maximal hyperemia was obtained (no further increase in maximal blood flow velocity) or side effects produced.

The Doppler device that was used to measure the intracoronary blood flow velocity consisted of a 20 MHz ultrasonic crystal mounted on the tip of the angioplasty catheter. Recently, Sibley et al (17) validated clinically and experimentally the ability of a similar catheter with an end-mounted

piezo electric crystal to provide accurate and continuous on-line measurement of coronary blood flow velocity and vasodilator reserve. The Doppler crystal has a 1.0 mm diameter annulus with a 0.5 mm central hole. Blood flow velocity is measured from the catheter tip transducer using a range gated 20 MHz pulsed Doppler device designed specifically for this purpose (Baylor College of Medicine). The master oscillator frequency of 20 MHz is pulsed at an oscillating frequency of 62.5 kHz. Each pulse is approximately 1 micros in width and therefore contains 20 cycles of the master oscillator frequency. This allows the recording of velocities up to 100 cm/s at a distance of up to 1 cm from the cathetertip. The sampling window can be adjusted individually to obtain the best signal. The output of the pulsed Doppler is in the form of a frequency shift (F) that can be related to flow velocity by the Doppler equation:

$F = 2f\ V/c,\ \cos a$

where f is the ultrasonic frequency (20 MHz), V is the mean velocity within the sample volume, c is the speed of sound in blood (1500 m/s) and a is the angle between the velocity vector and the sound beam. Using an end-mounted crystal with the catheter parallel (± 20°) to the vessel axis, cos a is 1 ± 6%, and the relation between the Doppler shift and velocity is approximately 3.75 cm/s/kHz. Previous calibration experiments in canine femoral and coronary arteries have shown that the measured doppler frequency shift is proportional to volume flow measured by timed collection (3,18,19).

Results

The patient characteristics are shown in table 1. The mean age of the patients was 53 years (range: 41-68). Ten of the twelve patients were men. Nine patients had one-vessel coronary artery disease and three patients two-vessel disease. The mean left ventricular ejection fraction was 56% (range: 38-71%).

Intracoronary papaverine

The effects of intracoronary papaverine are shown in table 2 and figure 1. Coronary blood flow velocity (mean ± SD) increased to 1.6 ± 0.3 times resting coronary blood flow velocity. The time (mean ± SD) from the intracoronary bolus injection to the peak of the hyperemic response was 26 ± 7 s. The time (mean ± SD) from injection to subsidence of the hyperemic response, that is return of the coronary blood flow velocity to its baseline level, was 108 ± 25 s. There was no significant effect of the intracoronary papaverine on systemic hemodynamics. Blood pressure: -1 ± 3% of baseline blood pressure and heart rate: 0 ± 4% of baseline heart rate, during the peak of the hyperemic response.

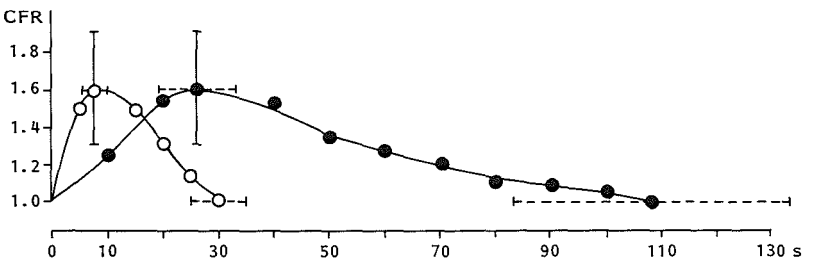

Figure 1
Timing and magnitude of the coronary flow reserve (CFR) after adenosine (○), and papaverine (●). I = SD of the magnitude, --- = SD of timing.

Table 1: Clinical data.

pat	sex	age	NYHA	VD	LVEF	pharmac. ther.
1	M	53	III	2	55	B,N
2	M	54	III	1	57	B,C.N
3	M	44	III	1	58	C,N
4	M	55	II	1	65	B,N
5	M	41	III	2	38	B,C,N
6	F	53	III	1	71	C,N
7	M	56	II	1	54	B,C
8	M	47	III	2	45	B,C,N
9	M	48	III	1	58	B,C,N
10	F	68	III	1	62	B,N
11	M	57	III	1	56	B,C,N
12	M	61	III	1	?	B,N

pat = patient; M = male; F = female; NYHA = New York Heart Association classification for angina pectoris; VD = number of vessels with a more than 50% diameter stenosis; LVEF = left ventricular ejection fraction; ? = unknown; pharmac. ther. = pharmacological therapy; B = beta blocker; C = calcium antagonist; N = nitrate.

Intracoronary adenosine

The effects of intracoronary adenosine are shown in table 2 and figure 1. The dose needed to produce a maximal hyperemic response varied widely. It was 0.05 mg in 2 patients, 0.1 mg in 4 patients, 0.2 mg in 2 patients, 0.4 mg in 2 patients and 0.8 mg in 1 patient. The mean (±SD) dose needed to produce maximal hyperemia was 0.23 (± 0.20) mg. Coronary blood flow velocity (mean ± SD) following this maximal effective dose of intracoronary adenosine increased to 1.6 ± 0.3 times resting coronary blood flow velocity. The magnitude of the hyperemic responses after papaverine and adenosine were related (linear regression analysis: r=0.83 SEE= 0.2). The time (mean ± SD) from the intracoronary bolus injection to the peak of the hyperemic response was 7.4 ± 2.2 s. The time (mean ± SD) from injection to subsidence of the hyperemic response was 30 ± 5 s.

Complications:

No complications were noted after intracoronary administration of papaverine. In 3 patients intracoronary administration of adenosine resulted in bradyarrhythmias. In 1 patient asystole occured, lasting 5.2 s (patient 5, table 1 and 2). In 2 patients a short lasting atrioventricular block was induced (patients 6 and 9, table 1 and 2). Apart from

Table 2: Results of intracoronary administration of vasodilators.

			papaverine 12.5 mg				adenosine		
Pat			CFR	tpeak	thyp	dos	CFR	tpeak	thyp
1	LAD	B	1.4	32	101	0.05	1.4	7	36
		A	1.4	28	145	0.2	1.6	10	35
2	CX	A	1.7	27	131	0.4	1.8	12	38
3	LAD	A	1.9	19	100	0.4	2.0	5	22
4	RCA	B	1.1	36	137	0.1	1.0		
5	LAD	B	1.4	24	142	0.2	1.5	6	24
6	LAD	A	1.6	22	93	0.8	1.6	5	33
7	LAD	A	1.9	18	82	0.2	2.0	6	25
8	CX	B	1.4	35	105	0.1	1.3	7	38
9	LAD	A	1.6	37	133	0.05	1.8	5	28
10	LAD	A	1.4	27	107	0.4	1.3	9	31
11	LAD	B	2.4	21	102	0.1	1.9	7	33
		A	1.2	19	111	0.2	1.4	10	32
12	LAD	B	1.3	15	58	0.1	1.5	6	22
		A	1.5	17	63	0.2	1.5	8	28

Pat = patient, LAD = left anterior descending artery, CX = circumflex artery, RCA = right coronary artery, B = before angioplasty, A = after angioplasty, CFR = coronary flow reserve (ratio of maximal coronary blood flow velocity to baseline velocity), tpeak = time from injection to maximal hyperemia(s), thyp = time from injection to subsidence of the hyperemia(s), dos = dose needed to produce a maximal hyperemia (mg).

these 3 patients with bradyarrhythmias no complications were noted following adenosine administration.

In the other 9 patients, intracoronary adenosine did not alter systemic hemodynamics. Blood pressure: -2 ± 2% of baseline blood pressure and heart-rate: -2 ± 3% of baseline heart rate during the peak of the maximal hyperemic response.

Discussion

Visual interpretation of the coronary angiogram is a poor means of assessing the physiological importance of obstructive coronary artery disease (20). Computer-based quantitative analysis of the coronary angiogram has solved, to a considerable extent, the problems of high interobserver and intraobserver variability and it has made possible the calculation of hydrodynamic parameters of the coronary artery lesion that correlate well with translesional pressure gradient and thallium perfussion scintigraphy (21-24). In patients with limited coronary artery disease, such as a single discrete

proximal obstructive lesion, the physiological significance of their coronary stenosis can be predicted with reasonable accuracy from quantitative assesment of the coronary artery dimensions (5,25). However, in the large majority of patients with coronary artery disease, the physiological importance cannot be inferred from morphological data alone. Therefore, methods to measure coronary flow reserve are needed. Various ways to study coronary flow reserve have been described (3-5,26), and the induction of a maximal hyperemic response is an essential part of all these methods.

Vasodilator agents

Widely used vasodilator agents are dipyridamol and hyperosmolar ionic contrast media (1,3,4,20). An intravenous infusion of dipyridamol in adequate dose results in maximal coronary vasodilation, but it has the disadvantage of a long-lasting duration of action which makes repeated assessment of the hyperemic response of a coronary vascular bed or assessment of different coronary vascular beds during the same procedure impossible (3,6). Hyperosmolar ionic contrast media do not produce maximal vasodilation (2,27,28). Bookstein and Higgins (27) have shown that in dogs, the hyperemic response after a intracoronary bolus injection of adenosine-triphosphate or papaverine is of the same magnitude as after a 15s - occlusion of the coronary artery. The exact dose of intracoronary papaverine needed to produce maximal coronary vasodilation has recently been established. Wilson and White (6) compared the coronary hyperemic response after 4,8,12 and 16 mg intracoronary papaverine and reported a maximal hyperemic response after 8 mg in most coronary arteries and after 12 mg in all coronary arteries. Papaverine in this dose (8-12 mg) produced a response equal to that of an intravenous infusion of dipyridamol in a dose of 0.56 to 0.84 mg/kg body weight. Coronary blood flow and /or flow velocity of normal coronary arteries in the absence of factors known to decrease flow reserve, increases four to six times the resting value after intracoronary papaverine (5,6).

Therefore, we compared the vasodilating potential of intracoronary adenosine with 12.5 mg intracoronary papaverine. Our results show that the coronary vasodilation after adenosine is of a comparable magnitude to that observed after papaverine. The time from intracoronary injection of adenosine to peak hyperemia as well as the total duration of the hyperemic response is about four times shorter than papaverine (see fig. 1). However, several characteristics of adenosine limit its practical applicability. First, the dose needed to induce maximal hyperemia varies widely from patient to patient and seems unpredictable. This makes adenosine an unsuitable agent for coronary vasodilation if a radiographic technique is used to measure coronary flow reserve (5). Second, three of

our twelve patients developed bradyarrhythmias immediately following adenosine administration in a dose close to that needed to produce adequate hyperemia. Although these bradyarrhythmias were short-lasting, they produced discomfort for the patients and precluded a meaningful interpretation of the coronary flow velocity data following this adenosine injection. These bradyarrhythmic effects of intracoronary adenosine are in accordance with its well-known electrophysologic effects when administered intravenously (13,14).

Magnitude of coronary hyperemic responses after papaverine and adenosine

Wilson and White (6) have shown that intracoronary papaverine and intravenous dipyridamol increase coronary blood flow velocity ranging from 3.5 to 6 times baseline velocity (in patients with normal coronary arteries). In our patients, who were studied in the setting of coronary angioplasty for significant coronary artery disease, vascular reserve was much lower, as might be expected (29-31). Introduction of a guide wire and a catheter with a Doppler device into a coronary artery may cause serious complications. Wilson et al (3) reported one patient with a total occlusion of a coronary artery following blood flow velocity measurements with an intracoronary Doppler catheter. Therefore we feel that to perform research with such devices is only justified in the setting of coronary angioplasty when the intracoronary positioning of guide wire and catheter is mandatory as a part of the procedure. A consequence of this is that our findings and conclusions are restricted to patients with symptomatic coronary artery disease.

Conclusion

Intracoronary adenosine is a potent and very short-acting vasodilator. However, its clinical applicability is limited by side effects and unpredictability of the dose needed to induce a maximal hyperemic response in the coronary circulation.

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CHAPTER 5: DOES THE QUANTITATIVE ASSESSMENT OF CORONARY ARTERY DIMENSIONS PREDICT THE PHYSIOLOGIC SIGNIFICANCE OF A CORONARY STENOSIS?

Summary

To study the relationship between the quantitatively assessed coronary artery dimensions and the regional coronary flow reserve as measured by digital subtraction cineangiography, we investigated 17 coronary arteries with a single discrete proximal stenosis and 12 normal coronary arteries, before and after intracoronary administration of papaverine. Coronary flow reserve was found to be curvilinearly related to minimal luminal cross-sectional area ($r = 0.92$, SEE = 0.73) and to percentage area stenosis ($r = 0.92$, SEE = 0.74). Normal coronary arteries had a coronary flow reserve of 5.0 (SD ± 0.8), which differed significantly from the coronary flow reserve of the coronary arteries with obstructive disease, in which values ranging from 0.5 to 3.9 were found. Coronary arteries with a percentage area stenosis between 50 and 70% and a minimal luminal cross-sectional area between 2 and 4.5 mm^2 differed significantly ($p = 0.001$) with respect to the coronary flow reserve, from coronary arteries with a percentage area stenosis in excess of 70% and a minimal luminal cross-sectional area less than 2 mm^2. With the use of hemodynamic equations that describe the pressure loss over a stenosis, a theoretical pressure-flow relation can be inferred that characterizes the severity of the stenosis. Based on this theoretical pressure-flow relationship, coronary arteries that have a limited coronary flow reserve and critical stenosis, (distal coronary perfusion pressure below 40 mmHg at coronary flow of 3 ml/sec) can be identified with high sensitivity (83%) and specifity (82%). Thus, in coronary artery disease the consequent reduction in coronary flow reserve can be predicted with reasonable accuracy by quantitative assessment of coronary artery dimensions.

Introduction

Visual interpretation of the coronary angiogram inadequately predicts the physiologic importance of obstructive coronary artery disease (CAD) (1). Computer-based quantitative analysis has helped minimize the problems of high interobserver and intraobserver variability in the assessment of the coronary angiogram (2-4), and it allows the calculation of the pressure-flow characteristics of the coronary artery lesion (5), that are correlated with the translesional pressure gradient and with exercise thallium perfusion scintigraphy (6,7). However, the relationship between the quantitative analyzed dimensions of an obstructive coronary artery

lesion and the consequent limitation in coronary blood flow is not yet fully understood. The recent description of a digital angiographic technique for the measurement of relative coronary blood flow has rendered the assessment of regional coronary flow reserve possible by use of the ratio of maximal coronary blood flow to resting flow as a measurement of this variable (8). The goal of this investigation was to study the relationship of quantitatively assessed coronary artery dimensions and calculated coronary artery pressure-flow characteristics to the regional coronary flow reserve as measured by digital subtraction cineangiography.

Patients and methods

Seventeen coronary arteries of patients with single vessel CAD and 12 coronary arteries of patients with normal coronary arteries were studied. The 17 coronary artery lesions were all single discrete stenoses in the proximal parts of the vessels before any significant sidebranch occurred. Coronary angiography by the Sones or Judkins technique was performed for chest pain syndromes. Informed consent was obtained for the additional investigation. All patients were studied without premedication, but their medical treatment (nitrates, calcium antagonists and beta-blockers) was continued on the day of the investigation. None had systemic hypertension, cardiac hypertrophy, anemia, polycythemia, documented previous myocardial infarction, valvular heart disease or angiographic evidence of collateral circulation.

The procedures for the determination of the CFR and the quantitative assessment of coronary arterial dimensions from 35 mm cinefilm were implemented on the computer-based Cardiovascular Angiography Analysis System (CAAS), and have been extensively described (4,9).

Angiographic procedure and induction of a maximal hyperemic response.

The heart was atrially paced at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery was made with Iopamidol at 37°C through a Medrad Mark IV infusion pump. This nonionic contrast agent has a viscosity of 9.4 cP at 37°C, an osmolality of 0.796 osm/kg and an iodium content of 370 mg/ml. For the left coronary artery 7 ml was injected at a flow rate of 4 ml/sec; the coronary angiogram was obtained in a left anterior oblique projection. For the right coronary artery 5 ml was injected at a flow rate of 3 ml/sec and the angiogram was taken in a left or right anterior oblique projection. The rate of injection the contrast medium was judged to be adequate when backflow of contrast medium into the aorta occurred. The angiogram was repeated 30 sec after a bolus injection of 10 mg papaverine

into the coronary artery (10).

Quantitative coronary cineangiography

For the assessment of the absolute and relative dimensions of selected coronary segments with the CAAS, the boundaries of a selected coronary segment are detected automatically from optically magnified and video digitized regions of interest (ROI) of a cineframe. Calibration of the diameter data in absolute values (mm) is achieved by detecting the boundaries of a section of the contrast catheter and comparison of the computed mean diameter in pixels with the known size in millimeters. Each catheter is measured individually (11). To correct the contour positions of the arterial and catheter segments for the pincushion distortion, a correction vector is computed for each pixel based on a computer-processed cineframe of a centimeter grid placed against the input screen of the image intensifier (9).

The procedure for contour detection requires the user to indicate a number of center positions with the writing tablet proximal and distal to the lesion such that the straight line segments connecting these points are within the artery. The contours of the vessel are detected on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions. From the detected contours the diameter function is determined in absolute millimeters. In this study, each lesion was analyzed in at least two, preferably orthogonal projections. Three projections were used if two orthogonal projections could not be obtained of a nonsymmetric lesion.

Since the functional significance of a stenosis is also related to the expected normal cross-sectional area of the vessel at the point of the obstruction, we use a computer estimation of the original arterial dimensions at the site of the obstruction to define the reference region (interpolated reference) (4,9). Representative examples of two orthogonal views with the detected contours of a right coronary artery and the reconstructed reference contours are shown in figure 1 . The computed reference diameter function allows for tapering of the vessel.

The interpolated percentage area stenosis (AS) is then computed by comparing the squared minimal diameter value at the obstruction with the squared value of the reference diameter function at this position assuming circular cross-section:

$$AS = \left(1 - (\text{minimal diameter}/\text{reference diameter})^2 \right) \times 100\%.$$

The estimation of the length of the obstruction is made on the basis of a curvature analysis of the diameter function (9).

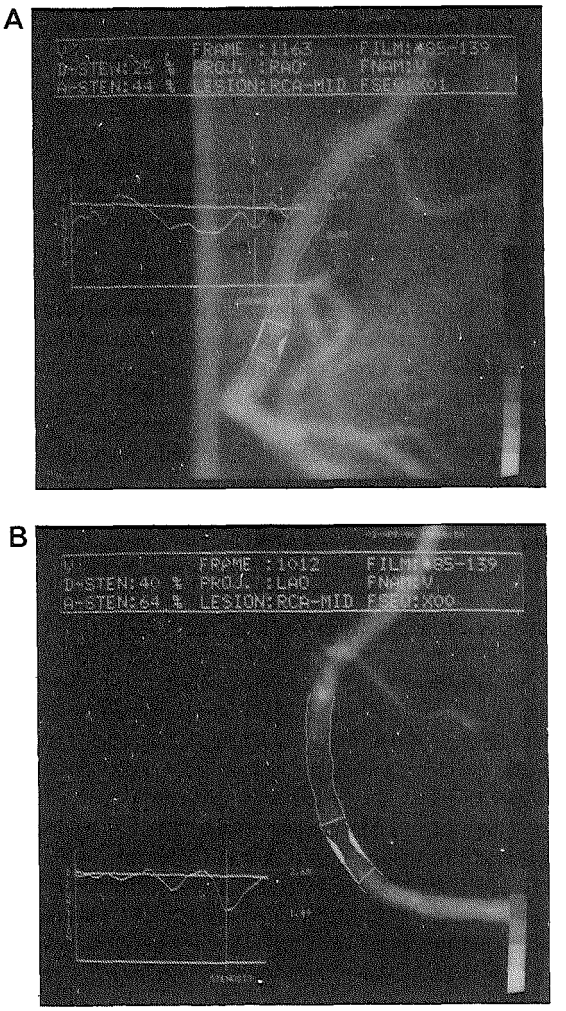

Figure 1
Detected contours from a representative stenosis in the right coronary artery superimposed on the original video image. The normal size of the artery over the obstruction is estimated by the interpolated method, and the resulting reference contours are shown.
A: Right anterior oblique projection.
B: Left anterior oblique projection.

Coronary perfusion pressure distal of the stenosis is estimated by subtracting from the mean aortic pressure the theoretical pressure drop over the stenosis for coronary flows of 1,2, and 3 ml/sec (5,12). The theoretical pressure drop was calculated according to the following hemodynamic equation:

$$PD = (25.1uL / MLCA^2)\ Q + d/0.266\ (1/MLCA - 1/NA)^2\ Q^2$$

where PD = pressure drop, u = absolute blood viscosity, L = stenosis length, NA = interpolated normal cross-sectional area, MLCA = minimal luminal cross-sectional area, Q = volume flow, d = blood density (13,14). Since each stenosis was analyzed in 2 or 3 angiographic projections, 2 or 3 pressure drops were calculated the mean value was used. To assess the influence of 10 mg intracoronary papaverine on the dimensions of the epicardial coronary arteries, coronary angiograms obtained before and during the measurement of coronary flow reserve were compared. Nine normal coronary arteries and 8 coronary arteries with a focal obstructive lesion were analysed quantitatively. These 8 coronary artery segments were selected because the obstructive lesions were clearly visible and perpendicular to the image intensifier during the measurement coronary flow reserve.

Coronary flow reserve measurements

For the quantitation of the relative coronary blood flow (8), five to eight end-diastolic cineframes were selected from successive cardiac cycles (8). Logarithmic nonmagnified mask-mode background subtraction was applied to the image subset to eliminate noncontrast medium densities. The last end-diastolic frame prior to contrast administration was chosen as the mask. Each digitized image was also corrected for the dark current of the video camera. From the sequence of background subtracted images, a contrast arrival time image was determined, with the use of a fixed density threshold. In this image, each pixel was labeled with the sequence number of the cardiac cycle in which the pixel intensity level for the first time exceeded the threshold, starting from the beginning of the ECG-triggered contrast injection. This density threshold was empirically derived by analyzing in 12 patients the relationship between the threshold and the baseline and hyperemic myocardial contrast medium appearance times as well as the resulting coronary flow reserve. The intensity level in more than 90% of pixels exceeded thresholds of 4,8 and 12% (table 1). In 25% of patients less than 90% of pixels reached the intensity level of 16% making calculation of the contrast medium accumulation unreliable. With a threshold of 4%, and to a lesser extent with a threshold of 8%, background noise was not eliminated resulting in very short contrast medium appearance times. Therefore we used a threshold of 12% in all our

Table 1: Influence of density threshold on myocardial contrast medium appearance time and coronary flow reserve (CFR)

DT	4%		8%		12%		16%
AT1	1.96		2.48		2.88		3.39
AT2	1.58		1.73		1.97		2.19
CFR	2.26	*	2.63	NS	2.66	*	2.82

DT = density threshold in percentage of the brightness scale, AT1 = baseline myocardial contrast medium appearance time, AT2 = hyperemic myocardial contrast medium appearance time, * = p less than 0,01, ns = not significant, AT1, AT2 and CFR are mean values calculated from 12 patients.

patients. In addition to the contrast arrival time image, a density image was computed, with each pixel intensity value being representative for the maximal local contrast medium accumulation. In the second step, the information from these two images was combined into a dual parameter image, the contrast medium appearance picture. In this picture the appearance time was color coded and the contrast medium accumulation was represented by the color intensity.

The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image divided by the regional flow of the corresponding baseline image. Regional flow values were quantitatively determined using the following videodensitometric principle: regional blood flow (Q) = regional vascular volume (RVV)/transit time. Regional vascular volume was assessed from the logarithmic mask-mode subtraction images. Since at the flow rates we used essentially all epicardial blood is replaced by contrast the brightness information is proportional (factor k) to the local thickness of the projected vascular system (Beers-Lambert relationship).

If the same regions of interest are used for baseline and hyperemic conditions, the coronary flow reserve can be determined from the regional blood flow values Q(h) and Q(b) at the hyperemic and baseline states respectively:

$$CFR = Q(h)/Q(b) = CD(h)/AT(h) : CD(b)/AT(b)$$

where CD is the mean contrast density and AT the mean appearance time.

Mean contrast medium appearance time and density were computed within user-defined ROI's. The ROI's were chosen in such a way that the epicardial arteries visible on the angiogram, including diagonal and septal branches, the aortic root, the coronary sinus and the great cardiac vein were excluded from the analysis.

When coronary angiograms were repeated within 5 min, no significant differences were found in AT and CD. The mean difference between duplicate measurements of AT was 7% with a standard deviation of 8%. The mean difference between duplicate measurements of CD was 6% with a standard deviation of 5%.

Statistical methods

Comparisons between groups were made with Student's t-test. Leastsquare regression analyses were used to find the "best fit" relationship between coronary flow reserve and the quantitatively assessed coronary artery dimensions.

Results

The mean age of the 29 patients was 56 years (range 31-71); four patients were women, 25 men. All 17 patients with CAD had single vessel disease and all 29 patients had a normal left ventricular ejection fraction (more than 55%).

The results of the quantitative analysis of the coronary arteries and the measurements of coronary flow reserve are shown in table 2. The investigated vessel was the left anterior descending coronary artery in 16 of the patients, the right coronary artery in 7 patients and the left circumflex coronary artery in 6 patients. An average of 2.2 angiographic projections was used for the quantitative morphologic analyses of the coronary angiogram. The mean cross-sectional area of the 12 normal coronary arteries, measured in the proximal parts before any branching was 7.6 mm^2 (range 5.4 to 10.3 mm^2). The interpolated reference cross-sectional area of the vessels with CAD was 7.0 mm^2 (SD ± 1.7 mm^2). In vessels with CAD the AS ranged from 51% to 93% (mean 76%). The minimal luminal cross-sectional area (MLCA) ranged from 0.4 to 4.1 mm^2 (mean 1.7 mm^2). The length of the obstructive lesions ranged from 3.0 to 13.6 mm, (mean 7.0 mm).

The influence of 10 mg intracoronary papaverine on the dimensions of normal coronary arteries and of coronary arteries with a focal obstructive lesion are shown in table 3. No change occurred in the cross-sectional areas of normal coronary arteries and of the pre-and post-stenotic coronary artery segments after intracoronary papaverine. There was a small but significant decrease in AS (p less than 0.05, mean 3% ranging from 0 to 9%). The MLCA increased from a mean value of 2.1 mm^2 to 2.6 mm^2 (p less than 0.05, mean 24%, range 8 to 39%).

The 12 normal coronary arteries had a mean coronary flow reserve of 5.0 (SD ± 0.8). coronary flow reserve in vessels with CAD ranged from 0.5 to 3.9, mean: 1.6 (SD ± 0.9) and differed significantly (p = 0.001) from the coronary flow reserve of normal coronary arteries. The relationship between coronary flow reserve and MLCA was best described by a quadra-

Table 2: Results

	QACA*			CFR-measurements						DPP			
ang pr	MLCA	AS	L	NA	A1	D1	A2	D2	CFR	Ao	P1	P2	P3
A LSO,RIO				7.6	2.7	77	1.1	202	6.5				
C CA,CR				10.3	3.7	54	1.8	162	6.2				
A CR,RIO				7.6	2.9	59	1.2	128	5.3				
R RAO,LAO				7.3	3.3	69	1.5	163	5.2				
C LAO,RIO				8.6	2.1	79	1.2	226	5.0				
C RAO,LAO				5.7	3.7	57	1.5	115	5.0				
A LSO,RIO				7.0	4.2	38	2.1	94	4.9				
R RAO,LAO				7.8	3.3	42	2.2	133	4.8				
A CR,CA				9.4	4.2	45	2.1	111	4.7				
R RAO,LAO				9.8	3.6	70	1.8	161	4.6				
A RAO,LSO				5.4	3.2	70	1.8	178	4.5				
A CR, CA				4.7	2.2	80	1.2	148	3.4				
R RAO,LAO	2.9	54	5.1	6.5	4.8	49	2.4	95	3.9	78	77	77	75
R RAO,LAO	2.2	66	8.5	6.4	3.3	98	1.9	174	3.1	92	90	88	85
A RAO,CR,CA	4.1	57	5.7	9.5	3.5	57	2.5	102	2.5	96	96	95	95
C RAO,LAO	3.5	63	5.7	9.4	3.2	76	2.1	123	2.5	94	94	93	92
R RAO,LAO	2.8	63	5.5	7.7	3.0	65	1.6	85	2.4	89	88	87	86
C LAO,RIO,CA	3.2	51	3.0	6.5	2.9	45	2.1	54	1.7	84	84	83	82
A LSO,CR,RIO	1.6	81	5.2	8.3	2.3	94	1.9	116	1.5	74	72	67	61
A CR,CA	0.7	90	8.7	6.8	2.0	74	2.1	105	1.4	101	81	50	6
A RAO,LSO,CR	0.9	82	13.6	5.1	2.8	60	2.6	73	1.3	86	70	48	20
A CR,RIO,LSO	1.6	82	7.9	8.9	2.2	74	2.3	100	1.3	84	81	75	68
A LAO,RIO	1.1	87	9.6	8.2	2.8	57	2.6	59	1.1	94	86	73	55
A CR,CA,RAO	0.8	89	5.9	7.4	2.4	74	2.1	62	1.0	84	72	51	21
A LSO,RAO	0.4	93	6.1	6.1	3.6	36	3.8	33	0.9	82	33	-58	-190
R RAO,LAO	0.7	91	6.2	7.2	2.8	103	2.5	80	0.9	89	73	45	4
A LSO,RAO	1.7	76	9.9	7.1	2.5	111	2.3	78	0.8	88	85	80	73
C LAO,CA	0.7	89	5.1	6.1	1.4	40	2.3	47	0.7	79	65	39	2
A CR,LSO,RIO	0.4	86	6.6	2.9	2.8	56	3.8	39	0.5	94	45	-38	-157

Abbreviations:
QACA = quantitative analysis of the coronary angiogram; ang pr= angiographic projection; MLCA= minimal luminal cross-sectional area (mm^2); AS= area stenosis (%); L= length of the obstructive lesions (mm); NA= normal area from normal coronary arteries or interpolated reference area of coronary arteries with CAD (mm^2); CFR= coronary flow reserve; A1= myocardial contrast appearence time of basal angiogram; D1= myocardial contrast density of basal angiogram; A2= myocardial contrast appearance time of angiogram after papaverine; D2= myocardial contrast density of angiogram after papaverine; Ao= mean aortic pressure; P%= actual pressure drop/Ao x 100% and DPP= distal coronary perfusion pressure at coronary flows of 1 ml/sec (P1), 2 ml/sec (P2) and 3 ml/sec (P3) ; LSO= left superior oblique; RIO= right inferior oblique; CR= cranial; RAO= right anterior oblique; LAO= left anterior oblique; CA= caudal. A= anterior descending, C= circumflex, R= right coronary artery.

tic equation:

$$CFR = 0.28 + 0.91\ MLCA - 0.039\ (MLCA)^2,$$
$$(r = 0.92,\ SEE = 0.73)$$

and is shown in fig 2. The relationship between coroanry flow reserve and AS was best described by a quadratic equation:

$$CFR = 5.0 - 3.3\ (AS \times 10^{-2}) - 1.3\ (AS \times 10^{-2})^2,$$
$$(r = 0.92,\ SEE = 0.74)$$

and is shown in fig 3. The 12 normal coronary arteries (group A) were compared with the 6 coronary arteries with a MLCA between 2 and 4,5 mm^2 and an AS between 50 and 70% (group B) and with the 11 coronary arteries with a MLCA less than 2 mm^2 and an AS in excess of 70% (group C). In group C, coronary flow reserve was 1.0 (SD ± 0.3) and differed significantly ($p = 0.001$) from that of group B: 2.6 (SD ± 0.7). The difference between group A and group B was also significant ($p = 0.001$), see Table 4.

From the MLCA, the length of the obstructive lesion and the normal cross-sectional area distal to the stenosis a theoretical pressure-flow relationship was calculated, for each angiographic projection from which the mean values were used for further analyzes (table 2). The pressure-flow relationship for group B arteries differed significantly ($p = 0.01$) from that for group C. Group C could be subdivided with respect to coronary flow reserve on the basis of these theoretical pressure-flow relationships. The pressure-flow relationship of coronary arteries with a coronary flow reserve of 1 or less differed significantly from those of coronary arteries with a coronary flow reserve greater than 1 ($p = 0.01$). A distal coronary perfusion pressure below 40 mmHg at a coronary flow of 3 ml/sec, identified 5 out of 6 patients with a coronary flow reserve of 1 or less, (sensitivity: 83%). Only 2 of 12 vessels with CAD and a coronary flow reserve greater than 1 had a distal coronary perfusion pressure below 40 mmHg (specifity: 82%).

Discussion

In the clinical setting assessment of the relationship between the angiographic degree of stenosis and the actual impairment of perfusion has been hampered by two basic problems that now seem to have been solved by new technical developments. First, the recent description of a technique using digital subtraction angiography has rendered the assessment of regional coronary flow reserve possible during cardiac catheterization[8]. Second, the large intraobserver and interobserver variability associated with the visual assessment of the coronary angiogram has led to development of methods of computer- based quantitative analysis, including automated contour detection, which improve accuracy and allow

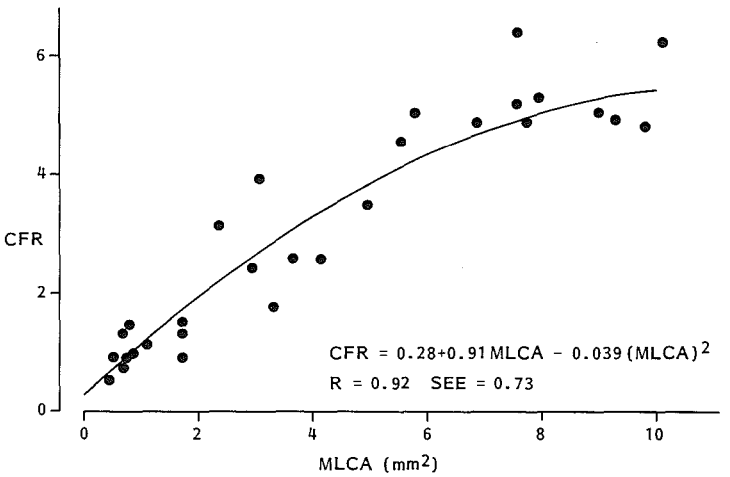

Figure 2
Relation between coronary flow reserve (CFR) and minimal luminal cross-sectional area (MLCA).

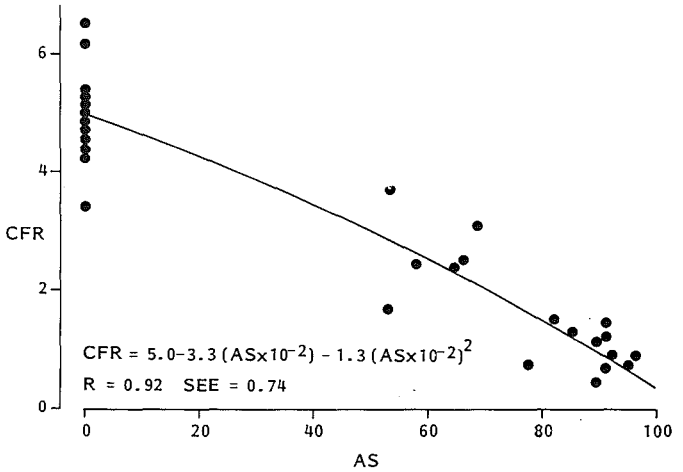

Figure 3
Relation between coronary flow reserve (CFR) and percentage area stenosis (AS).

Table 3: Influence of 10 mg intracoronary papaverine on coronary artery dimensions.

9 normal coronary arteries		8 coronary arteries with a focal obstructive coronary artery segment			
	area (mm^2)	pre-stenotic area (mm^2)	MLCA (mm^2)	AS %	post-stenotic area (mm^2)
A	10.2	9.1	2.1	75	6.6
	ns	ns	*	*	ns
B	10.2	9.6	2.6	72	6.6

A: before intracoronary papaverine, B: 30 sec after intracoronary papaverine, * = less than 0.05, NS = not significant.

for the precise determination of most dimensions of a given stenosis in a coronary artery (4,9).

Pharmacological vasodilation

One of the methodological cornerstones in the assessment of coronary flow reserve is the induction of a maximal hyperemic response (15). A wide range of values for the coronary flow reserve of normal coronary arteries has been reported, depending on the vasodilator used (16,17). Carefully validated studies with a Doppler-catheter suggest that the maximal coronary blood flow velocity of a normal coronary artery is 4 to 6 times the resting value (16). The most commonly used vasodilator agents are dipyridamole and hyperosmolar ionic contrast media. An adequate intravenous infusion of dipyridamole results in maximal coronary vasodilation, but its long-lasting effect makes repeated assessment of the hyperemic response of a coronary vascular bed or assessment of different coronary vascular beds during the same procedure impossible. Hyperosmolar ionic contrast media do not produce maximal vasodilation (10).

The exact dose of intracoronary papaverine that is needed to induce maximal coronary vasodilation has recently been established. Wilson an White compared the coronary hyperemic response after 4,8,12 and 16 mg intracoronary papaverine and reported a maximal hyperemic response after 8 or 12 mg in all coronary arteries (10). Conversely, coronary steal phenomenon has been observed following pharmacological vasodilation. We recorded a coronary flow reserve of less than 1.0, in some of

Table 4: Relation between quantitative assessed coronary artery dimensions and CFR.

	normal arteries		arteries with CAD		
	group A N = 12		group B N = 6		group C N = 11
MLCA(mm^2)	more than 4.5		2-4.5		less than 2
AS(%)	0		50-70		more than 70
CFR(mean ± SD)	5.0 ± 0.8	*	2.6 ± 0.7	*	1.0 ± 0.3

CFR = coronary flow reserve, MLCA = minimal luminal cross-sectional area, AS = area stenosis, * = p less than 0.01.

Table 5: Calculated distal coronary perfusion pressure (mmHg) for theoretical coronary flows of 1 (P_1),2 (P_2) and 3 (P_3) ml/sec, of vessels with CAD subdivided according to CFR.

	No of patients	CFR mean	range	AS (%)	MLCA (mm^2)	Ao	P1	P2	P3
							(mmHg)		
A	6	2.6	1.7-3.9	59	3.1	89	88	87	86
B	5	1.3	1.1-1.5	86	1.1	88	78	63	42
C	6	0.8	0.5-1.0	87	0.8	86	62	20	-41

Abbreviations: CAD = coronary artery disease, CFR = coronary flow reserve, AS% = percentage area stenosis, MLCA = minimal luminal cross-sectional area, Ao = mean aortic pressure, A = CFR greater than 1.6, B = CFR greater than 1.0 but less than 1.6, C = CFR 1.0 or less.

Table 6: Identification of coronary arteries with a critical stenosis on the basis of calculated distal coronary perfusion pressure (DPP)

DPP (mmHg)		CFR (mean ± SD)		CFR 1.0 or less	CFR greater than 1.0
				no of patients	
less than	40	0.96 ± 0.3	P = 0.01	5	2
greater than	40	2.1 ± 0.9		1	9

CFR = coronary flow reserve, sensitivity: 5/6 x 100% = 83%, specifity: 9/11 x 100% = 82%.

our patients who received papaverine, and Bates et al (17) made the same observation in patients receiving hyperosmolar ionic contrast medium.

Relationship between coronary artery dimensions and coronary flow reserve

In the experimental animal the physiological significance of artificially produced arterial stenoses has been extensively studied (14,18-21). Gould et al produced varying degrees of coronary narrowing and showed that stenoses in excess of 30-45% diameter narrowing reduced coronary vasodilator responses in a predictable fashion (20). However, in human beings with CAD the relationship between the visually estimated percentage diameter stenosis and the consequent reduction in coronary flow reserve is poor (1). Harrison et al found that MLCA predicted the coronary flow reserve better than percentage area stenose in proximal lesions in the left anterior descending coronary artery (22). Due to diffuse CAD the estimation of the normal coronary arterial dimensions was impossible, and precluded the use of relative measures of stenosis severity. In our patients the interpolated reference cross-sectional area of the vessels with CAD was on average 7.0 mm^2 and the cross-sectional areas of the 12 normal coronary arteries was on average 7.6 mm^2 which indicates the isolated and focal character of their coronary artery disease. Therefore, stenosis severity could be assessed in absolute measurements (MLCA) as well as relative percentage (AS) and these two parameters were similarly related to coronary flow reserve. AS and MLCA were curvilinearly related to coronary flow reserve and these relations were best described by quadratic equations. Harrison et al found in vessels with an expected normal cross-sectional area between 7 and 10 mm^2, that a MLCA below 3.5 mm^2 was predictive of a decreased coronary flow reserve. We observed in vessels with an expected normal cross-sectional area of 7.0 mm^2 (SD $\pm$ 1.7 mm^2) that a MLCA below 4.5 mm^2 was associated with a decreased coronary flow reserve.

In a previous study from our laboratory the relation between the pressure-drop over a stenosis and the MLCA was analyzed (7). A curvilinear relation was found with a steep increase in pressuredrop once the MLCA is less than 2 mm^2. The present study confirms the discriminant value of this criterium (table 4).

Other angiographic factors that are important in the prediction of coronary flow reserve.

A pressure-flow relationship that characterizes the severity of the coronary stenosis can be derived, by means of hemodynamic equations using MLCA, the length of the obstruc-

tive lesion and the normal distal cross-sectional area of the coronary artery. From the relation between coronary perfusion pressure and coronary flow under conditions of maximal coronary vasodilation as described by Bache and Schwartz (23), and assuming a resting coronary flow velocity of 15 cm/sec, Kirkeeide et al calculated a coronary flow reserve from the angiographic data.They showed in dogs the good correlation between such an angiographic approach and measured coronary flow reserve (21). In our patients the calculated pressure flow relations were related to the reduction in coronary flow reserve (table 5). A pressure drop over a stenosis at a flow of 3 ml/sec resulting in a distal perfusion pressure below 40 mmHg indicated the existence of a critical stenosis, defined as a vessel with a coronary flow reserve of 1 or less. With the use of this criterion, patients with severe CAD and a critical stenosis can be identified with a high sensitivity (83%) and specificity (82%) (table 6). The rationale for use of this pressure is based on previous observations that reactive coronary hyperemia is abolished when coronary artery perfusion pressure drops below this value (24).

Limitations

The intracoronary administration of contrast medium results in profound alterations in coronary blood flow, characterized by depression in the first seconds followed by hyperemia (25). The magnitude and timing of these changes depends primarily on amount, iodine concentration and injection rate of the contrast medium (26). The hyperemic to baseline coronary blood flow ratio nevertheless remains unchanged within the first 5 sec after contrast medium injection when care is taken to keep these factors constant (25,26). The selection of the fixed density threshold influences the measured myocardial contrast medium appearance time, and thus the resulting coronary flow reserve. When however, this threshold is chosen so that background noise is eliminated and more than 90% of pixels in the chosen ROI reach the threshold, this influence is insignificant (see table 1).

Although we found a clear relationship between AS, MLCA and coronary flow reserve, individual coronary arteries, with moderate CAD may differ considerably in coronary flow reserve. Approaches that integrate all angiographic dimensions are conceptually attractive (21), but limited by the fact that coronary flow is estimated. We used theoretical flows of 1, 2 and 3 ml/sec to define the pressure-flow relationship since resting coronary blood flow in a LAD is 1.3 (range 1.0 - 2.1) ml/s (6).

Many other factors are potential causes of a decreased coronary flow reserve. In addition to cardiac hypertrophy and previous myocardial infarction, anemia, polycythemia, valvular heart disease and collateral circulation may influence coro-

nary flow reserve (27-30). We have carefully tried to exclude patients with these conditions.

Changes in vasomotor tone are not only an important source of variability in the analysis of the coronary angiogram (4) but may also influence the coronary flow reserve measurement (30,31). Therefore, we continued the medical treatment including nitrates and calcium antagonists in all our patients with CAD on the day of the investigation. Most important to our study, this could affect the papaverine induced change in the geometry of stenosis. The increase in MLCA (mean 24%, range: 8-39%) and the decrease in AS (mean 3%, range: 0-9%) are methodologically disturbing, since they result in an increase in the measured coronary flow reserve and contribute to the variability in the relation between AS, MLCA and coronary flow reserve. Alterations in the volume of the epicardial coronary artery could also influence the measurement of coronary flow reserve by changing the coronary blood flow velocity and thus myocardial appearance time of the contrast medium. However, intracoronary papaverine did not change the diameter of normal coronary arteries nor the diameter of pre- and post-stenotic coronary artery segments. This is contrary to the findings of others (31), and probably a consequence of the medical treatment. Finally, these findings can not be extrapolated to other patient subsets, for instance patients with more diffuse CAD, collateral circulation or stenosis in more distal coronary arteries of smaller size.

In conclusion, the development of a digital angiographic technique to measure regional coronary flow reserve and computer based quantitative analysis of the coronary angiogram, including automated contour detection, has made the assessment of the relationship between a coronary artery stenosis and its physiological consequences possible in human beings during cardiac catheterization. The reduction in coronary flow reserve as a result of a coronary stenosis can be predicted with reasonable accuracy by quantitative assessment of coronary artery dimensions.

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CHAPTER 6: WHICH CINEANGIOGRAPHICALLY ASSESSED ANATOMIC PARAMETER CORRELATES BEST WITH FUNCTIONAL MEASUREMENTS OF STENOSIS SEVERITY? A COMPARISON OF QUANTITATIVE ANALYSIS OF THE CORONARY CINEANGIOGRAM WITH MEASURED CORONARY FLOW RESERVE AND EXERCISE/REDISTRIBUTION THALLIUM-201 SCINTIGRAPHY.

Abstract

The goal of this investigation was to establish which measured anatomic parameter of stenotic lesions correlates best with functional severity. Therefore, 38 patients with single vessel disease underwent coronary cineangiography and exercise/redistribution thallium-201 scintigraphy. The computerbased Cardiovascular Angiography Analysis System was used to determine the cross-sectional area at the site of obstruction (OA), percentage diameter stenosis (DS), and calculate the pressure drop over the stenosis (PD) using fluid dynamic equations. Coronary flow reserve was measured radiographically. Myocardial perfusion defects on thallium scintigrams were analysed quantitatively and by visual interpretation. The relations between coronary flow reserve (CFR) and the 3 anatomic parameters were described by the following equations:
CFR = 4.6 - 0.053 DS, r = 0.82, SEE: 0.79.
CFR = 0.5 + 0.75 OA, r = 0.87, SEE: 0.68.
CFR = 3.6 - 1.5 log PD, r = 0.90, SEE: 0.62.
The calculated pressure drop was highly predictive of the thallium scintigraphy results with a sensitivity of 94% and a specifity of 90%. The calculated pressure drop is a better anatomic parameter for assessing the functional importance of a stenosis than percentage diameter stenosis or obstruction area. However the 95% confidence limits of the relation between pressure drop and coronary flow reserve are wide making the measurement of coronary flow reserve an indispensable addition to quantitative angiography, especially when determining the functional importance of moderately severe coronary artery lesions.

Introduction

Visual interpretation of the coronary cineangiogram inadequately predicts the physiological importance of obstructive coronary artery disease (1). Computer-based quantitative analysis has helped minimize the problems of high interobserver and intraobserver variability in the assessment of the anatomic severity of a coronary obstruction (2), and allows the calculation of the pressure-flow characteristics of a coronary stenosis (3). Exercise/redistribution thallium-201 perfusion scintigraphy has been used extensively as a noninvasive means to study the functional consequences of a coronary artery stenosis (4,5,6). Recently, the concept of

coronary flow reserve has been introduced as a physiological measurement of stenosis severity (7,8) and the development of digital angiographic techniques has made this measurement possible during cardiac catheterization (9,10). In a previous study (10) we investigated the relation between minimal cross-sectional obstruction area, percentage area stenosis and coronary flow reserve. We found a considerable scatter of the data despite excellent overall correlations between these two quantitative angiographic parameters and coronary flow reserve. Approaches that integrate all angiographically determined dimensions of an obstruction, such as the calculated pressure-drop over the stenosis, are attractive as they may allow a better angiographic description of functional stenosis severity (10,11). The goal of this investigation was to study which quantitative cineangiographic parameter correlates best with functional measurements of stenosis severity. We compared percentage diameter stenosis, minimal cross-sectional obstruction area and calculated pressure-drop across the stenosis with radiographically measured coronary flow reserve and the results from exercise/redistribution thallium-201 perfusion scintigraphy.

Patients and methods

Thirty eight patients with single vessel coronary artery disease were studied. The diseased vessel was the left anterior descending coronary artery in 30 patients, the circumflex coronary artery in 5 patients and the right coronary artery in 3 patients. Their mean age was 53 years (range 31-68 years). Thirty four (89%) patients were male. Coronary cineangiography was performed as part of an ongoing restenosis study after percutaneous transluminal coronary angioplasty (28 patients), or for chest pain syndromes (10 patients). Informed consent was obtained for the additional investigations. All patients were studied without premedication, but their medical treatment was continued on the day of the investigation (the 28 angioplasty patients: calcium antagonist and antiplatelet agent, the remaining 10 patients: nitrates, calcium antagonists and beta-blockers). Left ventriculography was performed in all patients and showed normal systolic and diastolic wall motion with an ejection fraction of more than 55%. Patients with systemic hypertension, cardiac hypertrophy, documented previous myocardial infarction, valvular heart disease, angiographic evidence of collateral circulation, anemia or polycythemia were excluded as these conditions may influence coronary flow reserve (12-14).

Exercise thallium scintigraphy

The patients performed a symptom-limited exercise test on a bicycle ergometer with stepwise increments of 20 Watt/min on

the day before the cardiac catheterization. All patients exercised to more than 80% of their expected normal exercise capacity (corrected for age, sex and height). This procedure has previously been described (15-17). One minute prior to maximal exercise, 1,5 mCi Tl-201 was administered. Planar imaging was started 3 min. later in 3 views: anterior, left anterior oblique 45° and 65°. These same static planar images were repeated at rest 4 hours later (redistribution imaging). The exercise and redistribution images were processed on a DEC gamma-11 system with a quantification procedure developed at our institution (15,16). The exercise and redistribution images were spatially registered in the computer on the basis of the detected positions of point sources defined with a cobalt markerpen at two positions on the patients chest. Following automated left ventricular contour detection and interpolative background correction, exercise, redistribution and washout circumferential profiles were computed at 6° intervals (quantitative thallium perfusion analysis). The late circumferential profiles were normalized to a delay of 4 hours between the early and late images. The profiles of the early and late images were normalized to 100% and compared with normal values defined by the 10th and 90th percentiles of the profiles of a group of individuals without apparent heart disease. Semiquantitative thallium uptake in all regions was scored both in the immediate post exercise and late images on a 3-point scale. The scores of regions related to the diseased coronary artery were summed per patient and the difference between the post-exercise and late images was taken as a measure of the amount of redistribution between the post-exercise and late images. The analog Polaroid images from the gamma camera, the background corrected images and the circumferential profiles were interpreted prospectively on a routine basis by 3 experienced observers without knowledge of the angiographic data. Transient and persistent defects were considered abnormal (15,16).

Quantitative coronary cineangiography

The coronary arterial dimensions were determined with the computer-based Cardiovascular Angiography Analysis System (CAAS) (2,10,18). In essence, the boundaries of a selected coronary artery segment were detected automatically from optically magnified and video digitized regions of interest of a cineframe. Calibration of the diameter data in absolute values (mm) was achieved by detecting the boundaries of a section of the contrast catheter and comparing the mean diameter in pixels with the known size in millimeter (19). The contour positions of the arterial and catheter segments were corrected for the pincushion distortion (18). A computer-estimation of the original arterial dimensions at the site of obstruction was used to define the reference region (18). The

interpolated percentage diameter stenosis and the minimal obstruction area (mm^2) were calculated by averaging the values from at least two, preferably orthogonal angiographic views. The length of the obstructions was assessed from curvature analysis of the derived diameter function. A mean of 2.3 angiographic views per patient was used in this study.

The theoretical pressure drop for an hyperemic flow of three times resting coronary blood flow was calculated according to the following hemodynamic equation (10,11,20):

$$PD = f\ Q + s\ Q^2$$

where PD = pressure drop, f = coefficient of viscous resistance and s = coefficient of separation resistance. Volume flow was calculated from the interpolated reference cross-sectional area, assuming a coronary blood flow velocity of 15 cm/s.

Coronary flow reserve measurements

The coronary flow reserve measurement with digital subtraction cineangiography from 35 mm cinefilm has been implemented on the CAAS (10). The heart was atrially paced at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery was made with a fixed amount of jopamidol through a Medrad Mark IV infusion pump. The injection rate of the contrast medium was judged to be adequate when back flow of contrast medium into the aorta occurred. The angiogram was repeated 30 sec after pharmacologically induced hyperemia by a bolus injection of 12.5 mg papaverine into the coronary artery. Five end-diastolic cineframes were selected from successive cardiac cycles. Logarithmic nonmagnified mask-mode background subtraction was applied to the image subset to eliminate noncontrast medium densities. The last end-diastolic frame prior to contrast administration was chosen as the mask. From the sequence of background subtracted images, a contrast arrival time image was determined, using an empirically derived fixed density threshold (10). In addition to the contrast arrival time image, a density image was computed, with each pixel intensity value being representative for the maximal local contrast medium accumulation. Coronary flow reserve (CFR) was then be calculated as:

$$CFR = Qh/Qb = Dh/Th : Db/Tb$$

where Q is regional blood flow, D is the mean contrast density and T the mean appearance time at baseline (b) and hyperemia (h). Mean contrast medium appearance time and density were computed within user-defined regions of interest that were chosen in such a way that the epicardial coronary arteries

visible on the angiogram, the coronary sinus and the great cardiac vein were excluded from the analysis. Normal values for coronary flow reserve in our laboratory have been established. In 24 patients (12 have been published previously (10) with normal coronary arteries and absence of factors known to decrease vascular reserve, the coronary flow reserve (mean ± SD) was 5.0 ± 0.8. Therefore, a coronary flow reserve is defined as normal when greater or equal to 3.4.

Statistical analysis

Least squares linear and non-linear regression analyses were used to define the best-fit relations between the quantitative cineangiographic parameters and coronary flow reserve. The differences between the measured coronary flow reserve and the best-fit relations were compared with variance analysis and the student-t test for paired observations, to determine which quantitative angiographic parameter correlates best with coronary flow reserve.

Results

The measured coronary flow reserve ranged from 0.4 to 5.5. The interpolated reference area ranged from 2.9 to 9.4 mm^2, the length of the stenotic lesions ranged from 3.2 to 18.6 mm, the obstruction area ranged from 0.4 to 6.8 mm^2 and the diameter stenosis ranged from 6 to 75%. The calculated pressure-drop ranged from 0.3 to 144 mmHg. The thallium uptake score on the post exercise images ranged from 0 to 12, the thallium uptake score on the late images ranged from 0 to 8. The difference in score between post exercise and late images (redistribution) ranged from 0 to 10. The quantitative analysis of the circumferential post exercise and late thallium images revealed a mean defect on the post exercise image of 157 (range 0-1094), on the late image 68 (range 0-399) with a mean difference (redistribution) of 89 (range 0-1081). The final result of the thallium analysis procedure was that the 3 observers judged 18 thallium scintigrams to indicate exercise induced ischemia. The sensitivity and specifity of thallium scintigraphy to detect patients with an abnormal coronary flow reserve (less than 3.4) was 17/25 = 68% and 18/18 = 100% respectively.

Relations between percentage diameter stenosis, obstruction area, calculated pressure drop and measured coronary flow reserve.

The relation between coronary flow reserve (CFR) and percentage diameter stenosis (DS) was best described by the equation:
CFR = 4.6 - 0.053 DS, (r=0.82, SEE: 0.79), see fig. 1.

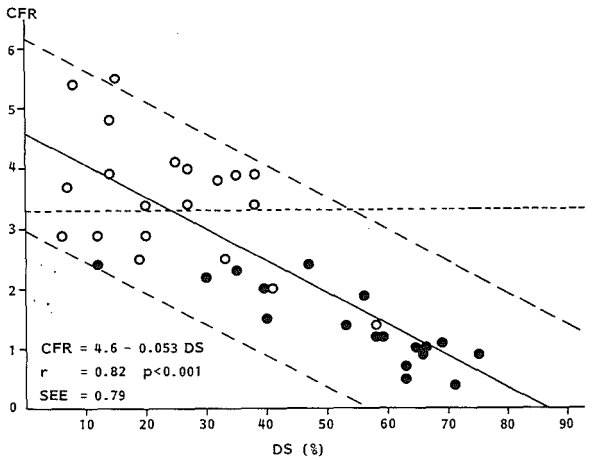

Figure 1
Relation between coronary flow reserve (CFR), thallium scintigraphy and percentage diameter stenosis (DS). The dashed horizontal line is the lower limit of mormal coronary flow reserve. The black circles represent patients with a positive thallium scintigram. The open circles represent patients with a negative thallium scintigram.

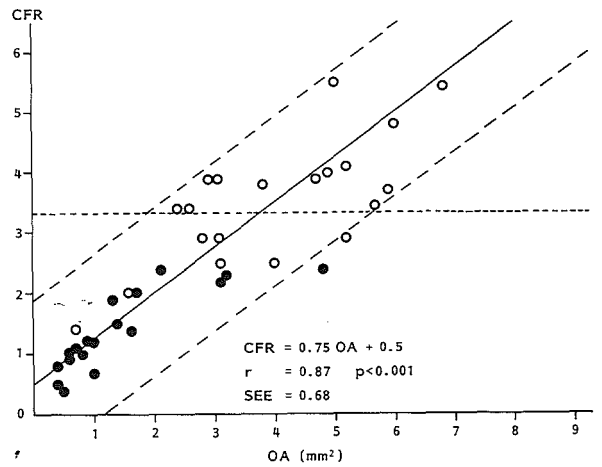

Figure 2.
Relation between coronary flow reserve (CFR), thallium scintigraphy and cross-sectional obstructive area (OA), in the same format as fig. 1.

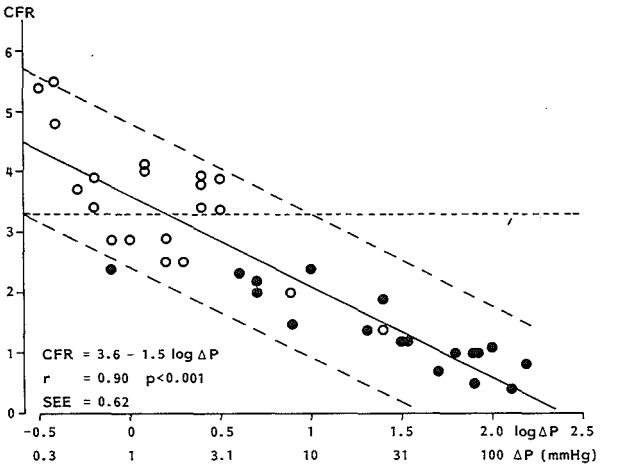

Figure 3
Relation between coronary flow reserve (CFR), thallium scintigraphy and calculated pressure-drop (PD), in the same format as fig. 1.

Table 1: Prediction of measured coronary flow reserve with quantitative cineangiography.

X-ray predicted CFR = 2.5	95% confidence limits measured CFR
DS: 40%	0.9 - 4.1
OA: 2.7 mm^2	1.1 - 3.9
PD: 5.6 mmHg	1.3 - 3.7

CFR = coronary flow reserve; DS = percentage diameter stenosis; OA = obstruction area; PD = calculated pressure-drop over the stenosis.

The relation between coronary flow reserve and obstruction area (OA) was best described by the equation:
CFR = 0.75 OA + 0.5, (r=0.87, SEE: 0.68), see fig. 2.
The relation between coronary flow reserve and the calculated pressure-drop (PD) was best described by the equation:
CFR = 3.6 - 1.5 log PD, (r=0.90, SEE: 0.62), see fig. 3.
The calculated pressure drop correlated significantly better (p = less than 0.05) with measured coronary flow reserve than percentage diameter stenosis and obstruction area.

The predictive value of the 3 angiographic parameters in relation to the measured coronary flow reserve is shown in table 1 by giving the 95% confidence intervals for a predicted coronary flow reserve of 2.5. The sensitivity and specificity of the 3 angiographic parameters in identifying patients with an abnormal measured coronary flow reserve is shown in figure 4 and a positive Thallium scintigram is shown in figure 5.

Discussion

In the experimental animal the physiological significance of artificially produced arterial stenoses have been extensively studied (20,22). Gould et al produced varying degrees of coronary narrowing and showed that stenoses in excess of 30-45% diameter narrowing reduced coronary vasodilator responses in a predictable fashion (22). However, in human beings with coronary artery disease the relation between the visually estimated percentage diameter stenosis and the consequent reduction in coronary flow reserve is poor (1). The two basic problems that have hampered the assessment of the relation between the angiographic degree of stenosis and the actual impairment of perfusion, now seem to have been solved by new technical developments. Firstly, the recent description of a technique using digital subtraction has rendered the assessment of regional coronary flow reserve possible during cardiac catheterization (9,10). Secondly, the visual assessment of the

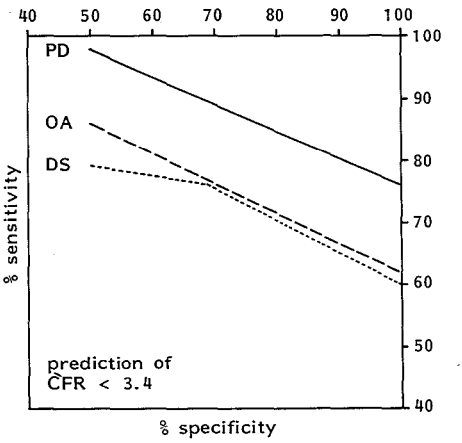

Figure 4
Sensitivity and specificity of the three angiographic parameters to predict an abnormal coronary flow reserve (< 3.4). PD = calculated pressure drop (range: 3 to 30 mmHg), OA = obstruction area in mm^2 (range: 0.5, to 4.5 mm^2) and DS = percentage diameter stenosis (range: 30 to 60 %)

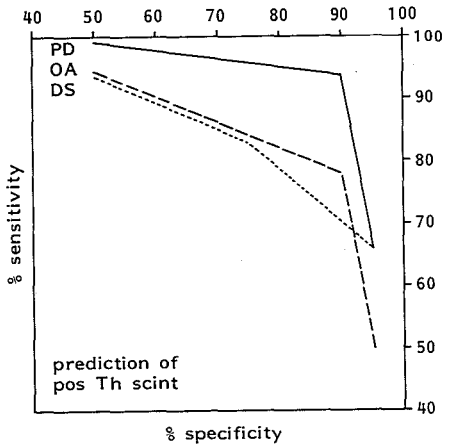

Figure 5
Sensitivity and specificity of the three angiographic parameters to predict a positive thallium scintigram. Abbreviations as fig. 4.

coronary angiogram with its large intraobserver and interobserver variability has made way for computer-based quantitative analysis of the coronary angiogram including automated contour detection, which improves accuracy and allows for the precise determination of most dimensions of a given stenosis in a coronary artery (2,18).

Description of stenosis severity.

The measurement of percent diameter narrowing is the most commonly employed descriptor of stenosis severity, but its use has several disadvantages. Firstly, McPherson et al (23) have documented that substantial diffuse intimal atherosclerosis is often present, even when angiograms reveal only discrete lesions. This may make the estimation of the normal dimensions of a coronary artery impossible and precludes the use of relative measures of stenosis severity. This may explain why 12 of our patients with a percentage diameter stenosis of less than 50% had a (moderately) reduced coronary flow reserve. The obstruction area (mean ± SD) of these patients was 3.0 ± 1.0. Six of these patients also had a thallium scintigram indicating exercise induced ischemia. Secondly, many factors besides percentage diameter stenosis have a significant influence on the pressure-flow characteristics of a stenosis (24). Harrison et al (25) compared relative and absolute measurements of stenosis severity to coronary flow velocity reserve and concluded that obstruction area (mm^2) was a better descriptor of stenosis severity than percentage area stenosis in a patient population with probably extensive diffuse coronary artery disease. In patients with a discrete stenosis and little diffuse disease, relative and absolute measurements of stenosis severity convey the same information (10,26).
The present study confirms that both percentage diameter stenosis and obstruction area correlate well with functional measurements of stenosis severity such as measured coronary flow reserve and thallium scintigraphy. However, for individual patients the prediction of coronary flow reserve using percentage diameter stenosis and/or obstruction area is limited by the wide 95% confidence intervals (see table 1). Wilson et al. reported a comparable correlation between these two parameters and flow reserve with similar wide 95% confidence intervals (26). Approaches that integrate several angiographic dimensions are conceptually attractive, and have been validated in dogs (11). The 95% confidence limits of the relationship between pressure drop and coronary flow reserve are less than those between obstruction area or percentage diameter stenosis and coronary flow reserve. This indicates that the calculated pressure drop over the stenosis as an integrated measurement of multiple angiographic parameters is indeed a more accurate anatomic description of the functional consequences of a coronary artery lesion. The calculated

pressure drop is a better parameter to differentiate patients with normal from abnormal coronary flow reserve, and predicts the results of thallium scintigraphy more accurately. A reliable non-invasive method to predict measured coronary flow reserve in individual patients would be a valuable tool for clinical decision making. Our results show that planar exercise/redistribution thallium-201 scintigraphy, even with semiquantitative or quantitative analysis only partly fulfills this task. The results of the thallium perfusion analysis procedure showed that thallium perfusion may be normal when coronary flow reserve is moderately reduced (between 2.5 and 3.4). Nevertheless, almost all patients with severe reduction in flow reserve (less than 2.5) had a positive thallium scintigram. Therefore thallium scintigraphy can be useful in selected patients, for instance to assess the occurrence of restenosis after angioplasty for single vessel coronary artery disease (17).

Limitations

The fact that our study involved predominantly lesions of the proximal left anterior descending artery should be taken into consideration, and our results can therefore not be extrapolated to mid and/or distal lesions in the coronary tree.

Conclusion

The calculated pressure drop over a stenosis, as an integrated measurement of multiple angiographic dimensions, is a better anatomic predictor of the functional importance of a coronary stenosis than percentage diameter stenosis and obstruction area. However, the 95% confidence limits of the relation between pressure-drop and coronary flow reserve are wide, making practical means to measure coronary flow reserve an indispensable addition to quantitative angiography especially to determine the functional importance of moderately severe coronary artery lesions.

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CHAPTER 7:CORRELATIONS BETWEEN ANGINA PECTORIS, NON-INVASIVE EVIDENCE OF MYOCARDIAL ISCHEMIA, CORONARY ARTERY DIMENSIONS AND CORONARY FLOW RESERVE.

Summary

The correlations between clinical manifestations of obstructive coronary artery disease (angina pectoris and non-invasive evidence of myocardial ischemia), quantitatively determined coronary artery geometry and radiographically measured coronary flow reserve were studied in 81 patients. 57 patients had a single, discrete and proximal lesion, with coronary flow reserves ranging from 0.4 to 5.5, 24 patients had angiographically normal coronary arteries, with coronary flow reserves ranging from 3.4 to 6.5 (mean ± SD: 5.0 ± 0.8). Therefore, we defined a normal coronary flow reserve as greater or equal 3.4. The correlations between measured coronary flow reserve (CFR) and cross-sectional obstruction area (OA), percentage area stenosis (AS) and X-ray predicted coronary flow reserve (X-ray), were best described by the following equations respectively: CFR= 0.18 + 1.07 OA -0.058 OA^2,r= 0.98, SEE=0.66, CFR= 4.8 -0.024 AS -0.00022 AS^2, r= 0.98, SEE= 0.73, and CFR= 1.58 - 0.36 $(X\text{-ray})^2$ + 0.097 $(X\text{-ray})^3$, r= 0.98, SEE= 0.68. The sensitivity and specificity of the 3 angiographic parameters to identify patients with a normal or abnormal measured coronary flow reserve was virtually the same.

All 37 patients without angina pectoris at rest or during exercise testing, and without non-invasive evidence of myocardial ischemia had a coronary flow reserve greater than 2.5 (mean ± SD: 4.4 ± 1.0, range: 2.5 - 6.5). All 27 patients with angina pectoris at rest or during exercise testing, and non-invasive evidence of myocardial ischemia had a coronary flow reserve 2.5 (mean ± SD: 1.1 ± 0.5, range: 0.4 - 2.4). 17 patients had either angina pectoris or non-invasive evidence of myocardial ischemia, with flow reserves ranging from 0.9 - 5.5.

Introduction

Atherosclerosis, the most important disease affecting the coronary circulation, manifests itself primarily by producing vascular obstruction. As the atherosclerotic plaque enlarges within the vessel wall, the vascular lumen is progressively compromised. The clinical manifestations of coronary heart disease (angina, non-invasive evidence of myocardial ischemia, myocardial dysfunction, acute myocardial infarction, sudden death) depend in large part on the severity of the obstructive lesions (1). Consequently, a major effort has been put forth to define the physiological significance of coronary stenoses

in animals (2-6) as well as patients (7-10). Recently, measurement of the coronary flow reserve has been proposed as method to evaluate the hemodynamic repercussions of a coronary stenosis (11,12). Two techniques have been developed that allow the measurement of regional coronary flow reserve in conscious humans. The first uses a pulsed Doppler coronary artery catheter which can measure intracoronary blood flow velocity (13). The second technique is based on the radiographic assessment of myocardial perfusion using contrast medium (9,10,14-17). This technique has the advantage that no guide wire or other hardware has to be introduced into the coronary artery, and it can therefore be applied during routine cardiac catheterization.

Visual interpretation of the coronary angiogram correlates poorly with the measured coronary flow reserve (7). Computer-based quantitative analysis has solved the problems of high interobserver and intraobserver variability in the assessment of the coronary angiogram (18,19), and it allows the accurate determination of coronary artery dimensions (20). Quantitatively determined percent area stenosis and minimal cross-sectional area at the site of obstruction show a good overall correlation with measured coronary flow reserve in patients with limited coronary artery disease (8,9). However, the prediction of coronary flow reserve of an individual coronary artery is hampered by the wide 95% confidence limits of these relations. Kirkeeide et al (21) have proposed to calculate an X-ray predicted coronary flow reserve taking percent narrowing, absolute stenosis area and the length of the stenotic segment into account by use of fluid dynamic equations. A good correlation between such an angiographic approach and measured coronary flow reserve was found in dogs (21).

The purpose of this study was to investigate the correlations between the clinical manifestions of obstructive coronary artery disease (angina pectoris, non-invasive evidence of myocardial ischemia), quantitatively determined coronary artery dimensions (minimal cross-sectional area, percentage area stenosis, X-ray predicted coronary flow reserve) and radiographically measured coronary flow reserve.

Patients and methods

57 patients with single vessel coronary artery disease and 24 patients with angiographically normal coronary arteries were studied. Cardiac catheterization was performed for clinical indications without premedication. The pharmacological treatment of the patients with angina pectoris and/or non-invasive evidence of myocardial ischemia (N=44) was continued on the day of the catheterization. It consisted of metoprolol (N=37), and/or isosorbidemononitrate (N=33), and/or nifedipine (N=43). All coronary artery obstructions were

single, discrete lesions in a proximal part of a coronary artery that apart from this lesion appeared angiographically normal. In 53 patients the left anterior descending coronary artery was the investigated vessel, in 18 patients the circumflex coronary artery and in 10 patients the right coronary artery. None of the patients had systemic hypertension, cardiac hypertrophy, anemia, polycythemia, documented previous myocardial infarction, valvular heart disease or angiographic evidence of collateral circulation. Before the cardiac catheterization the clinical history of the patients was obtained by a cardiologist not involved in the quantitative analyses of coronary artery dimensions or the coronary flow reserve measurements. 10 patients had unstable angina pectoris with chest pain at rest and concommitant ischaemic ST-T segment changes. The presence or absence of angina pectoris and non-invasive evidence of myocardial ischemia during exercise testing were recorded in the remaining 71 patients. 25 patients had angina pectoris during exercise testing. Non-invasive evidence of myocardial ischemia was defined as ST-T segments changes during exercise and/or reversible defects on thallium perfusion scintigrams. The methodology of exercise testing and thallium scintigraphy employed in our institution has been described (22).

Quantitative coronary cineangiography

The coronary arterial dimensions were determined with the computer-based Cardiovascular Angiography Analysis System (20). The boundaries of selected coronary artery segments were detected automatically from optically magnified and video-digitized regions of interest of a cineframe. Calibration of the diameter data in absolute values (mm) was achieved by detecting the boundaries of a section of the contrast catheter and comparing the mean diameter in pixels with the known size in millimeter (23). Pincushion distortion was corrected (20). A computer estimation of the original arterial dimensions at the site of obstruction was used to define the reference region (20). The interpolated percentage area stenosis and the minimal cross-sectional area (mm^2) at the site of obstruction were calculated by averaging the values from at least two, preferably orthogonal projections. The length of the stenotic segments was determined using curvature analysis. X-ray predicted coronary flow reserve was calculated as developed by Kirkeeide et al (21) and modified by Herrold and Borer (24).

Coronary flow reserve measurements

This procedure has been described (9,17,25). The heart was atrially paced at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery was made with a fixed amount of jopamidol through a Medrad Mark IV

infusion pump. The injection rate of the contrast medium was judged to be adequate when back flow of contrast medium into the aorta occurred. The angiogram was repeated 30 sec after a bolus injection of 12.5 mg papaverine into the coronary artery (9). Five or six end-diastolic cineframes were selected from successive cardiac cycles. Logarithmic non-magnified mask-mode background subtraction was applied to the image subset, to eliminate non-contrast medium densities. The last end-diastolic frame prior to contrast administration was chosen as the mask. A contrast appearance time was determined, using an empirically derived density threshold (9). A density image was computed, with each pixel intensity value being representative for the maximal local contrast medium accumulation. The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image (Qh) divided by the regional flow of the corresponding baseline image (Qb). Coronary flow reserve (CFR) was then calculated as:

$$CFR = Qh/Qb = Dh/Th : Db/Tb$$

where D is the mean contrast density and T the mean appearance time at baseline (b) and hyperemia (h). Appearance time and density were computed within user-defined regions of interest that were chosen in such a way that the epicardial coronary arteries visible on the angiogram, the coronary sinus and the great cardiac vein were excluded from the analysis (9).

Statistical methods

Least square regression analyses were used to find the "best fit" relation between coronary flow reserve and the quantitatively assessed coronary artery dimensions.

Results

The minimal cross-sectional area of the 81 coronary arteries ranged from 0.4 to 10.3 mm^2, the percentage area stenosis ranged from 0 to 93%, the calculated X-ray predicted coronary flow reserve ranged from 1.6 to 5.0. The measured coronary flow reserve ranged from 0.4 to 5.5 in the 57 patients with single vessel disease. The 24 patients with angiographically normal coronary arteries had a measured coronary flow reserve ranging from 3.4 to 6.5 with a mean value (± SD) of 5.0 (± 0.8). The relationship between coronary flow reserve (CFR) and cross-sectional area at the site of obstruction (OA) was best described by the equation:

$$CFR = 0.18 + 1.07\ OA - 0.058\ OA^2,\ r = 0.98,\ SEE = 0.66,$$

and is shown in figure 1. The relationship between coronary flow reserve and percentage area stenosis (AS) was best described by the equation:

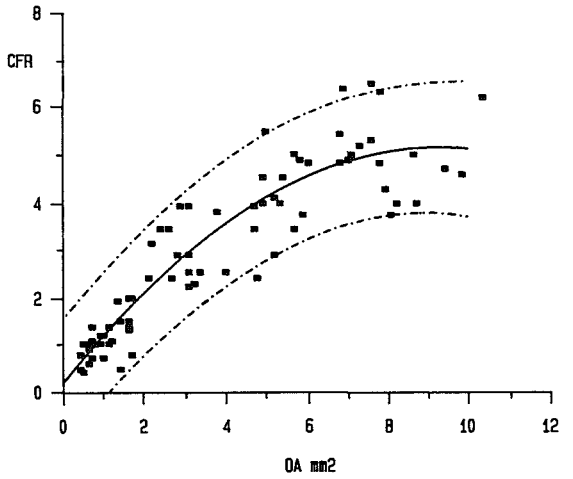

Figure 1
Correlation between coronary flow reserve and cross-sectional area at the site of obstruction. CFR = coronary flow reserve, OA = cross-sectional area at the site of obstruction. The best fit curve and the 95 % confidence limits (dashed lines) are shown.

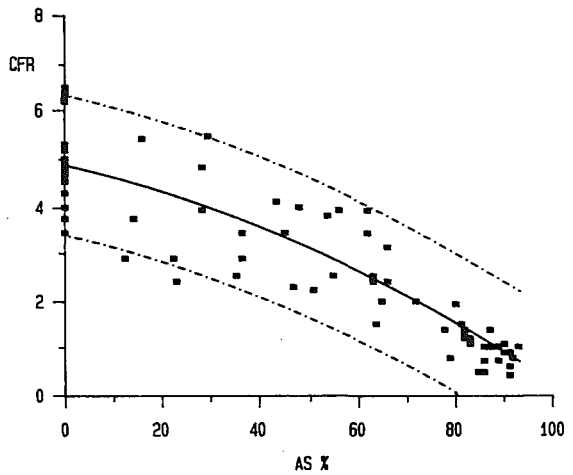

Figure 2
Correlation between coronary flow reserve and percentage area stenosis. CFR = coronary flow reserve, AS = percentage area stenosis. The best fit curve and the 95 % confidence limits (dashed lines) are shown.

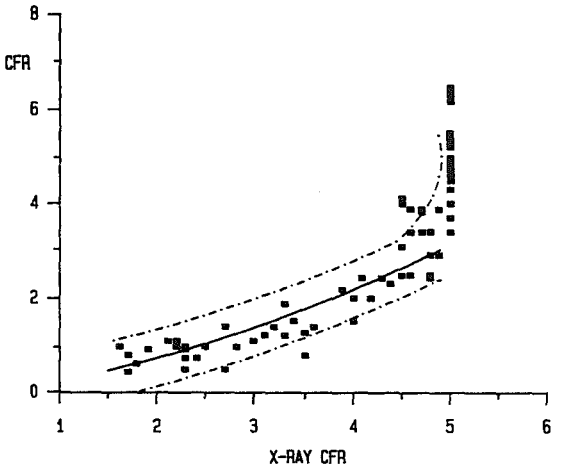

Figure 3
Correlation between coronary flow reserve and X-ray predicted coronary flow reserve calculated according to Kirkeeide et al [20]. CFR = coronary flow reserve, X-ray CFR = X-ray predicted coronary flow reserve. The best fit curve and the 95 % confidence limits (dashed lines) are shown.

$CFR = 4.8 - 0.024\ AS - 0.00022\ AS^2$, $r = 0.98$, $SEE = 0.73$,

and is shown in figure 2. The relationship between measured coronary flow reserve and X-ray predicted coronary flow reserve (X-ray) was best described by the equation:

$CFR = 1.58 - 0.36\ (X\text{-ray})^2 + 0.097\ (X\text{-ray})^3$, $r = 0.98$, $SEE = 0.68$,

and is shown in figure 3.

We defined a normal measured coronary flow reserve as greater or equal to 3.4 (2 SD below the mean coronary flow reserve of the 24 angiographically normal coronary arteries). The sensitivity and specificity of cross-sectional obstruction area, percentage area stenosis and X-ray predicted coronary flow reserve to identify patients with a normal measured coronary flow reserve is shown in figure 4.

The patients were subdivided into 4 groups according to the clinical manifestations of coronary artery disease. 37 patients had no angina pectoris and no non-invasive evidence of myocardial ischemia (group I), 9 patients had non-invasive evidence of myocardial ischemia without angina pectoris (group II), 8 patients had angina pectoris and no non-invasive evidence of myocardial ischemia (group III), 27 patients had angina pectoris as well as non-invasive evidence of myocardial ischemia (group IV), see table 1. The relationship between cross-sectional obstruction area, percentage area stenosis, X-ray predicted coronary flow reserve, measured coronary flow reserve and the clinical manifestations (angina pectoris, non-invasive evidence of myocardial ischaemia) is shown in figures 5A,5B,6A and 6B respectively. The measured coronary flow reserves of all patients in group I were greater or equal to 2.5, whereas all patients in group IV had a coronary flow reserve less than 2.5. A cutt-of value of 2.5 for measured coronary flow reserve therefore separates patients with clear-cut evidence of ischemia from those without clinical evidence of ischemia.

The predictive value of angina pectoris at rest or during exercise testing to identify patients with a coronary flow reserve less than 2.5 was 91% (32 of 35 patients). The predictive value of no angina pectoris to identify patients with a coronary flow reserve greater or equal to 2.5 was 89% (41 of 46 patients). The predictive value of non-invasive evidence of myocardial ischemia to identify patients with a coronary flow reserve less than 2.5 was 86% (31 of 36 patients). The predictive value of no non-invasive evidence of myocardial ischemia to identify patients with a coronary flow reserve greater or equal 2.5 was 89% (40 of 45 patients).

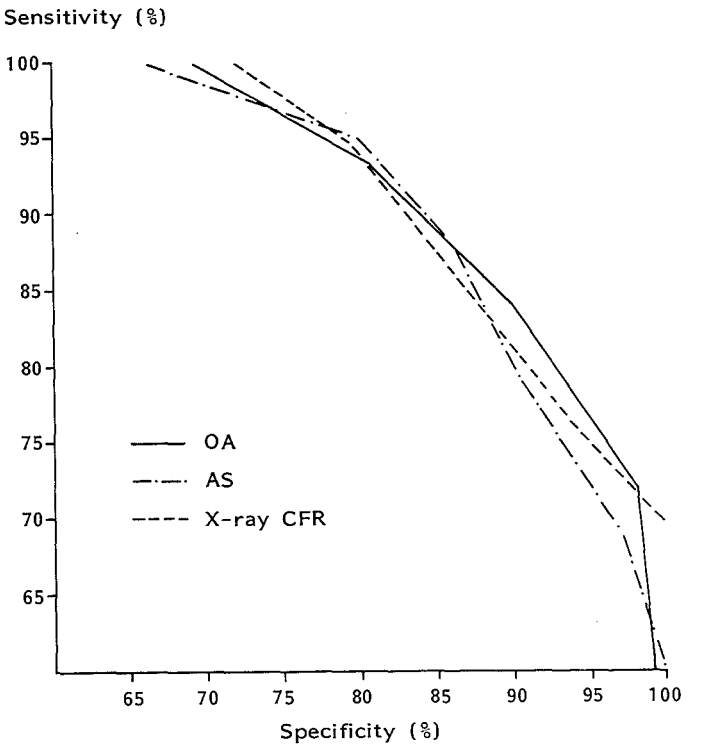

Figure 4
Sensitivity and specificity of cross-sectional obstruction area (OA), percentage area stenosis (AS) and X-ray predicted coronary flow reserve (X-ray CFR), to identify patients with a normal measured coronary flow reserve (> 3.4).

Table 1: Relation between angina pectoris, non-invasive evidence of myocardial ischemia, coronary artery dimensions and coronary flow reserve

	N	coronary artery dimensions											
		OA (mm^2)			AS %			X-ray pred CFR					
		mean	SD	range	mean	SD	range	mean	SD	range	mean	SD	range
I	37	6.2	2.1	2.4-10.3	15	23	0-62	4.9	0.2	4.5-5.0	4.4	1.0	2.5-6.5
II	9	3.1	1.3	1.6-4.9	50	20	22-78	4.3	0.5	3.6-4.9	2.4	0.7	1.4-4.0
III	8	2.7	2.2	0.6-6.8	62	26	16-91	4.0	0.9	2.3-5.0	2.8	1.8	0.9-5.5
IV	27	1.0	0.6	0.4-3.2	84	10	47-93	2.7	0.8	1.6-4.4	1.1	0.5	0.4-2.4

I = no angina pectoris and no non-invasive evidence of myocardial ischemia, II = no angina pectoris and non-invasive evidence of myocardial ischemia, III = angina pectoris without non-invasive evidence of myocardial ischemia, IV = angina pectoris and non-invasive evidence of myocardial ischemia, N = number of patients, OA = cross-sectional area at the site of obstruction, AS = percentage area stenosis, X-ray pred CFR = X-ray predicted coronary flow reserve.

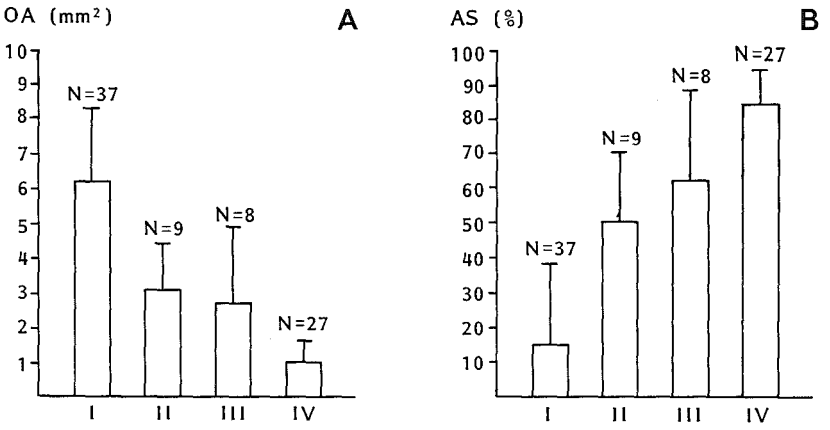

Figure 5A
Correlation between cross-sectional area at the site of obstruction (OA) and clinical manifestations of coronary artery disease. N = number of patients, I = no angina pectoris and no non-invasive evidence of myocardial ischemia, II = non-invasive evidence of myocardial ischemia without angina pectoris, III = angina pectoris without non-invasive evidence of myocardial ischemia, IV = angina pectoris and non-invasive evidence of myocardial ischemia.
Figure 5B
Correlation between percentage area stenosis (AS) and clinical manifestations of coronary artery disease. Abbreviations as figure 5A.

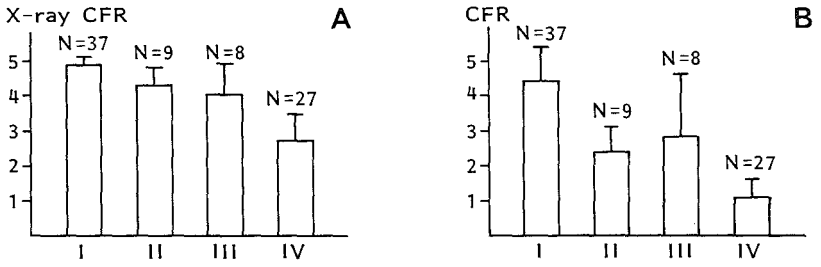

Figure 6A
Correlation between X-ray predicted coronary flow reserve calculated according to Kirkeeide et al [20] (X-ray CFR) and clinical manifestations of coronary artery disease. Abbrebiations as figure 5A.
Figure 6B
Correlation between radiographically measured coronary flow reserve (CFR) and clinical manifestations of coronary artery disease. Abbreviations as figure 5A.

Discussion

The major finding of this study is that the clinical manifestations of coronary artery disease correlate closely to measured coronary flow reserve, and quantitatively determined coronary artery dimensions, in a selected patient population with limited coronary artery disease. Many studies have investigated the relationship between the degree of coronary stenosis and the functional capacity of the coronary artery (3,4,7-9). Two approaches have been proposed to analyze this relationship in the clinical setting. Firstly, several methods have been developed to measure the regional coronary flow reserve (10,13), which is defined as the maximal coronary blood flow divided by the resting coronary blood flow (11,12). This approach has been validated in animals (4). Some recent studies in humans, as well as the results of this study, suggest that at least in selected patients, the measurement of coronary flow reserve reflects the physiological significance of a coronary stenosis (8,9). In angiographically normal coronary arteries we measured a coronary flow reserve (mean ± SD) of 5.0 ± 0.8, which is in accordance with other reports (9,13,26). Secondly, the development of computer-based quantitative analysis of the coronary angiogram has made the accurate determination of coronary artery dimensions possible (20). Not only the commonly used gold standard of stenosis severity, percent stenosis, but also other geometrical parameters such as absolute cross-sectional area at the site of obstruction, the angiographically normal cross-sectional area before and after the obstruction, length of the lesion, eccentricity and plaque area can be quantified. Based on fluid dynamic equations first derived by Young et al (27-29), the pressure flow characteristics of a coronary stenosis can be calculated. This has the advantage that multiple parameters of stenosis severity are taken into account (21,30). The calculated pressure drop across the stenosis has been shown to correlate with the measured transluminal pressure gradient and exercise thallium perfusion scintigraphy (31,32) and to predict with reasonable accuracy the consequent reduction in measured coronary flow reserve (9).

From the relationship between coronary perfusion pressure and coronary flow under conditions of maximal coronary vasodilation as described by Bache and Schwartz (33), and assuming a resting coronary flow velocity of 15 cm/s, Kirkeeide et al (21) calculated an X-ray predicted coronary flow reserve from the angiographic data. They showed in dogs a good correlation between such an angiographic approach and measured coronary flow reserve. This X-ray predicted coronary flow reserve is a function of the cross-sectional area of the stenosis, the cross-sectional area of the angiographically normal part of the coronary artery and the length of the lesion. Other factors, such as the exit angle and the relative asymmetry of

the stenosis are not taken into account, although they may be of hemodynamic significance (27-29). Nevertheless, we found that the 95% confidence limits of the relation between X-ray predicted coronary flow reserve and measured coronary flow reserve are somewhat less wide than the confidence limits of the correlations between flow reserve and percentage area stenosis or cross-sectional area. Unfortunately, the sensitivity and specificity of X-ray predicted coronary flow reserve to identify patients with a normal or abnormal coronary flow reserve is not superior to that of cross-sectional obstruction area or percentage area stenosis. The relationship between X-ray predicted and measured coronary flow reserve that we found, suggests that one or more of the assumptions made in these calculations that seem valid in animals, may not hold true in humans with coronary artery disease.

Limitations

Firstly, the present study is restricted to a highly selected patient population, with only one circumscript stenosis in an otherwise angiographically normal coronary artery. Our results cannot be extrapolated to the large majority of patients with coronary artery disease, who have multiple lesions in the same coronary artery and/or more than one diseased vessel. Furthermore, the relation between coronary flow reserve and coronary artery dimensions can be influenced by systemic hypertension (34), cardiac hypertrophy (35),previous myocardial infarction, valvular heart disease (36), anemia or polycythemia (37) or collateral circulation. Therefore we excluded patients with these conditions. Secondly, the extent of coronary atherosclerosis may be difficult to delineate angiographically. Mc Pherson et al (38) documented that substantial intimal atherosclerosis resulting in diffuse obstructive disease that involves the entire length of an epicardial artery is often present, even when angiograms reveal only discrete lesions. As a consequence, angiographic parameters of stenosis severity, especially when the angiographically "normal" part of the coronary artery is taken into account as is the case for percent area stenosis and X-ray predicted coronary flow reserve, may underestimate the functional severity of a lesion and therefore overestimate the functional capacity of the coronary artery.

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CHAPTER 8: A COMPARISON OF TWO METHODS TO MEASURE CORONARY FLOW RESERVE IN THE SETTING OF CORONARY ANGIOPLASTY: INTRACORONARY BLOOD FLOW VELOCITY MEASUREMENTS WITH A DOPPLER CATHETER, AND DIGITAL SUBTRACTION CINEANGIOGRAPHY.

Abstract

Intracoronary blood flow velocity measurements with a Doppler balloon catheter, and the radiographic assessment of myocardial perfusion with contrast media, before and after the intracoronary administration of papaverine, have previously been used to investigate regional coronary flow reserve. In the present study we applied both techniques in 21 patients to measure coronary flow reserve in the setting of coronary angioplasty. Pre-angioplasty (N=14) and post-angioplasty (N=19) measurements of coronary flow reserve were obtained by digital subtraction cineangiography in the myocardial region supplied by the dilated coronary artery, and with the Doppler probe in the proximal part of the dilated vessel. The reactive hyperemia following the final balloon inflation was recorded with the Doppler balloon catheter still positioned across the stenotic lesion. Coronary stenosis geometry was quantified with the Cardiovascular Angiography Analysis System.

When the epicardial stenosis was the only factor causing a reduction in coronary flow reserve, flow reserve measured with both digital subtraction cineangiography and with the Doppler probe correlated well with the cross-sectional area at the site of obstruction, r=0.88, SEE=0.36 and r=0.77, SEE=0.45 respectively. In contradistinction, if other factors decreasing coronary flow reserve were present (intimal dissection, left ventricular hypertrophy, previous myocardial infarction, collaterals) measurements obtained with both techniques correlated poorly with the cross-sectional area (r=0.55, SEE=0.57, and r=0.59, SEE=0.50). Flow reserve measurements obtained with digital subtraction cineangiography correlated well with the measurements obtained with the Doppler probe (r=0.85, SEE=0.38, and r=0.87, SEE=0.34), although the two approaches have methodologically nothing in common and their respective regions of interest (myocardium for the radiographic technique and intracoronary lumen for the Doppler technique) are basically different. Furthermore, the reactive hyperemia following the final balloon inflation was related to both the flow reserve measured with the angiographic technique (r=0.85, SEE=0.34) and the Doppler technique (r=0.83, SEE=0.32) using pharmacologically induced coronary vasodilation with intracoronary papaverine. This suggests that the same quantity of coronary flow reserve that can be recruited pharmacologically can be recruited by ischemia following a transluminal occlusion.

Introduction

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977 (1), the procedure has gained increasing importance in the treatment of coronary artery obstructions. So far, the immediate results of the procedure have been assessed by coronary angiography and the residual pressure gradient. However, the change in luminal size of an artery following the mechanical disruption of its internal wall cannot be assessed accurately from the detected angiographic contours (2,3). The measured residual pressure gradient may have short and long-term prognostic value, but it reflects only the hemodynamic state at rest (4-6). Recently the assessment of coronary flow reserve has been proposed as a better method to evaluate the functional results of dilatation of a coronary artery obstruction (7-10). Papaverine is currently regarded as the vasodilator of choice for the induction of maximal hyperemia, as intracoronary administration results in an immediate, potent and short-lasting hyperemia (11,12). Intracoronary blood flow velocity measurements with a Doppler probe, and the radiographic assessment of myocardial perfusion with contrast media have previously been used to investigate regional coronary flow reserve (13-17). In the present study we compared both techniques in the setting of PTCA, and compared the pharmacologically induced vasodilation after intracoronary papaverine with reactive hyperemia following transluminal occlusion.

Patients and Methods

Twenty-one patients undergoing elective PTCA for angina pectoris were studied. All patients had evidence of myocardial ischemia as indicated either by ECG changes at rest or during exercise thallium scintigraphy. Informed consent was obtained for the additional investigations. All patients were studied without premedication, but their medical treatment (nitrates, calcium antagonists and beta-blockers) was continued on the day of the procedure.

Protocol of the investigational procedure

1. Coronary cineangiography was performed in at least two, preferably orthogonal projections for quantitative analysis of the coronary artery stenosis, after intracoronary administration of 2 or 3 mg intracoronary isosorbidedinitrate. The intracoronary administration of isosorbidedinitrate was repeated at regular intervals (20-30 min) to ensure constant and maximal epicardial coronary vasodilation during the entire procedure (18).

2. Coronary flow reserve was measured by digital subtraction cineangiography.

3. A long guide wire (length: 315 cm, diameter: 0.014 inch) was passed through the coronary artery stenosis.

4. A balloon catheter with a Doppler probe at the tip (9) was advanced over the guide wire into the coronary artery to measure coronary blood flow velocity. The precise location of the tip of the balloon catheter with respect to the stenotic lesion - immediately proximal to the lesion and beyond any major side branches - was determined by injection of contrast medium. After recording the baseline intracoronary blood flow velocity, hyperemia was induced by injecting 12.5 mg papaverine through the guiding catheter. The ratio of peak mean intracoronary blood flow velocity to baseline was then determined as previously described by Wilson et al (13). This measurement was obtained in 14 patients. (see table 1). An example is shown in figure 1.

5. Thereafter the balloon was advanced across the stenosis and 3 to 7 inflations, lasting 40 to 80 s, and up to 12 atmospheres were used to dilate the stenosis until repeat cineangiography showed a good result (less than 50% diameter stenosis). The mean total inflation time was 162 s/patient (range: 120-352 s). Immediately following the final balloon inflation the reactive hyperemia was recorded as previously described (9). An example is shown in figure 2.

6. After subsidence of this reactive hyperemic response, the Doppler tip was pulled back into the proximal part of the coronary artery and the ratio of peak mean intracoronary blood flow velocity after 12.5 mg papaverine i.c. to baseline velocity was again determined . This measurement was obtained in 19 patients (see table 1).

8. After removal of the balloon catheter and the guide wire, coronary flow reserve was measured with digital subtraction cineangiography, at the same pacing rate and using the same radiographic and injection parameters as before PTCA.

9. Coronary cineangiography was repeated post-PTCA in the same projections as used at the start of the procedure, for quantitative analysis of the coronary artery stenosis.

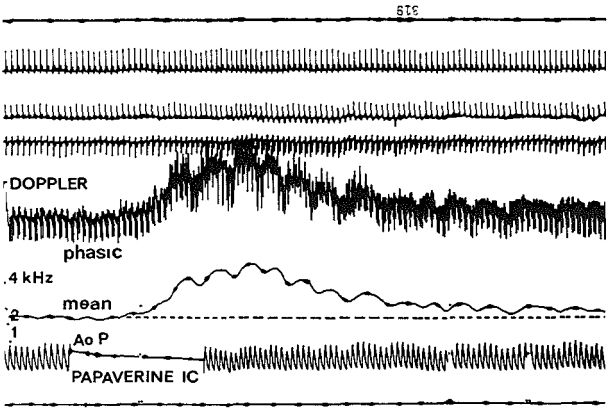

Figure 1
Measurement of the ratio of peak to baseline mean intracoronary blood flow velocity with the Doppler balloon catheter. From top to bottem, 3 ECG leads, phasic intracoronary Doppler signal, mean intracoronary Doppler signal and aortic pressure. Hyperemia was induced by a bolus injection of 12.5 mg papaverine through the guiding catheter.

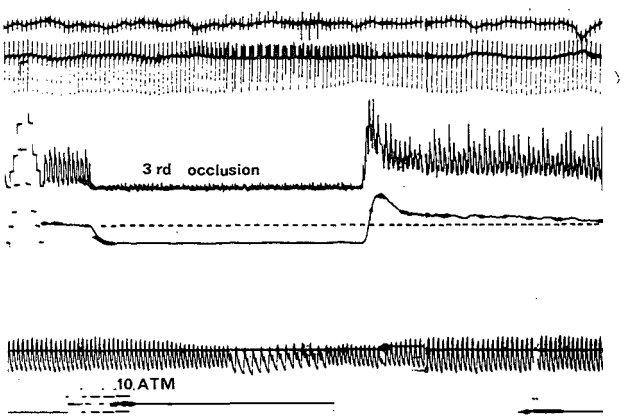

Figure 2
Measurement of reactive hyperemia following the final balloon inflation. In this patient 3 inflations up to 10 athmosphere were performed. From top to bottem 2 ECG leads, phasic intracoronary Doppler signal, mean intracoronary Doppler signal and aortic pressure.

Quantitative analysis of the coronary artery

The determination of coronary arterial dimensions from 35 mm cinefilm was performed with a computer-based Cardiovascular Angiography Analysis System (CAAS), previously described in detail (15,19,20). In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest of a cineframe. The absolute diameter of the stenosis in mm is determined using the guiding catheter as a scaling device. This involves the automatic edge-detection of the boundaries of the catheter in situ and the comparison of this value with the actual diameter measurement of the catheter using a micrometer. Calibration of the diameter in absolute values (mm) is achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimeters. Each catheter is measured individually (21). To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector is computed for each pixel based on a computer-processed cineframe with a centimeter grid placed against the input screen of the image intensifier (20). Since the functional significance of a stenosis is related to the expected normal cross-sectional area of the vessel at the point of obstruction, we use a computer-estimation of the original arterial dimension at the site of the obstruction to define the interpolated reference area (19,20). The percentage diameter and area stenosis and the minimal luminal diameter (mm) and cross-sectional area (mm^2) are then calculated.

Coronary flow reserve measurements with digital subtraction cineangiography

The coronary flow reserve measurement from 35 mm cinefilm has been implemented on the CAAS (15). The heart was atrially paced at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery was made with Iopamidol at 37°C through a Medrad Mark IV infusion pump. This nonionic contrast agent has a viscosity of 9.4 cP at 37°, an osmolarity of 0.796 osm/kg and an iodine content of 370 mg/ml. The angiogram was repeated 30 s after a bolus injection of 12.5 mg papaverine into the coronary artery by way of the guiding catheter (11,12). The injection rate of the contrast medium was judged to be adequate if back flow of contrast medium into the aorta occurred. When this was not observed on the hyperemic image, baseline and hyperemic image acquisition were repeated at a higher flow rate, necessitating flow rates of up to 6 ml/s in some patients . Five or six consecutive end-diastolic cineframes were selected for analysis. Logarithmic nonmagnified mask-mode background subtraction was applied to the image subset to eliminate noncontrast medium densities

(22). The last end-diastolic frame prior to the administration of contrast was chosen as the mask. From the sequence of background subtracted images, a contrast arrival time image was determined using an empirically derived fixed density threshold (15). Each pixel was labeled with the sequence number of the cardiac cycle numbered from the cycle in which the pixel intensity level first exceeded the threshold. In addition to the contrast arrival time image, a density image was computed, with the intensity of each pixel being representative of the maximal local contrast medium accumulation. The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image divided by the regional flow of the corresponding baseline image.

Regional flow values were quantitatively determined using the following videodensitometric principle: regional blood flow (Q) = regional vascular volume/transit time (15). Regional vascular volume was assessed from logarithmic mask-mode subtraction images, using the Lambert Beer relationship. Coronary flow reserve was then calculated as:

$$CFR = Qh/Qb = Dh/Th : Db/Tb$$

where D is the mean contrast density and T the mean appearance time at baseline (b) and hyperemia (h). Mean contrast medium appearance time and density were computed within a user-defined region of interest, which was chosen so that the epicardial coronary arteries visible on the angiogram, the coronary sinus, and the great cardiac vein were all excluded from the analysis (15). Reproducibility data are shown in table 2. Normal values for coronary flow reserve measured with this technique have previously been established (10,15). The coronary flow reserve of 24 angiographically normal coronary arteries was 5.0 ± 0.6. Therefore a flow reserve below 3.4 (2 SD below the mean) is taken to be abnormal.

Intracoronary blood flow velocity measurements

Instantaneous mean cross-sectional flow velocity was measured with a Doppler unit operating at 20 mega Hz using an ultrasonic crystal mounted on the tip of the angioplasty catheter. A balloon diameter size of 3.0 mm or, 3.4 mm was used. The cross-sectional area at the tip, the site of the balloon and the shaft of the catheter was measured by means of a microcaliper. The cross-sectional areas at the three different sites were respectively: 1.2 mm^2, 0.65 mm^2 and 1.5 mm^2. The Doppler cristal has a 1.0 mm diameter annulus with a 0.5 mm central hole. Two leads are soldered to the crystal and pass through the catheter between the original 0.5 mm lumen and a thin-walled tube which serves as a new 0.4 mm lumen. The leads exit near the proximal luer hub and are wired to a two pin plug for connection to the pulsed Doppler instrument. The

connector cable contains an integral torroidal isolation transformer which insulates the patient from the instrument and which also provides impedance matching for more efficient energy transfer. The new inner lumen extends from the luer hub through the cristal providing a smooth unobstructed path for a guide wire. Blood flow velocity is detected by the zero cross method from the catheter tip transducer using a bidirectional range-gated 20 MHz pulsed Doppler velocimeter designed specially for this purpose (Baylor College of Medicine). The master oscillator frequency of 20 MHz is pulsed at a frequency of 62.5 KHz. Each pulse is approximately one milli second in width and therefore contains 20 cycles of the master oscillator frequency. The parameters chosen (master oscillator frequency = 20 MHz and pulse repetition frequency = 62.5 KHz) allow velocities up to 100 cm/s to be recorded at a distance of up to 1 cm from the catheter tip. The sampling window was individually adjusted to obtain the optimal signal which (usually) resulted in a sampling window of 1.8 mm (range 1.5-2.0).

The output of the pulsed Doppler is a frequency shift (F,kHz) which can be related to blood velocity by the Doppler equation: $F = 2 f (V/c) \cos a$, where f is the ultrasonic frequency (20 MHz), V is the velocity within the sample volume, c is the speed of sound in blood (1.500 m/s), and a is the angle between the velocity vector and the sound beam. Using an end-mounted crystal with the catheter parallel (± 20°) to the vessel axis, $\cos a = 1 \pm 6\%$, and the relation between the Doppler shift and velocity is approximately 3.75 cm/s per KHz (17). Previous calibration experiments in canine femoral and coronary arteries have shown that the measured doppler shift frequency is proportional to volume flow measured by timed collection (13,24). Recently, Sibley et al (17) validated clinically and experimentally the ability of a similar catheter with an end-mounted piezo-electric crystal to provide accurate continuous on line measurement of coronary blood flow velocity and vasodilator reserve. In our laboratory, we verified the accuracy of these velocity probes by correlating velocity recorded with the Doppler probe in an 9 F femoral sheath with the volume flow measured by a timed collection of blood from the side branch of the same sheath. Graduated flow rates (range: 12-165 ml/min) and the corresponding velocities (range: 1.2-8.2 Khz) were obtained by incremental balloon inflation with the balloon positioned in the sheath. This simple model allows the assessment of the flow velocity relation at different levels. As previously demonstrated, this relation is linear with correlation coefficients generally equal or greater than 0.95 (13,17). Reproducibility data are shown in table 2.

Statistical methods

Results are expressed as mean ± SD unless stated otherwise. Least squares linear regression analyses were used to define the relationships between the various measurements.

RESULTS

The clinical characteristics, results of the quantitative analysis of the coronary angiogram and the coronary flow reserve measurements are shown in table 1. The mean age of the 21 patients was 57 years (range: 37-76), 17 were male. Eighteen patients had single vessel coronary artery disease and 3 patients two vessel disease. The investigated and dilated coronary artery was the left anterior descending artery in 14, the circumflex artery in 3 and the right coronary artery in 4 patients. In none of the patients a sidebranch was involved at the site of the lesion. The mean left ventricular ejection fraction was 67% and ranged from 38 to 81%. Patient 9 had sustained a myocardial infarction in the anterior wall resulting in a large akinetic segment and an ejection fraction of 38%. None of the other patients had clinical evidence for a myocardial infarction and all had normal wall motion and an ejection fraction of more than 55%. In two patients (patients 4 and 11) the coronary arteriogram showed grade III/IV collateral filling of the PTCA vessel (23). Patient 12 (see table 1) had long standing arterial hypertension with left ventricular hypertrophy. None of the other patients had electrocardiographic, echocardiographic or angiographic evidence of left ventricular hypertrophy. The mean number of balloon inflations was 4.3/patient and ranged from 3 to 7. The dilation was successful in all patients, and none of the patients had a CPK-rise after the procedure. Seven patients had a dissection of the dilated coronary artery segment after the procedure. Five dissections were small (patients 1,7,10,11 and 20), two dissections were of moderate severity (patients 17,18). None of the dissections had clinical repercussions. The hemodynamic data of the individual patients are shown in table 1 and mean values (±SD) of the heart rate and aortic pressure are given in table 3.

The cross-sectional area at the site of obstruction was 1.1 ± 0.6 mm^2 before, and 3.2 ± 1.1 mm^2 after PTCA. Percentage diameter stenosis was 58 ± 9% before, and 32 ± 10% after PTCA. Percentage area stenosis was 82 ± 8% before, and 52 ± 14% after PTCA. The interpolated reference area was 6.6 ± 1.6 mm^2 and ranged from 3.9 to 9.8 mm^2. During the measurements with the Doppler catheter just proximal to the stenosis, the tip of the catheter (1.2 mm^2) occupied 18 ± 5% (range 12 to 31%) of the cross-sectional area of the coronary artery. The reactive hyperemia was measured with the balloon part of the Doppler catheter (0.65 mm^2) across the stenosis. In this situation the

Table 1: Results

	age		DV	B/A	OA	AS	DS	HR1	Ao1	CFR DSC	HR2	Ao2	CFR DOP	RH
1	F	48	1 LAD	A	5.4	35	19	70	91	2.0	67	104	2.1	2.2
2	M	43	1 LAD	A	4.8	51	30	70	95	3.3	51	92	2.9	2.9
3	M	58	1 RCA	A	2.9	64	40	70	93	2.8	68	98	3.0	2.8
4	M	69	1 RCA	A	2.2	66	42	80	91	1.2	72	87	1.1	1.0
5	M	58	2 LAD	B	1.2	86	62	70	99	0.6	57	95	0.9	
				A	3.3	63	39	70	83	2.4	70	89	2.9	2.3
6	M	62	1 LAD	B	0.9	86	62	90	97	1.0	69	101	0.9	
				A	3.5	40	23	90	97	2.0	83	103	1.8	2.0
7	F	53	1 LAD	B	1.6	72	47	90	82	2.0	71	80	1.8	
				A	3.5	51	30	90	78	2.4	81	76	2.7	2.3
8	M	56	1 LAD	B	0.7	88	64	100	83	0.8	91	85	1.1	
				A	3.7	24	17	100	88	2.2	85	98	2.3	2.2
9	M	53	1 LAD	B	1.2	83	59	80	90	1.1	70	90	1.3	
				A	4.5	37	21	80	88	3.0	82	89	2.3	2.6
10	M	55	1 CX	A	2.5	49	28	80	96	1.7	70	97	1.9	1.7
11	M	53	1 CX	A	2.7	69	45	70	85	2.2	60	79	2.0	2.1
12	F	57	1 LAD	B	2.9	59	35	70	115	1.1	66	112	1.0	
				A	5.3	41	23	70	111	1.7	62	108	2.2	2.1
13	M	66	2 LAD	B	0.7	82	58	70	81	1.4	59	83	1.2	
				A	2.9	44	25	70	84	2.7	61	83	2.4	1.9
14	M	56	1 RCA	B	0.7	87	63	70	81	1.2	61	83	1.1	
15	M	67	2 CX	B	0.9	86	68	70	88	1.3	58	88	1.0	
				A	1.7	69	37	70	76	1.8	60	79	1.7	1.5
16	M	60	1 LAD	B	1.3	78	53	80	93	1.4	73	89	1.6	
17	M	56	1 LAD	B	0.8	86	62	70	91	1.1	61	96	2.5	
				A	2.7	61	37	70	92	1.0	57	99	1.4	1.3
18	M	37	1 LAD	A	1.8	70	45	70	87	1.1	63	89	1.1	1.0
19	M	49	1 RCA	B	1.4	84	60	80	95	1.3	73	99	1.4	
				A	2.5	73	48	80	86	1.6	76	83	1.7	1.3
20	F	76	1 LAD	B	1.1	75	50	80	91	1.3	63	90	1.4	
				A	2.8	36	20	80	82	2.3	81	80	2.5	1.5
21	M	58	1 LAD	B	0.6	90	69	70	80	1.0	65	82	1.2	
				A	2.2	64	40	70	75	2.2	63	76	2.3	1.6

Pat= patient, F= female, M= male, No of DV= number of diseased coronary arteries (diameter stenosis greater than 50%), LAD= left anterior descending coronary artery, RCA= right coronary artery, CX= circumflex artery, B= before PTCA, A= after PTCA, OA= cross-sectional area at the site of obstruction (mm^2), AS= percentage area stenosis, DS= percentage diameter stenosis, HR= Heart rate in beats/min and Ao= mean aortic pressure (mmHg) 1 = immediately preceding CFR-DSC measurements.2 = immediately preceding the CFR-DOP and RH measurements. CFR-DSC= coronary flow reserve measured with distal subtraction cineangiography, CFR-DOP= coronary flow reserve measured with Doppler.

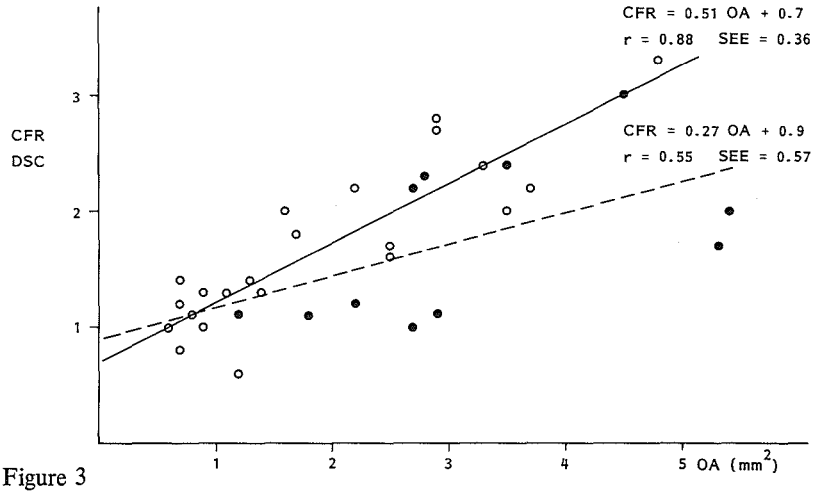

Figure 3

Relationship between coronary flow reserve measured with digital subtraction cine-angiography (CFR-DSC) and cross-sectional area at the site of obstruction (OA). The open symbols are the patients with any of the following characteristics: left ventricular hypertrophy, hypertension, previous myocardial infarction, collaterals or dissection after PTCA. The closed symbols are the patients without any of the above listed characteristics.

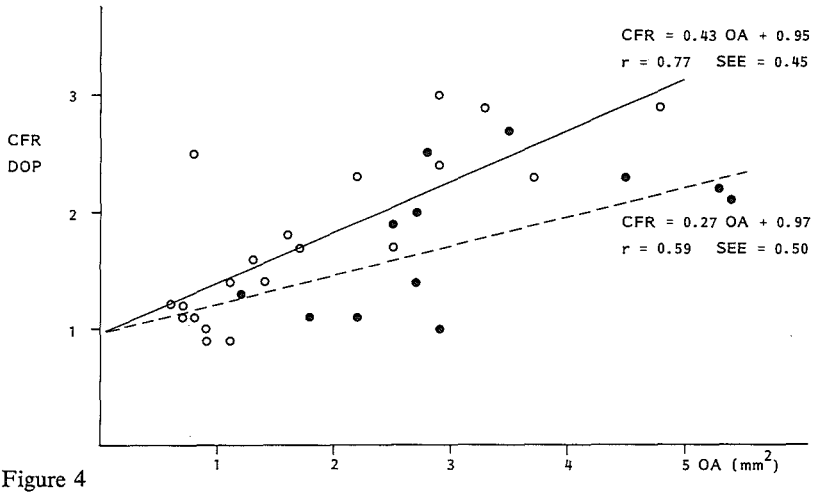

Figure 4

Relationship between coronary flow reserve measured with the Doppler probe (CFR-DOP) and cross-sectional area at the site of obstruction (OA). See for explanation of symbols figure 3.

catheter occupied 20 ± 5%, (range: 12-37%) of the luminal cross-sectional area at the site of the stenosis. This implies that coronary flow reserve assessed with both techniques after PTCA was measured in the presence of an area stenosis of 52 ± 14%, whereas reactive hyperemia was assessed in the presence of a residual area stenosis of 62 ± 16%. In 14 patients a coronary flow reserve measurement with the angiographic technique was also obtained in a myocardial region supplied by a coronary artery which was not dilated and which had no significant stenosis (less than 50% diameter stenosis). The mean coronary flow reserve of these vessels was 3.4 ± 0.8 before PTCA and 3.3 ± 0.9 after PTCA.

The relationship between coronary flow reserve measured with digital substraction cineangiography (CFR-DSC) and the cross-sectional area at the site of obstruction (OA) is shown in figure 3. Patients 1,4,7,9,10,11,12,17,18 and 20 had conditions associated with a reduced coronary flow reserve, in addition to the presence of a coronary stenosis. In these patients only a weak relationship was found between these two parameters: CFR-DSC = 0.27 OA + 0.9, (r = 0.55, SEE = 0.57). In the other patients in whom the epicardial narrowing was the sole factor determining the coronary flow reserve, a good relationship was found between these two parameters: CFR-DSC = 0.51 OA + 0.7, (r = 0.88, SEE = 0.36).

The relationship between coronary flow reserve measured with Doppler (CFR-DOP) and the cross-sectional area at the site of obstruction (OA) is shown in figure 4. The resting Doppler-shift before PTCA was 1.4 ± 0.7 kHz and after PTCA 1.5 ± 0.7 kHz. In the patients with conditions associated with a reduced coronary flow reserve aside from the presence of a coronary stenosis the relationship between these two parameters was weak: CFR-DOP = 0.27 OA + 1.0 (r= 0.59, SEE = 0.50). In the other patients a reasonably good relationship was found between these two parameters: CFR-DOP= 0.43 OA + 1.0 (r= 0.77, SEE = 0.45).

The relationship between the coronary flow reserve measured with the angiographic technique and the coronary flow reserve measured with Doppler probe is shown in figure 5. There is a good relationship between the measurements made with these two techniques, irrespective of whether the flow reserve is limited solely by the severity of the coronary stenosis (CFR-DSC = 0.88 CFR-DOP + 0.12, r = 0.85, SEE = 0.38) or whether there are additional patient characteristics present such as previous infarction, hypertrophy, collaterals or dissection after PTCA (CFR-DSC = 0.96 CFR-DOP + 0.01, r = 0.87, SEE = 0.34).

The relationships between the reactive hyperemia (RH) recorded after the final balloon inflation with the angioplasty catheter still across the lesion, and coronary flow reserve measured with the angiographic technique (CFR-DSC=0.27 + 0.95RH, r=0.85, SEE=0.34) and with the Doppler catheter

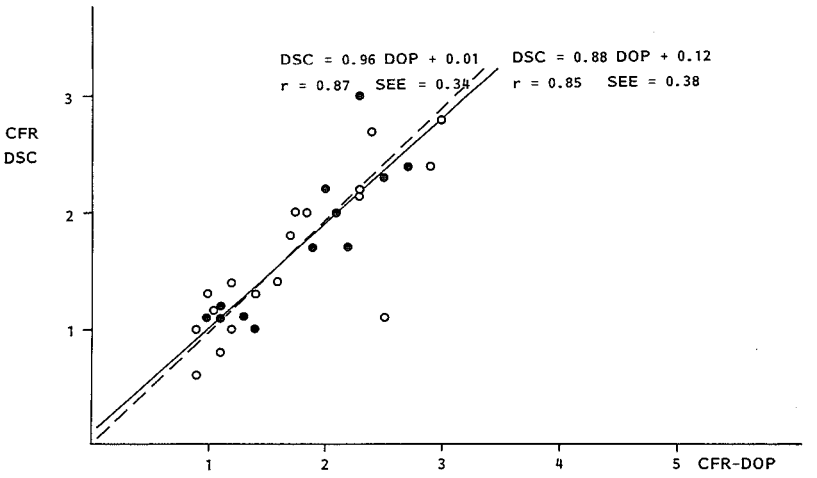

Figure 5
Relationship between coronary flow reserve measured with digital subtraction cineangiography (CFR-DSC) and coronary flow reserve measured with the Doppler probe (CFR-DOP). See for explanation of symbols figure 3.

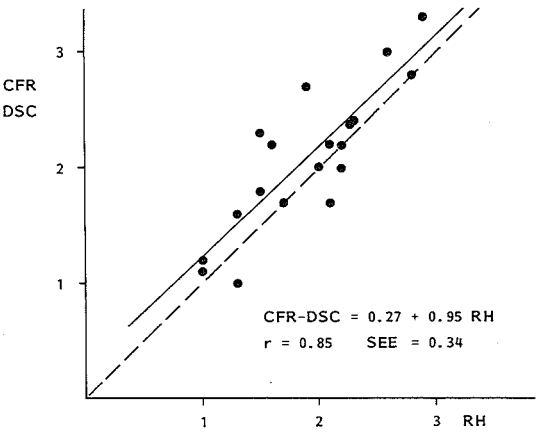

Figure 6
Relationship between coronary flow reserve measured with digital subtraction cineangiography (DFR-DSC) and the reactive hyperemia recorded with the Doppler probe across the dilated lesion after the final balloon inflation (RH).

(CFR-DOP=0.51 + 0.84RH, r=0.83, SEE=0.32) are shown in figures 6 and 7 respectively. As expected the mean reactive hyperemia was somewhat lower than the coronary flow reserves measured with the angiographic technique or with the Doppler probe located proximal to the dilated stenosis. Reactive hyperemia was 1.9 ± 0.6, coronary flow reserve measured with the angiographic technique 2.1 ± 0.6 and coronary flow reserve measured with the Doppler catheter 2.1 ± 0.6.

Table 2: Reproducibility of the coronary flow reserve measurements.

		1°	2°	difference ± SD	r	SEE
DSC	N=13	2.1 ± 1.2	2.1 ± 1.2	-0.02 ± 0.26	0.98	0.26
DOP	N=15	1.6 ± Q.3	1.6 ± 0.3	+0.03 ± 0.18	0.88	0.19

1°= first determination (mean ± SD), 2°= second determination (mean ± SD), DSC= digital subtraction cineangiography, analysis of repeated image acquisition taken 5 min apart, without change in patient position, pacing rate, contrast injection parameters or X-ray gantry settings, DOP= repeated intracoronary Doppler blood flow velocity measurements 5 min apart without change in patient - or Doppler catheter position.

Table 3 Hemodynamic data.

	Before PTCA		After PTCA		
	DSC-CFR	DOP-CFR	DSC-CFR	DOP-CFR	DOP-HR
HR	78 ± 10	67 ± 9	76 ± 9	69 ± 10	69 ± 10
Ao	90 ± 9	91 ± 9	88 ± 8	90 ± 10	90 ± 10

Heart rate (HR, beats/min) and mean aortic pressure (Ao, mmHg) immediately preceding the coronary flow reserve measurements with digital subtraction cineangiography (DSC-CFR) and coronary flow reserve and reactive hyperemia measurements with the Doppler catheter (DOP-CFR and DOP-RH).

Discussion

The purpose of the present study was twofold: firstly, to compare in the setting of an angioplasty procedure two different techniques of assessing regional coronary blood flow; secondly, to compare the pharmacologically induced vasodilation after intracoronary papaverine with reactive hyperemia following transluminal occlusion.

Rationale for comparison of the two techniques to measure coronary flow reserve

Extensive validation studies with the Doppler technique have been performed in which the measured changes in velocity have been compared with changes in perfusion measured with

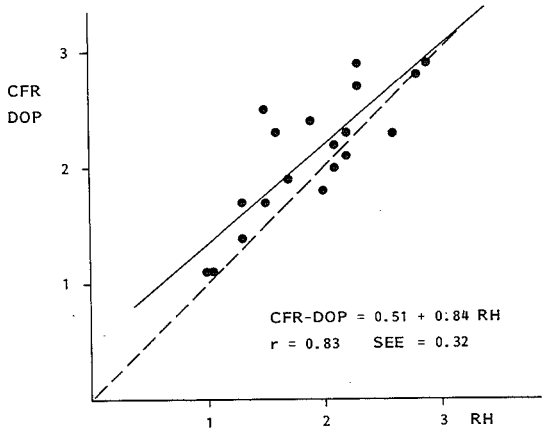

Figure 7
Relationship between coronary flow reserve measured with the Doppler probe (CFR-DOP) proximal to the dilated lesion and the reactive hyperemia recorded with the Doppler probe across the dilated lesion after the final balloon inflation (RH).

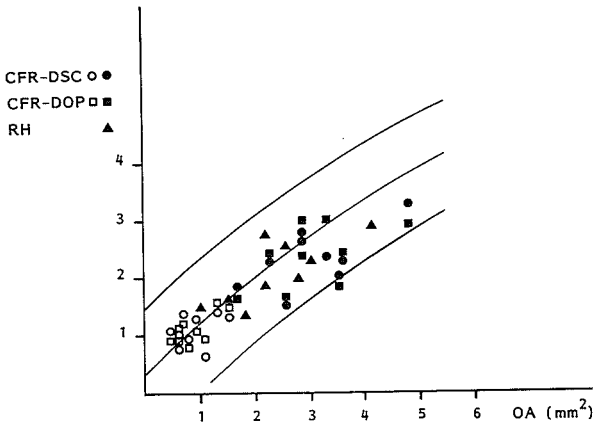

Figure 8
Relationship between flow reserve and cross-sectional area at the site of obstruction (OA) as described in a previous report of our laboratory (16). The lines indicate the best fit curve and the 95 % confidence limits. The data of the present study are superimposed. The open symbols are the measurements obtained before PTCA. The closed symbols are the measurements obtained after PTCA. CFR-DSC = coronary flow reserve measured with digital subtraction cineangiography, CFR-DOP = coronary flow reserve measured with the Doppler probe, RH = reactive hyperemia recorded following the final balloon inflation.

timed-venous coronary sinus collection (13,24), labeled microspheres (25), and electromagnetic flow probes (24). These studies indicate that under a great variety of conditions, changes in coronary blood flow velocity measured by the Doppler technique accurately reflect changes in flow (26). Recently, small sized Doppler catheters have been developed and validated. They are able to make selective measurements of flow velocity in the major proximal coronary arteries (9,13,17), without causing coronary obstruction (26). For instance, in this report the cross-sectional area of the Doppler balloon catheter was only 18 ± 5% of the cross-sectional area of the coronary artery in the segment proximal to the stenosis. However, two important limitations of the Doppler technique are, firstly: it measures flow velocity rather than volume flow - which may lead to inaccurate values for flow reserve if significant change occurs in cross-sectional areas between baseline and hyperemia (18) - and secondly: subselective coronary cannulation increases the risk during cardiac catheterization (13,26). Therefore less invasive approches to determine the regional coronary flow reserve are urgently needed.

Selective coronary angiography is the standard means for obtaining anatomical information and is the most important tool for clinical decision making used by the clinician caring for patients with coronary artery disease. Recently, several attempts have been made to measure coronary blood flow parameters during cardiac catheterization using recent developments in radiographic technology (16). However, radiographic contrast media cannot be used to measure coronary blood flow by the traditional methodological approaches (16); an essential prerequisite of indicator-dilution (Stewart-Hamilton), inert substance washout (Kety-Schmidt), or firstpass distribution (Sapirstein) techniques is that the indicator substance does not affect the regional flow being measured (8). Unfortunately, all radiographic media have substantial vascular effects (27), although nonionic media may disturb blood flow less than ionic agents (16). Using ECG-gated power injection of a contrast agent at a rate that is presumed to be sufficiently rapid to achieve complete replacement of blood with contrast, Hodgson et al (28) developed a mask mode subtraction technique that determines myocardial time-density curves before and during maximal hyperemia before the vascular effects of the contrast medium disturb the ratio between resting and hyperemic coronary blood flow. Since some of this techniques fundamental assumptions may not be met under clinical conditions, validation studies are of special interest (29). In this study we found a reasonable good correlation between radiographically determined coronary flow reserve and the coronary flow velocity reserve measured with a Doppler probe, despite the fact that the two approaches have methodologically nothing in common and that their respective regions

of interest (myocardium for the radiographic technique and intracoronary lumen for the Doppler technique) are basically different.

Maximal coronary blood flow after pharmacological vasodilation versus reactive hypermia induced by coronary occlusion

In the animal laboratory it has been shown that pharmacologically induced vasodilation after intracoronary administration of papaverine is of the same magnitude as the reactive hyperemia after a 15 s occlusion of the coronary artery (30). There is some question as to whether the same quantity of flow reserve that can be recruited pharmacologically, can be recruited during ischemia (29). In this study, we found that reactive hyperemia in patients without hypertrophy, infarction, hypertension, collaterals or dissection was 2.1 ± 0.6 (range 1.3 to 2.9), whereas coronary flow reserves in these patients both with the Doppler probe and the radiographic technique were 2.3 ± 0.6 (range 1.6 to 3.3) after PTCA. The cross-sectional area at the site of obstruction averaged 3.05 mm^2 in these patients. Since the balloon catheter was still across the lesion the functional lumen averaged 2.4 mm^2 (see table 1). In a previous study from this laboratory we established the relationship between cross-sectional area at the site of obstruction and the measured coronary flow reserve in a patient population with single vessel coronary disease and the absence of other factors that might reduce flow reserve such as hypertrophy, infarction, hypertension, collaterals or dissection (15). This relationship is shown in figure 6. A coronary artery with an obstruction area of 2.4 mm^2 would be expected to have a vascular reserve of 2.2 with confidence limits extending from 1.3 to 3.0, which corresponds almost exactly to the range found in this study. Therefore, we feel that our data support the conclusion that the coronary vasodilation after an optimal dose of intracoronary papaverine (11) is equipotent to the reactive hyperemia following a transluminal occlusion of more than 40 s in patients with significant coronary artery disease.

Limitations

When comparing these three measures of the functional capacity of a coronary artery one has to bear in mind the potential sources of data scatter. Fortunately, the radiographic technique as well as the Doppler technique have a good reproducibility. Coronary flow reserve and reactive hyperemia are both ratios between maximal coronary blood flow and resting flow. Resting coronary blood flow is mainly determined by aortic pressure and heart rate and coronary blood flow during maximal vasodilation is linearly related to the prevailing perfussion pressure (7,8). These two hemodynamic

parameters change little between the measurements of flow reserve and reactive hyperemia (see table 1 and 3), although they certainly contribute to the scatter of the data (see figures 5,6 and 7).

Several studies have shown that in selected patients a close relationship exists between quantitatively determined stenosis geometry and measured coronary flow reserve (15,31). However, coronary flow reserve can be influenced by many factors other than epicardial coronary stenosis, such as myocardial hypertrophy, tachycardia, hypertension prior myocardial infarction, collaterals, dissection after PTCA (33), changes in coronary vasomotor tone and changes in ventricular end-diastolic and intrathoracic pressures (7,8). Therefore, in order to relate the measured coronary flow reserve to quantitatively determined stenosis geometry, we have carefully divided our study population into a group of patients (A) with one or more of the above mentioned characteristics and a group of patients (B) without any of these characteristics (see figures 3 and 4). We tried to prevent changes in vasomotor tone which is relevant to both techniques (18) by inducing a constant maximal epicardial coronary vasodilation with repeated intracoronary administration of isosorbide dinitrate (18). In accordance with previous reports (15,31) we found a good correlation between cross-sectional area at the site of obstruction and measured coronary flow reserve in group B, in contrast to a poor correlation between these two parameters in group A.

Coronary flow reserve immediately after PTCA

Several authors (10,32) have shown that the coronary flow reserve of the myocardial region supplied by the dilated vessel increases substantially after PTCA, but is not restored to normal values. The measurements obtained in the present study with two independant techniques confirm this fact. We also measured the coronary flow reserve of an adjacent myocardial region supplied by a not significantly diseased coronary artery, by the radiographic technique and found a marked difference in vasodilator response. For ethical reasons we did not obtain this measurement with the Doppler catheter as we felt that introduction of the Doppler probe into a second coronary artery might introduce additional risks to the investigational part of the procedure. Nevertheless, the results of the radiographic technique indicate that the abnormal vasodilatory response is restricted to the myocardium supplied by the dilated coronary artery. There are several potential explanations for this phenomenon.

First, since coronary flow reserve is a ratio between resting flow and maximal coronary blood flow, any increase in resting flow results in a decrease of this ratio. Neither of the techniques we used, provided us with absolute measurements

of volume flow. Therefore, we cannot make a definite conclusion regarding resting coronary volume flow after the PTCA. However, the resting Doppler shift was virtually the same before and after the PTCA procedure, 1.4 ± 0.7 kHz and 1.5 ± 0.7 kHz respectively. Furthermore, several authors using the thermodilution technique in the coronary sinus or the great cardiac vein have reported comparable resting volume flows before and after PTCA (34-36).

Secondly, metabolic, humoral or myogenic factors could potentially play a role in the limited restoration of coronary flow reserve after PTCA. However, the metabolic derangements due to the PTCA seem quickly reversible (34,37,38). Although humoral factors may play a role in a specific subgroup of patients with complicated PTCA, sofar no evidence has been presented that implicates that humoral factors are important in this regard in the majority of patients (39). The long standing reduction in perfusion pressure distal to the stenotic lesion may induce alterations in the complex mechanism of autoregulation and a prolonged period of time may be needed before these abnormalities subside (40).

Thirdly, the impaired coronary flow reserve could be directly related to the residual stenosis (10). Cross-sectional area measured immediately after PTCA generally increases about threefold due to the procedure but remains grossly abnormal (10,41). The relationship between cross-sectional area at the site of obstruction and coronary flow reserve as found in a previous study from our laboratory (15), is shown in figure 8 with the 95% confidence intervals. The data of the present study for patients fullfilling the same exclusion criteria (group B) are superimposed: coronary flow reserve measured with both techniques and the reactive hyperemia following the final balloon inflation with residual obstruction area corrected for the presence of the Doppler balloon catheter. The large majority of measurements fall within the 95% confidence limits of this relation, suggesting that the persisting reduction in cross-sectional area perse constitutes a sufficient explanation for the limited restoration of coronary flow reserve, although it does not exclude other contributing pathophysiological mechanisms.

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CHAPTER 9: NORMALIZATION OF CORONARY FLOW RESERVE BY PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY.

Summary

15 patients undergoing routine follow-up angiography 5 months after successful percutaneous transluminal coronary angioplasty (PTCA) without angina and with normal exercise thallium scintigraphy were selected for analysis. The coronary flow reserves of these patients were compared to those of 24 patients with angiographically normal coronary arteries, to establish whether PTCA can restore to normal the coronary flow reserve of patients with chronic coronary artery disease. The quantitative cineangiographic changes and the concomitant alterations in coronary flow reserve as an immediate result of the PTCA and the subsequent changes 5 months later are described. Coronary flow reserve was measured with digital subtraction cineangiography. PTCA resulted in an increase in minimal obstruction area from 0.8±0.3 to 3.4±0.7 mm^2 and in coronary flow reserve (mean ± SD) from 1.0±0.3 to 2.5±0.6. Five months later a further substantial and significant (p less than 0.05) late increase in obstruction area (3.8±0.9 mm^2) and flow reserve (3.6±0.5) had occurred. In 11 of 15 patients coronary flow reserve was restored to normal. Changes in stenosis geometry are likely to be one of the major determinants of this late normalization of coronary flow reserve.

Introduction

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977 (1), this procedure has gained increasing importance in the treatment of coronary artery obstructions. The immediate and long-term results of PTCA are usually assessed by coronary angiography. Recently, the measurement of coronary flow reserve has been proposed as a better method to evaluate the hemodynamic repercussions of coronary artery obstructions (2,3). Three techniques have been developed that allow the measurement of regional coronary flow reserve during cardiac catheterization. The first uses a pulsed Doppler coronary artery catheter which can measure intracoronary blood flow velocity (4). The second technique is based on the radiographic assessment of myocardial perfusion using contrast medium (5,6). The third technique is an indicator dilution technique with a platinum-tipped PTCA guide wire, using hydrogen as the indicator (7). Although PTCA has been shown to result in symptomatic, hemodynamic and functional improvement (8-10), doubt has remained whether this procedure can restore coronary flow reserve of atherosclerotic coronary arteries to a normal level (11-14). Therefore we selected 15 patients that were free of angina and had a normal

exercise thallium scintigram 5 months after PTCA, and compared their radiographically measured coronary flow reserve with the flow reserve of 24 patients with angiographically normal coronary arteries. We describe the quantitative cineangiographic changes and the concomitant alterations in coronary flow reserve, resulting from the acute intervention as well as the subsequent changes as observed 5 months after PTCA.

METHODS

Patients

The study population consisted of 24 patients with angiographically normal coronary arteries (data on 12 have been previously published) (5) and 15 patients with single vessel coronary artery disease. These 15 patients had undergone successful PTCA for disabling angina refractory to intensive pharmacological treatment. They were selected on the basis of a normal exercise thallium scintigram and complete relief of chest pain 5 months after PTCA, when coronary angiography and left ventriculography were performed as part of an ongoing study on restenosis after PTCA. Informed consent was obtained for all investigations. Before PTCA pharmacologic treatment consisted of nitrates, calcium antagonists and beta-blockers, and during the 5 months after PTCA the patients were treated with aspirin 500 mg/day and nifedipine 60 mg/day which medication was continued on the day of the cardiac catheterization. All 39 patients had normal systolic and diastolic wall motion and an ejection fraction greater than 55%. Patients with left ventricular hypertrophy, valvular heart disease, angiographic evidence of collateral circulation, anemia, polycythemia or hypertension were excluded because these conditions may influence coronary flow reserve (15-17).

Exercise thallium scintigraphy

The patients performed a symptom-limited exercise test on the bicycle ergometer with stepwise increments of 20 watt/min. All patients exercised to more than 80% of their expected normal exercise capacity (for age, sex and length). Images were obtained immediately after exercise and 4 hours later, and analyzed prospectively by 3 experienced observers without knowledge of the angiographic data. Redistribution and persistent defects were considered abnormal (18,19).

Quantitative coronary cineangiography

Before PTCA, immediately after PTCA and during repeat catheterization 2 or 3 identical angiographic projections were filmed. The coronary arterial dimensions were determined with

the computer-based Cardiovascular Angiography Analysis System (5,20,21). In essence, the boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest of a cine-frame. Calibration of the diameter data in absolute values (mm) is achieved by detecting the boundaries of a section of the contrast catheter and comparing the mean diameter in pixels with the known size in millimeter (22). Pincushion distortion is corrected (21). A computer estimation of the original arterial dimensions at the site of obstruction was used to define the reference region (21). The interpolated percentage diameter stenosis and the minimal obstruction area (mm^2) were then calculated by averaging the values from at least two, preferably orthogonal projections. A mean of 2.2 angiographic projections per patient was used in this study.

Coronary flow reserve measurements

The heart was atrially paced at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery 300 ms after the R-wave was made with a fixed amount of jopamidol at 37°C through a Medrad Mark IV infusion pump. This nonionic contrast agent has a viscosity of 9.4 cP at 37°, an osmolality of 0.8 osm/kg and an iodine content of 370 mg/ml. The injection rate of the contrast medium was judged to be adequate when back flow of contrast medium into the aorta occurred. In every patient the injection rate was identical for each coronary injection. The field size of the X-ray equipment was 7 inch. The angiogram was repeated 30 sec after pharmacologically induced hyperemia by a bolus injection of 12.5 mg papaverine into the coronary artery (5,23). Five end-diastolic cineframes were selected from successive cardiac cycles.

Logarithmic nonmagnified mask-mode background subtraction was applied to the image subset, to eliminate noncontrast medium densities. The last end-diastolic frame prior to contrast administration was chosen as the mask. A contrast appearance time was determined, using an empirically derived density threshold that was constant for each study and all patients (5). A density image was computed, with each pixel intensity value being representative for the maximal local contrast medium accumulation. The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image (Qh) divided by the regional flow of the corresponding baseline image (Qb). Coronary flow reserve (CFR) was then be calculated as:

$$CFR = Qh/Qb = Dh/Th : Db/Tb$$

where D is the mean contrast density and T the mean appearance time at baseline (b) and hyperemia (h). Appearance time and

density were computed within user-defined regions of interest that were chosen in such a way that the epicardial coronary arteries visible on the angiogram, the coronary sinus and the great cardiac vein were excluded from the analysis (5).

Statistical analysis

Comparisons between groups were made after variance analysis with the Student's t-test for paired or unpaired observations.

RESULTS

Quantitative cineangiography

The changes in minimal cross-sectional obstruction area are shown in table 1 and fig. 1, the changes in percentage diameter stenosis are shown in table 1 and fig. 2. Percentage area stenosis (mean ± SD) decreased from 89 ± 7% to 51 ± 11% immediately following PTCA. Five months later percentage area stenosis was further decreased to 42 ± 14% (p less than 0.05).

Coronary flow reserve

In the 24 patients with angiographically normal coronary arteries, coronary flow reserve ranged from 3.4 to 6.5 (table 2). The mean value was 5.0 (SD ± 0.8). The lower limit for a normal coronary flow reserve is therefore 3.4 (2 x SD below the mean coronary flow reserve). This is comparable to the normal values for coronary flow reserve reported by other groups (4,14). Coronary flow reserve was measured in the myocardial region supplied by the dilated coronary artery before PTCA, immediately following PTCA as well as 5 months later. Consecutive measurements were also obtained in 12 adjacent myocardial regions supplied by a non-dilated coronary artery, (table 1 and fig. 3). The coronary flow reserve of these adjacent myocardial regions remained unchanged immediately following PTCA as well as after 5 months follow-up. Coronary flow reserve (mean ± SD) in the myocardial region supplied by the dilated coronary artery increased from 1.0 ± 0.3 to 2.5 ± 0.6 immediately following PTCA (p less than 0.001). In none of these patients coronary flow reserve was restored to a normal level immediately following PTCA. A substantial late improvement (p less than 0.01) in coronary flow reserve had occurred 5 months later. Coronary flow reserve in the myocardial region supplied by the dilated coronary artery 5 months after PTCA was of the same magnitude as the coronary flow reserve in the myocardial region supplied by a non-dilated and angiographically not diseased coronary artery. In 11 of the 15 patients (73%) coronary flow reserve

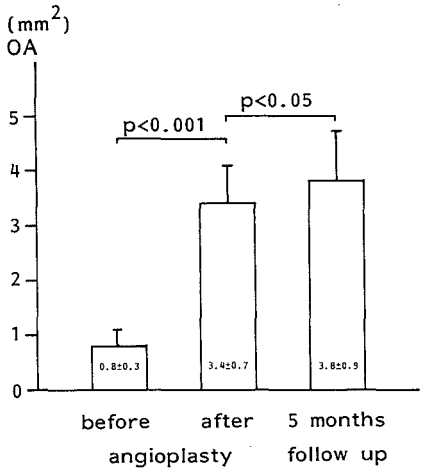

Figure 1
Results of quantitative analyses of coronary angiograms, before, immediately after and 5 months after percutaneous transluminal coronary angioplasty. OA = minimal cross sectional obstruction area (mm^2).

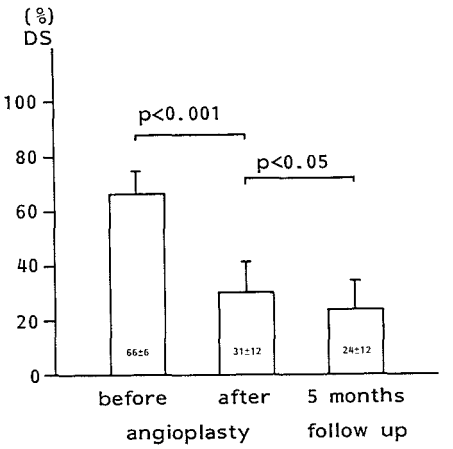

Figure 2
Results of quantitative analyses of coronary angiograms, before, immediately after and 5 months after percutaneous transluminal coronary angioplasty. DS = percentage diameter stenosis.

Table 1: Results: Coronary flow reserve and quantitative angiographic data of PTCA patients.

				before			after			5 months follow-up		
Pat	age	sex	vessel	OA	DS	CFR	OA	DS	CFR	OA	DS	CFR
1	54	M	LAD	1.2	53	1.0	5.4	14	3.0	5.2	6	2.9
			LC			3.9			3.7			4.3
2	31	M	LAD	0.5	70	1.0	3.7	15	2.3	3.1	19	2.5
			LC			3.3			2.5			3.1
3	53	F	LAD	0.5	72	0.6	3.3	27	2.8	5.9	7	3.7
			LC			2.6			2.5			2.2
4	36	M	LAD	0.4	70	1.2	3.7	14	3.3	2.8	20	2.9
			LC			3.2			3.4			3.3
5	62	M	LAD	0.8	66	1.0	2.5	44	2.1	3.8	32	3.8
			LC			2.6			2.8			2.9
6	42	M	LC	0.7	66	0.7	3.8	24	1.5	2.6	38	3.4
			LAD			3.8			3.6			4.1
7	53	M	R	1.3	65	0.9	3.6	31	2.2	2.9	35	3.9
8	66	M	LAD	0.7	58	1.4	2.9	26	2.7	3.1	12	2.9
			LC			3.5			3.8			3.4
9	59	M	LAD	1.1	64	1.0	3.5	36	1.4	4.7	21	3.7
			LC			3.2			3.5			3.5
10	52	M	LC	1.4	61	0.9	3.0	32	2.9	3.9	28	4.3
			LAD			3.9			4.0			3.7
11	64	M	LAD	0.6	68	1.0	2.4	38	3.1	4.1	14	4.1
			LC			3.8			3.3			4.6
12	53	M	R	0.7	72	0.9	3.2	49	2.1	3.5	39	3.5
13	47	M	LAD	0.8	76	0.6	3.7	47	1.8	4.2	38	3.9
			LC			4.1			3.6			4.4
14	58	M	R	0.6	71	1.4	2.9	40	2.8	3.6	31	3.8
15	66	M	LAD	0.7	58	1.4	2.9	23	2.7	3.9	13	4.2
			LC			3.3			3.5			3.6

CFR = coronary flow reserve; DS = percentage diameter stenosis; F = female; LAD = left anterior descending artery; LC = circumflex artery; M = male; OA = minimal cross-sectional obstruction area (mm^2); pat = patient; PTCA = percutaneous transluminal angioplasty; R = right coronary artery.

of the dilated coronary artery was restored to a normal level of greater or equal to 3.4, whereas in 4 of 15 patients (27%) coronary flow reserve was still abnormal (fig. 4 and 5). Coronary flow reserve 5 months after PTCA was related to the change in minimal cross-sectional obstruction area occurring between immediately after PTCA and at follow-up (linear regression analysis: r=0.61, SEE=0.46, fig 6). In 10 patients the minimal cross-sectional obstruction area 5 months after PTCA was larger than immediately following the procedure (late improvement). Only one had a coronary flow reserve of less

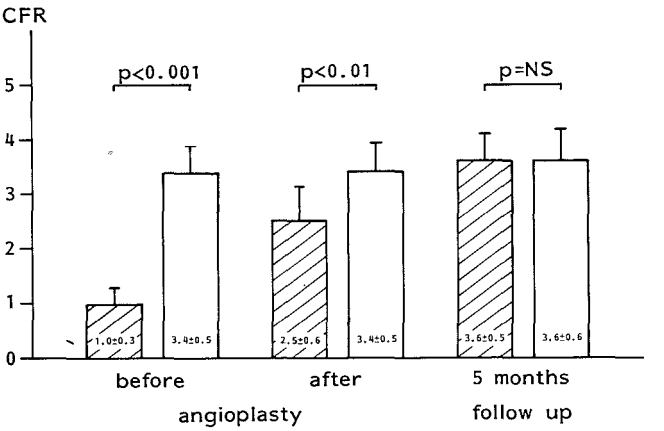

Figure 3
Coronary flow reserve (CFR) measured with digital subtraction cineangiography, before, immediately after and 5 months after percutaneous transluminal coronary angioplasty. The shaded bars represent the CFR of the myocardial region supplied by the dilated coronary artery. The open bars represent the CFR of an adjacent myocardial region supplied by a nondilated and angiographically normal coronary artery.

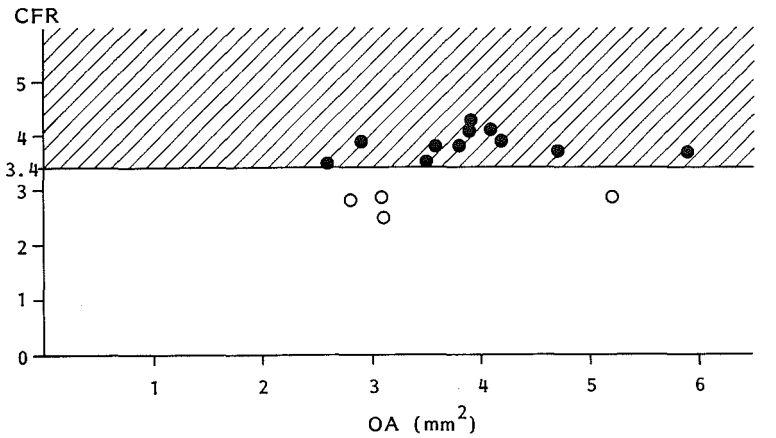

Figure 4
Coronary flow reserve (CFR) plotted against minimal cross-sectional obstruction area (OA) 5 months after percutaneous transluminal coronary angioplasty. The lower limit of the normal value for CFR as measured with the digital subtraction cineangiographic technique is 3.4.

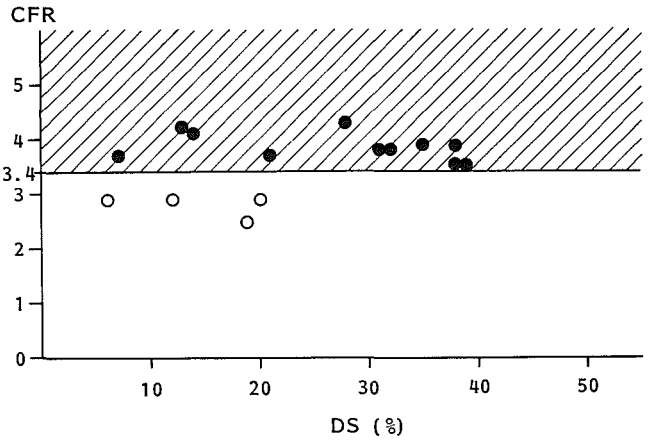

Figure 5
Coronary flow reserve (CFR) plotted against percentage diameter stenosis (DS) 5 months after percutaneous transluminal coronary angioplasty. The lower limit of the normal value for CFR as measured with the digital subtraction cineangiographic technique is 3.4.

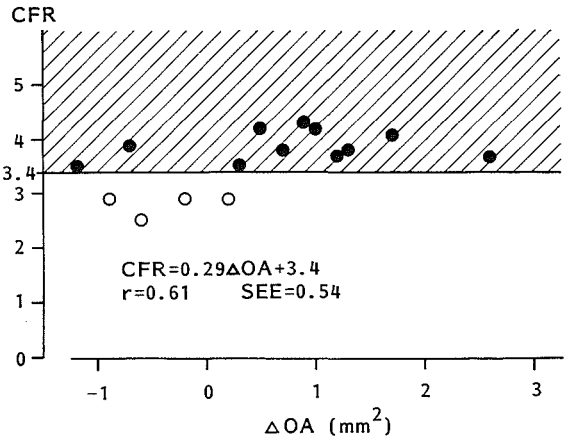

Figure 6
Relation between coronary flow reserve (CFR) 5 months after percutaneous transluminal angioplasty and the change that occurred in minimal cross-sectional obstruction area ($\triangle$ OA) between immediately after percutaneous transluminal coronary angioplasty and 5 months later. The lower limit of the normal value for CFR as measured with the digital subtraction cineangiographic technique is 3.4.

than 3.4. In 5 patients the minimal cross-sectional obstruction area 5 months after PTCA was smaller than the area immediately following the procedure (late deterioration). The percentage of patients showing normalization of coronary flow reserve 5 months after PTCA is substantially higher (p less than 0.05, Chi Square test) in the group with late angiographic improvement (90%) compared to the group with late deterioration (40%).

Table 2: Results: Coronary flow reserve of patients with angiographically normal coronary arteries.

Pat	age	sex	vessel	CFR
1	38	M	LAD	6.5
2	41	M	LC	6.2
3	62	F	LAD	5.3
4	31	M	R	5.2
5	60	M	LC	5.0
6	63	M	LC	5.0
7	54	M	LC	5.0
8	48	M	LC	4.0
9	66	F	LC	4.5
10	52	M	LAD	4.0
11	59	M	LAD	5.0
12	59	M	LC	4.8
13	47	M	LC	4.9
14	58	M	LAD	3.7
15	59	M	LAD	4.3
16	54	F	LC	6.4
17	61	M	LAD	4.9
18	62	M	R	4.8
19	58	M	LAD	4.7
20	57	M	R	4.6
21	64	M	LAD	4.5
22	61	M	LAD	3.4
23	50	M	LAD	6.3
24	58	M	LAD	4.0

CFR = coronary flow reserve; F = female; LAD = left anterior descending coronary artery; LC = circumflex artery; M = male; R = right coronary artery.

Discussion

The purpose of the present study was to establish whether coronary flow reserve in a myocardial region supplied by a stenotic coronary artery could be restored to normal by PTCA. Immediately after PTCA coronary flow reserve is not normalized (11-14). In 11 of our 15 patients without angina and with normal exercise thallium scintigraphy 5 months after PTCA, coronary flow reserve was normalized. There are several

possible explanations for this phenomenon.

First, since coronary flow reserve is a ratio between maximal coronary blood flow and resting flow, an increase in resting flow results in a decrease of this ratio. The radiographic technique we used does not provide us with absolute measurements of volume flow and we therefore cannot draw any conclusion regarding the resting coronary volume flow after the PTCA procedure. However, several authors using the thermodilution technique in the coronary sinus or the great cardiac vein have reported comparable resting volume flows before and after PTCA (24-26).

Second, metabolic, humoral or myogenic factors may limit coronary flow reserve after PTCA. The metabolic derangements due to the PTCA seem quickly reversible, as shown by the fast decline of temporarily increased lactate, hypoxanthine and K+ concentrations (24,27), and are therefore not likely to be of major significance. Although humoral factors such as thromboxane release (28) may influence vasoactive regulation in a specific subgroup of patients with complicated PTCA, so far no evidence has been presented for the persistence of humoral derangements after PTCA. The long-standing reduction in perfusion pressure distal to the stenotic lesion may induce alterations in the complex mechanism of coronary blood flow autoregulation (11), and a prolonged period of time might be needed before these abnormalities subside (29).

Third, the impaired coronary flow reserve could be directly related to the severity of the residual stenosis. Cross sectional area as measured immediately after PTCA, generally is about threefold increased as a result of the procedure, but it remains grossly abnormal (30,31). In the 6 months after PTCA important morphological changes may take place. Johnson et al (30) reported a late increase in cross-sectional obstruction area in about one-third of their patients. In our selected group of patients with no angina an a normal exercise thallium scintigram, the percentage of patients with late angiographic improvement was even higher (66%). In a previous study in our laboratory the relationship between cross-sectional obstruction area and coronary flow reserve in patients with stable angina and single vessel coronary artery disease has been established (5). In figure 7 this relation is shown with the results of the sequential coronary flow reserve and obstruction area measurements of the present study superimposed. The data of the present study are within the 95% confidence limits of the relation between flow reserve and obstruction area. Therefore, the persisting reduced obstruction area is by itself a sufficient explanation for the limited restoration of coronary flow reserve although it does not rule out other contributing pathophysiological mechanisms.

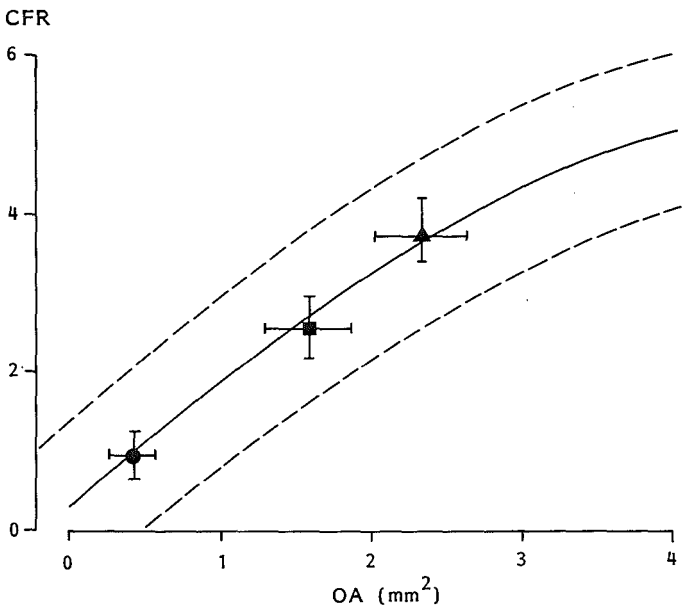

Figure 7
Relation between coronary flow reserve (CFR) and cross-sectional obstruction area (OA) as previously reported.[5] The solid line is the best fit curve and the shaded area corresponds to the 95 % confidence limits. The mean values and standard deviations of coronary flow reserve and obstruction area as obtained in the present study, before percutaneous transluminal coronary angioplasty (circle), immediately after (square) and 5 months later (triangle), are plotted on this diagram.

Limitations

There are two important limitations of coronary angiography in the setting of PTCA. Firstly, the changes in luminal size of an artery following the mechanical disruption of its internal wall may be difficult to assess by angiographic means (31,32). The irregular shape with intimal tears that fill with contrast medium to a variable extent will result in some overestimation of the true functional luminal size immediately following PTCA. Secondly, the extent of coronary atherosclerosis may be difficult to delineate angiographically. Mc Pherson et al (33) documented that substantial intimal atherosclerosis resulting in diffuse obstructive disease that involves the entire length of an epicardial artery, is often present, even when angiograms reveal only discrete lesions. As a consequence relative measurements of stenosis severity are an inadequate approach to assessing the severity of coronary obstructions. This may explain why 4 of our PTCA patients with only very mild residual stenoses 5 months after PTCA still had an abnormal vasodilatory reserve.

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CHAPTER 10: ASSESSMENT Of THE IMMEDIATE AND LONG-TERM FUNCTIONAL RESULT OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY.

Abstract

The assessment of the functional significance of coronary artery lesions during cardiac catheterization has recently become possible by calculating coronary flow reserve from the myocardial contrast appearance time and density in the resting and hyperemic states determined from digitized coronary cineangiograms. However, the inter- and intra-observer variabilities, as well as the short-, medium-, and long-term variabilities of the coronary flow reserve measurements have to be established prior to the use of this technique as a means of assessing the immediate and long-term functional results of revascularization procedures such as percutaneous transluminal coronary angioplasty (PTCA). Variability was defined as the mean difference and standard deviation of the difference between duplicate determinations of coronary flow reserve. The intraobserver variability (mean difference ± SD) in the measurement of coronary flow reserve was - 0.01 ± 0.07. Interobserver variability by two observers was + 0.08 ± 0.52. Short-term variability based on the analysis of two coronary cineangiograms taken 5 min. apart was - 0.02 ± 0.26. Medium-term variability (repeated coronary cineangiographies 1-3 hours apart) was found to be - 0.06 ± 0.52. Long-term variability (repeated coronary cineangiographies 3 to 5 months apart) was 0.11 ± 0.63. Having established the reproducibility of this radiographic method, we studied the prospective changes in coronary flow reserve in 25 patients undergoing PTCA for single vessel coronary artery disease. Coronary flow reserve measurements and quantitative coronary cineangiography were performed before PTCA, immediately after PTCA and 3 to 5 months later. PTCA resulted in an immediate increase in coronary flow reserve from 1,0 ± 0,3 to 2,3 ± 0,6 with a concommitant increase in obstruction area from 0,9 ± 0,3 to 3,3 ± 0,7 mm^2. Nine of our 25 patients developed restenosis defined as a diameter stenosis greater than 50% at follow-up. The other 16 patients had 3 to 5 months after PTCA a coronary flow reserve of 3,3 ± 0,6. Coronary flow reserve measurement from digitized coronary cineangiograms is a reproducible method for the assessment of the physiological importance of coronary artery obstructions. Short-, medium-, and long-term investigations of the functional results of interventions such as pharmacological therapy or revascularization procedures can be performed reliably with this technique.

Introduction

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977 (1), this procedure has gained increasing importance in the treatment of coronary artery obstructions. The immediate and long-term results of PTCA are usually assessed by visual interpretation of coronary angiograms. However, the visual interpretation of the coronary angiogram provides inadequate information about the physiological importance of obstructive coronary artery disease (2), and is prone to inter- and intra-observer variations. Although computer-based quantitative analysis procedures have reduced the high interobserver and intraobserver variabilities (3,4) in the assessment of percent diameter stenosis and provides absolute data on the stenosis geometry (5), the physiological importance of a coronary stenosis can not be inferred from geometrical data alone (6,7). Recently, measurement of the coronary flow reserve has been proposed as a better method to evaluate the hemodynamic repercussions of a coronary stenosis (7,8). Three techniques have been developed that allow the measurement of regional coronary flow reserve during cardiac catheterization. The first uses a pulsed Doppler coronary artery catheter which can measure intracoronary blood flow velocity (9,10). The second technique is an indicator dilution technique with a platinum-tipped angioplasty guidewire, using hydrogen as the indicator (11). The third technique is based on the radiographic assessment of myocardial perfusion using contrast medium (6,12-16). The major advantage of this technique is that no guide wires or other hardware need to be introduced into the coronary artery, so that it can be employed during routine cardiac catheterization. Although the technique is computer-based, a crucial component of the analysis procedure is the user-dependent selection of the boundaries of the regions of interest, making intra- and interobserver variability potential pitfalls. Knowledge about the short-, medium-, and long-term variabilities in the measurements of coronary flow reserve is an essential prerequisite, if this radiographic technique is to be used for the determination of the immediate and/or long-term functional results of pharmacological therapy or revascularization procedures such as PTCA. The aims of this investigation were: firstly, to determine the inter- and intraobserver variabilities, as well as the short-, medium-, and long-term variabilities in coronary flow reserve measurements from digitized coronary cineangiograms; secondly, to assess the immediate and long-term functional result of PTCA and its relation to quantitatively determined coronary stenosis geometry.

PATIENTS AND METHODS

Patient selection

Twenty-five patients underwent PTCA for disabling angina pectoris despite optimal pharmacological therapy. The right coronary artery was dilated in 5 patients, the circumflex artery in 5 patients and the left anterior descending artery in 15 patients. Their mean age (±SD) was 54 (±9) years. Twenty-four patients were male. Recatheterization was performed 3 to 5 months later, as part of an ongoing study on restenosis after PTCA. Informed consent was obtained for the additional investigations. Patients were selected on the basis of the following criteria: primary successful PTCA for single vessel coronary artery disease (residual diameter stenosis less than 50%), normal blood pressure (mean aortic pressure ranged from 85 to 105 mmHg), normal left ventricular wall motion with an ejection fraction of more then 55%, normal left ventricular end-diastolic pressure, no angiographic evidence of collateral circulation, cardiac hypertrophy, anemia, polycythemia, documented previous myocardial infarction, or valvular heart disease.

Coronary flow reserve measurements

The procedure for the coronary flow reserve measurement from digitized coronary cineangiograms recorded on 35 mm cinefilm has been implemented on the Cardiovascular Angiography Analysis System (13). The film speed was 25 frames/s with a pulse time of 4 ms. For the right coronary artery a left or right anterior oblique projection was used, for the left coronary artery a left anterior oblique projection. The X-ray gantry settings were standardized in the short- and medium-term variability studies. This resulted in a good reproducibility of isocenter-image intensifier distance, focus-isocenter distance and object-isocenter distance (see table 1). Voltage (kV) and current (mA) of the X-ray generator are adjusted automatically in our catheterization laboratory by a microprocessor system, during the first 3 or 4 cineframes of each cinerun (17). The on-line recorded voltage and current are than held constant during the cinerun. This microprocessor based technique used results in good reproducibility of both voltage and current of the X-ray generator (see table 1). The heart was atrially paced at a rate just above the spontaneous heart rate, ranging from 70 to 90 beats/min. An ECG-triggered injection into the coronary artery was performed with iopamidol at 37°C through a Medrad Mark IV infusion pump. This non-ionic contrast agent has a viscosity of 9.4 cP at 37°, an osmolality of 0.796 osm/kg and an iodine content of 370 mg/ml. The injection rate and volume of the contrast medium were judged to be adequate when back flow of contrast medium

Table 1: Variability in X-ray gantry settings and voltage and current of the X-ray generator, with repeated cineangiographic studies (n = 20).

		overall mean value	mean difference	p-value	SD diff.
LAO	(degrees)	53	0.1	NS	0.2
IID	(cm)	23.6	- 0.1	NS	2.0
FID	(cm)	72.3	0.0	NS	0.1
OID	(cm)	5.4	0.0	NS	0.1
Voltage	(kV)	71.2	0.1	NS	2.9
Current	(mA)	717	- 5.5	NS	16.1

LAO = left anterior oblique projection, IID = Isocenter-Image intensifier distance, FID = Focus-Isocenter distance, OID = Object-Isocenter distance, SD diff = standard deviation of the difference.

into the aorta occurred. The injection rate ranged from 3 to 6 ml/s and the injection volume ranged from 5 to 9 ml, depending on the size of the coronary artery. The angiogram was repeated with identical patient position and X-ray gantry settings, 30 s after pharmacologically induced hyperemia by a bolus injection of 12.5 mg papaverine into the coronary artery (12). Five or six end-diastolic cineframes were selected from successive cardiac cycles. Logarithmic non-magnified mask-mode background subtraction was applied to the image subset, to eliminate non-contrast medium densities. The last end-diastolic frame prior to contrast administration was chosen as the mask. From the sequence of background-subtracted images, a contrast arrival time image was determined, using an empirically derived fixed density threshold (13). Each pixel was labeled with the sequence number of the cardiac cycle in which the pixel intensity level for the first time exceeded the threshold, starting from the beginning of the ECG-triggered contrast injection. In addition to the contrast arrival time image, a density image was computed, with each pixel intensity value being representative for the maximal local contrast medium accumulation. The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image (Q(h)) divided by the regional flow of the corresponding baseline image (Q(b)). Regional flow values were quantitatively determined from the relationship that regional blood flow equals regional vascular volume divided by the transit time (13). Regional vascular volume was assessed from the logarithmic mask-mode subtraction images, using the Lambert-Beer relationship. Coronary flow reserve (CFR) can then be calculated as:

$$CFR = Q(h)/Q(b) = D(h)/D(b) : T(h)/T(b)$$

where D is the mean contrast density and T the mean appearance time at baseline (b) and hyperemia (h). Mean contrast medium appearance time and density were computed within user-defined regions of interest that were chosen in such a way that the epicardial coronary arteries visible on the angiogram, the coronary sinus and the great cardiac vein were excluded from the analysis (13). For each of the 3 major coronary arteries (right coronary artery, left anterior descending coronary artery, and circumflex artery) only one region of interest was chosen and analyzed. Normal values for coronary flow reserve as measured with this technique in our laboratory have previously been established (18). The mean coronary flow reserve of 24 angiographically normal coronary arteries was 5.0 (SD: ± 0.6). A normal coronary flow reserve is therefore 3.4 (2 SD below 5.0). This is comparable to the values for normal coronary flow reserve measured with intracoronary Doppler catheters as reported by Wilson et al (9,10).

Intraobserver variability

Intraobserver variability was assessed by measuring the coronary flow reserve in 11 regions of interest in 6 patients twice from the same cineangiograms by the same observer. In 5 patients two regions of interest in the myocardium supplied by the left coronary artery were analyzed, and in one patient a region of interest was analyzed in the myocardium supplied by the right coronary artery. Care was taken to ensure that the regions of interest in the duplicate determinations were identical.

Interobserver variability

Interobserver variability was assessed by measuring the coronary flow reserve in 12 regions of interest in 7 patients from the same coronary cineangiograms by two observers. In 5 patients two regions of interest in the myocardium supplied by the left coronary artery were analyzed, and in 2 patients a region of interest was analyzed in the myocardium supplied by the right coronary artery. The selected boundaries of the regions of interest were unknown to the other observer.

Short-term variability (5 min.)

The short-term variability was defined as the variation in measured coronary flow reserve from two coronary cineangiograms taken 5 min apart with identical position of patient, X-ray source and image intensifier. Coronary flow reserve was measured in 13 regions of interest in 7 patients. In 6 patients two regions of interest in the myocardium supplied by the left coronary artery were analyzed, and in one patient a region of interest was analyzed in the myocardium supplied by

the right coronary artery. Care was taken to ensure that the selected regions of interest in the duplicate determinations were identical.

Medium-term variability (1-3 hours) and immediate functional result of PTCA

Coronary flow reserve was measured before and immediately after PTCA in 25 patients. In 5 patients the right coronary artery was dilated. In 20 patients undergoing PTCA of the left anterior descending coronary artery or the circumflex artery, coronary flow reserve was measured in both myocardial regions. To calculate the medium-term variability, regions of interest (n = 20) were chosen in the myocardium supplied by the non-dilated coronary arteries. To assess the immediate alterations in coronary flow reserve due to PTCA, regions of interest (n = 25) were chosen in the myocardium supplied by the dilated coronary arteries. During the PTCA procedure various vaso-active drugs were administered (nitrates, Ca-antagonists) as clinically indicated, probably resulting in changes in vaso-motor tone. Care was taken to ensure that cineangiographic projection and X-ray gantry settings as well as the analyzed regions of interest were identical before and after the PTCA.

Long-term variability (3-5 months)and long-term functional result of PTCA

During follow-up coronary cineangiography 3 to 5 months (mean 4,2 months) later coronary flow reserve was measured again in these 25 patients. To calculate the long-term variability regions of interest (n = 20) were chosen in the myocardium supplied by the non-dilated coronary arteries. To assess the long-term alterations in coronary flow reserve after PTCA regions of interest (n = 25) were chosen in the myocardium supplied by the dilated coronary arteries. The follow-up investigation was always performed in a second cineangiographic room with different X-ray equipment. There was no standardized protocol for the administration of vasoactive medication before data acquisition; therefore, vasomotor tone in both conditions was unknown and ignored. Care was taken to ensure that identical regions of interest were analyzed.

Quantitative coronary cineangiography

The coronary arterial dimensions were determined before PTCA, immediately after PTCA and at follow-up, with the computer-based Cardiovascular Angiography Analysis System (5,19). The boundaries of selected coronary artery segments were detected automatically from optically magnified and video-digitized regions of interest of a cineframe. Calibration of the diameter data in absolute values (mm) was achieved

by detecting the boundaries of a section of the contrast catheter and comparing the mean diameter in pixels with the known size in millimeter. Pincushion distortion was corrected. A computer estimation of the original arterial dimensions at the site of obstruction was used to define the reference region. The interpolated percentage diameter stenosis and the minimal cross-sectional area (mm^2) at the site of obstruction were calculated by averaging the values from at least two, preferably orthogonal projections.

Statistical analysis

The results from the various studies were analyzed for significant differences with Student's t-test for paired observations (border of significance $p = 0.05$). Least squares linear repression on analysis were used to describe the relationships between coronary flow reserve measurements and the quantitatively determined coronary artery dimensions.

RESULTS

Intraobserver variability

Figure 1 shows the results of measuring twice the coronary flow reserve in 11 regions of interest in 6 patients by the same observer, from the same coronary cineangiograms. There is no significant difference between the first and second measurements.

Interobserver variability

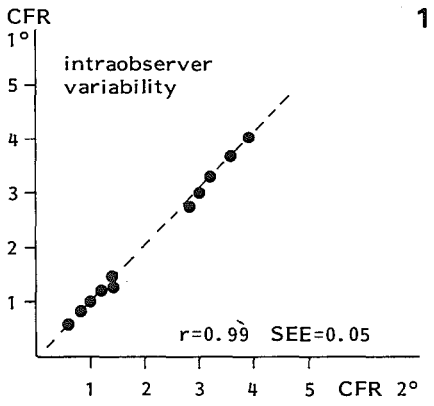
Coronary flow reserve measurements by two observers without the knowledge of each others selected regions of interest using the same coronary cineangiograms in 12 regions in 7 patients is shown figure 2. There is no significant difference in the measurements between the two observers.

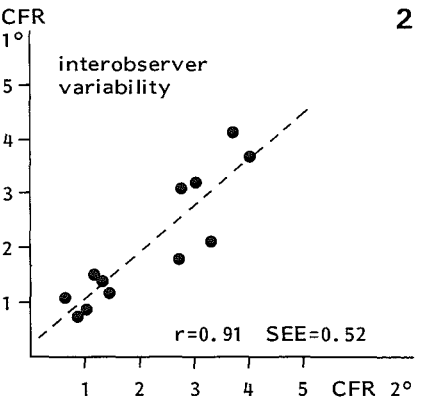
Short-term variability (5 min.)

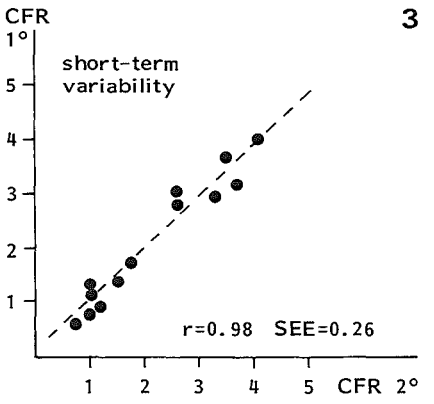
Figure 3 gives the coronary flow reserve as measured in 13 regions of interest in 7 patients from repeated acquisition and analysis of coronary cineangiograms taken 5 min apart. No significant differences between the two measurements were found. The hemodynamic data are shown in table 2.

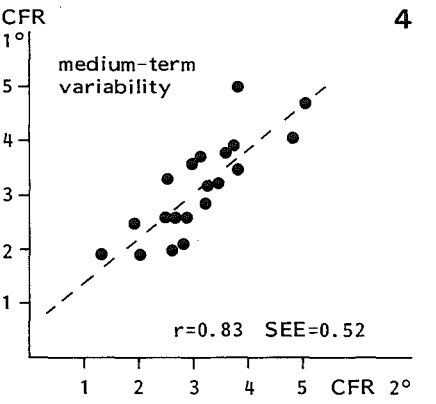
Medium-term variability (1-3 hours, n = 20)

Figure 4 provides the data on the coronary flow reserve measurements for a myocardial region supplied by a coronary artery not involved in the dilatation process in 20 patients immediately before and after angioplasty. No significant









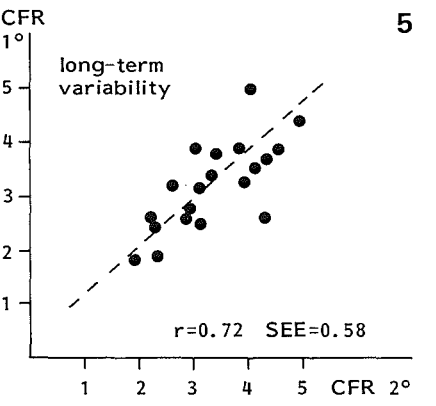


Fig. 1 CFR 1° = first determination of coronary flow reserve, CFR 2° = second determination of coronary flow reserve, r = linear regression correlation coefficient, SEE = standard error of the estimate

Fig. 2, 3, 4 and 5: abbreviations as in fig. 1.

Table 2
Hemodynamic data of short-term variability study (N=7).

	1°	2°	difference	
Pao	97 ± 10	98 ± 9	1 ± 3	NS
HR	77 ± 12	77 ± 12	0 ± 0	NS

Pao = mean aortic pressure (mmHg), HR = heart rate (beats/min)

Table 3
Hemodynamic data of medium-term variability study (N=20).

	1°	2°	difference	
Pao	95 ± 12	91 ± 11	4 ± 8	NS
HR	79 ± 11	79 ± 11	0 ± 0	NS

Pao = mean aortic pressure (mmHg), HR = heartrate (beats/min).

Table 4
Hemodynamic data of long-term variability study (N=20).

	1°	2°	difference	
Pao	91 ± 11	97 ± 15	6 ± 13	NS
HR	79 ± 11	81 ± 13	2 ± 8	NS

Pao = mean aortic pressure (mmHg), HR = heart rate (beats/min).

differences were found between the measurements obtained before and after the angioplasty. The hemodynamic data are shown in table 3.

Long-term variability (3-5 months, n = 20)

Figure 5 gives the coronary flow reserve as measured in a myocardial region supplied by a non-dilated coronary artery, immediately following angioplasty as well as 3 to 5 months later. There is no significant difference between the two measurements. The hemodynamic data are shown in table 4.

Immediate functional and anatomical result of PTCA (n = 25).

Diameter stenosis (mean ± SD) decreased from 65 ± 6 to 32 ± 10%. The coronary flow reserves (mean ± SD) of the dilated coronary arteries increased from 1,0 ± 0,3 to 2,3 ± 0,6, and the cross-sectional area at the site of obstruction (mean ± SD) increased from 0,9 ± 0,3 to 3,3 ± 0,7 mm^2. The data of the individual patients are shown in figures 6 and 7. Eighteen of the 25 patients (72%) had an increase of coronary flow reserve greater than 2 SD of the medium-term variability.

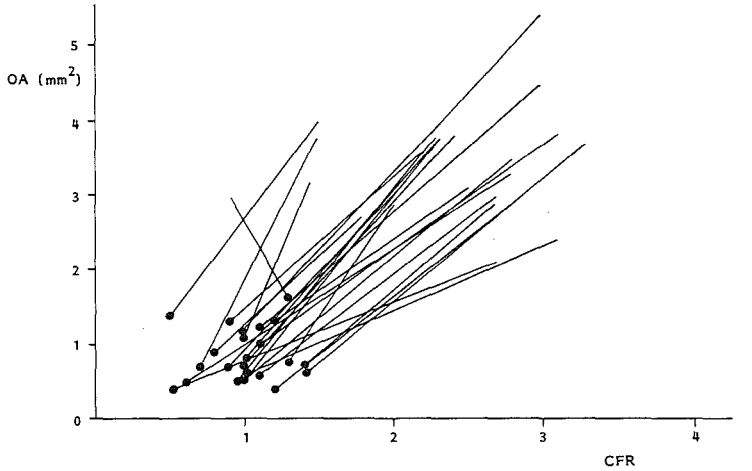


Figure 6.
Cross-sectional area at the site of obstruction (OA) and coronary flow reserve (CFR) before and immediately after PTCA.

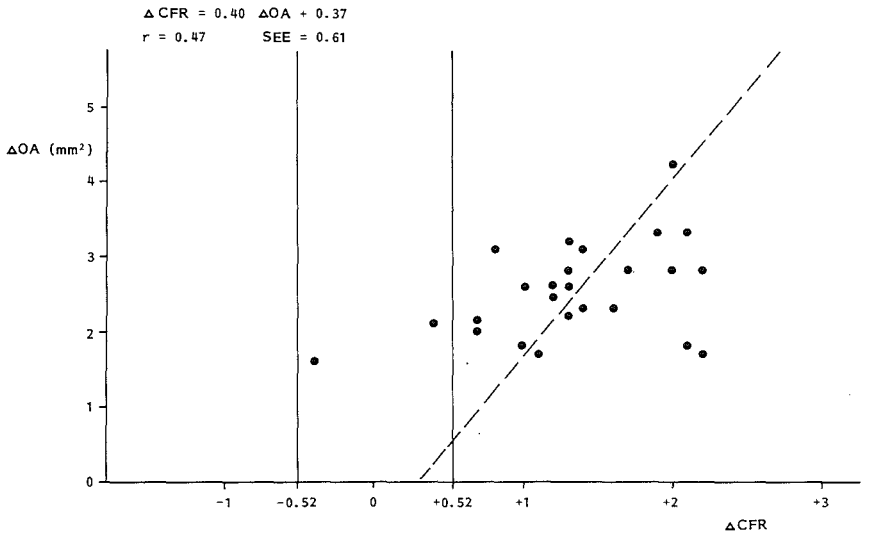


Figure 7.
Relation between change in obstruction area (△ OA) and change in coronary flow reserve (△ CFR) as immediate result of PTCA. The vertical lines mark 1 SD of the medium-term variability.

Long-term functional and anatomical result of PTCA (n = 25).

Three to five months after PTCA the mean percentage diameter stenosis (mean ± SD) was 38 ± 18%. The coronary flow reserve (mean ± SD) of the dilated coronary arteries was 2,6 ± 1,0, and the cross-sectional area at the site of obstruction was 2,8 ± 1,4 mm^2. The alterations in these two parameters of the individual patients during the 3 to 5 months after PTCA are shown in figures 8 and 9. Nine of the 25 patients (36%) had restenosis defined as diameter stenosis greater than 50% during follow-up angiography. These 9 patients had an obstruction area (mean ± SD) of 1,3 ± 0,4 mm^2, and a coronary flow reserve of 1,5 ± 0,4. The patients without restenosis had an obstruction area of 3,6 ± 1,0 mm^2 and a coronary flow reserve of 3,3 ± 0,6. Seven of the 25 patients (28%) had an increase of coronary flow reserve greater than 2 SD of the long-term variability, and 4 of the 25 patients (16%), all with restenosis, had a decrease of coronary flow reserve greater than 2 SD of the long-term variability.

DISCUSSION

To understand the implications of coronary artery disease in an individual patient, the clinician must have information on anatomy as well as functional capacity of coronary arteries and left ventricle. Coronary flow reserve defined as the ratio of maximal to resting coronary blood flow has been introduced as measure of the functional capacity of coronary arteries (7,8). The relation between coronary artery anatomy and functional capacity/coronary flow reserve, has been extensively studied in animal models (20-22). Gould et al produced varying degrees of coronary narrowing and showed that stenoses in excess of 30-45% diameter narrowing reduced coronary vasodilator responses in a predictable fashion (22). Although the reduction in coronary flow reserve can be predicted by quantitative determination of stenosis geometry in selected patients with limited coronary artery disease (10,13), in many patients the functional capacity of their coronary arteries cannot be inferred from anatomical data alone. For instance, the functional capacity of a coronary artery with two or three obstructive lesions cannot be predicted by quantitative analysis of the coronary angiogram. This implies that accurate and reproducible means to measure regional coronary flow reserve are a necessary addition to quantitative coronary cineangiography.

The first aim of the present study was to determine inter-, intra-, as well as short-, medium-, and long-term variability in radiographic coronary flow reserve measurements

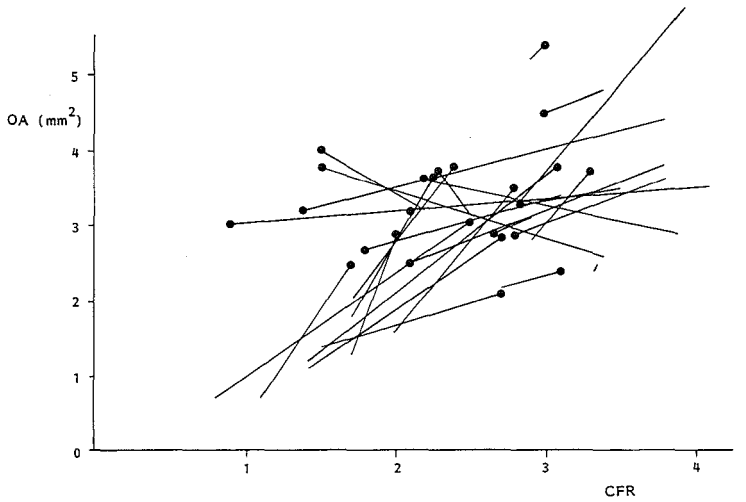


Figure 8.
Cross-sectional area at the site of obstruction (OA) and coronary flow reserve (CFR) immediately after PTCA and 3 to 5 months later.

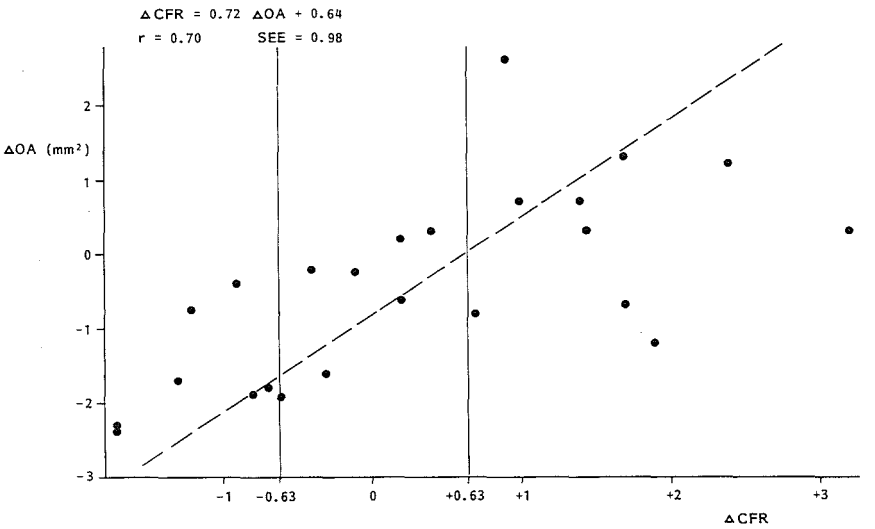


Figure 9.
Relation between change in obstruction area (△ OA) and change in coronary flow reserve (△ CFR) occurring between immediately after PTCA and follow-up 3 to 5 months later. The verticle lines mark 1 SD of the long-term variability.

Multiple factors potentially contribute to these variabilities.

First, X-ray gantry settings and voltage and current of the X-ray generator must be identical to permit a valid comparison of the myocardial contrast density measurements on both the baseline and hyperemic cineangiograms. This is also a prerequisite if a comparison of two or more coronary flow reserve measurements at different times is to be made. The X-ray equipment used in this study seems adequate in this regard (table 1).

Second, cine film development must be very stable. In our laboratories a 21 step (log 1.5 increment) sensitometric full frame strip is generated on each cinefilm with a dummy camera prior to the angiographic investigation. This strip is developed together with the angiographic data and is used to control the chemical process. The replenishment of developer is done per meter cinefilm instead of per unit of time and therefore independant of the speed of the machine. Together with accurate temperature control and the use of a medium grain developer, this results in a reliable chemical process characterized by a mean density of 0.82 and a gradient of 1.25.

Third, many patient related factors are important determinators of the measured coronary flow reserve and contribute to the variability of this radiographic method. Changes in heart rate may influence the coronary flow reserve (23,24). Furthermore, subtraction of the digitized selected end-diastolic cineframes is only possible when a strictly regular rhythm is present. Therefore, atrial pacing is mandatory. Changes in blood pressure can influence coronary flow reserve in two ways (8). Firstly, myocardial oxygen consumption and therefore baseline coronary blood flow is to a large degree determined by the systemic arterial pressure. Since coronary flow reserve is defined as the ratio of maximal to resting coronary blood flow, an increase in resting coronary blood flow as result of an increase in myocardial oxygen consumption results in a decrease of this ratio. Secondly, the coronary blood flow during maximal coronary vasodilation is linearly related to the coronary driving pressure (25). Cineangiograms that are used for the calculation of flow reserve during baseline and hyperemic conditions, or repeated radiographic coronary flow reserve measurements should thus be obtained with the same blood pressure. As shown in tables 2, 3 and 4 alterations in blood pressure or heart rate were negligible in this study. Coronary flow reserve measured in the animal laboratory can be reduced by a large increase in left ventricular diastolic pressure (8) or a marked change in contractility and systolic function (26). At present there are no data regarding the influence of abnormal systolic left ventricular function on coronary flow reserve in humans as measured with this radiographic technique, but a study on coronary flow reserve after

reperfusion in the acute and chronic phase of myocardial infarction is currently underway at our institution. Preliminary results suggest a marked decrease in coronary flow reserve in both the acute and chronic phase of myocardial infarction. As all patients in the present study had a normal left ventricular function, it seems unlikely that these factors play a role in the variabilities described in this report. Medium-, and long-term variabilities are certainly affected by changes in vasomotor tone (27,28). Alterations in collateral channel filling patterns during and after angioplasty may also play a role. Although we excluded patients with angiographically visible collaterals, collateral vessels not visible by standard angiographic techniques are often present (29). Especially the long-term study might be influenced by changes in neurohumoral factors. Endothelium derived relaxing factor has a physiological dilator role by acting as a local autocoid on subjacent smooth muscle and may be an important controlling variable in coronary flow and flow reserve (30,31).

Fourth, an prerequisite of this radiographic technique is the use of an ECG triggered pump to inject a fixed volume at a fixed contrast injection rate (6,15). Although injection of a radiographic contrast agent induces profound alterations in coronary blood flow (32), the ratio of hyperemic coronary blood flow to baseline flow is unaffected by the contrast agent during the first 5 s after injection when injection rate and volume are identical in hyperemic and baseline conditions (15,16). The injection rate and volume should be sufficient to ensure complete filling of the epicardial coronary arteries with contrast during pharmacologically induced hyperemia (6,15,16). The disturbance in coronary blood flow due to the radiographic contrast agent lasts for less then 20 s, and sequential injections of contrast agent in doses as used in this investigation do not result in persisting changes in coronary blood flow (32,33,34).

Fifth, the method of induction of an hyperemic response in the coronary circulation should be reproducible. Intracoronary papaverine induces a strong and short-lasting hyperemia that is reasonably reproducible in magnitude as well as in timing (35). Wilson and White (36) recently investigated the dose of intracoronary papaverine needed to produce maximal coronary vasodilation and reported a maximal hyperemic response after 8 mg in most coronary arteries and after 12 mg in all coronary arteries.

Sixth, the analysis of the cineangiogram to permit calculation of coronary flow reserve from measured myocardial contrast appearance time and density involves the selection of end-diastolic cineframes, digitization and selection of a region of interest. The boundaries of the regions of interest are drawn by the observer with a writing tablet which is interfaced with the computer. Although the entire analysis

procedure can be performed with high reproducibility (see figure 1), the observer-dependent selection of the boundaries of the regions of interest introduces interobserver variability (figure 2). Consequently, rigid criteria should be applied to the selection of the boundaries of the regions of interest, preferably in an automated manner, not dependant on the user.

The second aim of the present study was to assess the immediate and long-term functional result of PTCA.

Although PTCA resulted in an immediate increase of coronary flow reserve from 1,0 ± 0,3 to 2,3 ± 0,6, coronary flow reserve in the myocardium supplied by the dilated coronary artery immediately after PTCA was still substantially lower than the coronary flow reserves of the myocardium supplied by non-dilated and angiographically not significantly diseased coronary arteries (diameter stenosis less than 50%) that was 3,2 ± 0,9 (see figure 4). During the 3 to 5 months follow-up 9 patients developed restenosis defined as a diameter stenosis greater than 50%. The other 16 patients had 5 months after PTCA a coronary flow reserve of the dilated coronary arteries of 3,3 ± 0,6, which is comparable to the coronary flow reserve of adjacent myocardial regions, supplied by non-dilated coronary arteries of these patients. There are several possible explanations for the limited restoration of coronary flow reserve immediately after PTCA. Since coronary flow reserve is a ratio between maximal and resting flow, an increase in resting flow results in a decrease of this ratio. Although several authors using the thermodilution technique have reported comparable volume flows before and after PTCA (33,34), recent work performed in our laboratory (37) with intracoronary Doppler catheters, suggests that resting coronary blood flow velocity increases during the PTCA procedure. Further studies are necessary to resolve this controversy. Metabolic, humoral or myogenic factors may limit coronary flow reserve after PTCA. The metabolic derangements due to the PTCA seem quickly reversible, as shown by the fast decline of temporarily increased lactate, hypoxanthine and K+ concentrations (33,38). The long-standing reducton in perfusion pressure distal to the stenotic lesion may induce alterations in the complex mechanism of coronary blood flow autoregulation (39), and a prolonged period of time might be needed before these abnormalities subside (40). Finally, the impaired coronary flow reserve could be directly related to the residual stenosis. The cross-sectional obstruction area measured immediately after PTCA, generally is about threefold increased as result of the procedure but remains grossly abnormal (18,19,41).

Although changes in cross-sectional area due to the PTCA procedure do not particularly correlate absolutely with

changes in coronary flow reserve, there is nevertheless a tendency towards changes in the same direction despite the marked scatter of the data, see figure 7. In the 6 months after PTCA important morphological changes may take place. Johnson et al (41) reported a late increase in obstruction area in about 1/3 of their patients. Nine of our 25 patients had a late increase in obstruction area. The relation we found between the change in obstruction area and the change in flow reserve occuring between immediately after PTCA and 3 to 5 months later, suggests that these morphological alterations play an important role in the restoration of coronary flow reserve (see figure 9).

There are two important limitations of coronary angiography in the setting of PTCA. Firstly, the mechanical disruption of its internal wall may be difficult to assess by angiographic means (19,42). The irregular shape with intimal tears that fill with contrast medium to a variable extent will result in some overestimation of the true functional luminal size immediately following PTCA. Secondly, the extent of coronary atherosclerosis may be difficult to delineate angiographically. McPherson et al (43) documented that substantial intimal atherosclerosis resulting in diffuse obstructive disease that involves the entire length of an epicardial artery is often present, even when angiograms reveal only discrete lesions. This may explain why despite only minimal residual stenosis, our patients that had no restenosis, had a coronary flow reserve of the dilated as well as the non-dilated coronary arteries still somewhat lower than the normal values for coronary flow reserve as previously reported (9,13,18).

Conclusion

Coronary flow reserve measurement from digitized coronary cineangiograms is a reproducible means to assess the functional capacity of coronary arteries. Short-, medium-, and long-term investigations of the functional results of interventions such as PTCA can be performed reliably with this technique.

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Samenvatting

In 1959 ontwikkelde Sones de selectieve coronaire angiografie. Tot nu toe is deze techniek de enige manier gebleven die ons in staat stelt de aanwezigheid en de ernst van vernauwingen in de kransslagaderen met een adequate resolutie af te beelden. Daardoor is coronaire angiografie het belangrijkste hulpmiddel geworden dat de cardioloog ter beschikking staat bij het nemen van beslissingen omtrent het te voeren beleid bij patiënten met aandoeningen van de kransslagaderen. De relatie tussen de angiografische ernst van een vernauwing en de daaruit voortkomende vermindering of beperking van de doorbloeding van de kransslagader is echter nog steeds een onzekere faktor.

In hoofdstuk 1 worden de vorm en de functie van de coronaire circulatie in het kort beschreven. Het concept van de coronaire doorstromingsreserve wordt geschetst. De vele methoden die parameters van de coronaire doorstroming meten, worden beschreven met nadruk op radiologische technieken. Een essentieel onderdeel van alle methoden om de coronaire doorstromingsreserve te meten is de pharmacologische inductie van een (kort-durende) maximale coronaire doorstroming. De waarde en de beperkingen van intracoronaire toediening van papaverine en adenosine voor de bepaling van de doorstromingsreserve worden respectievelijk beschreven in hoofdstukken 2 en 3 en hoofdstuk 4.

In hoofdstuk 5 wordt de radiologische bepaling van de coronaire doorstromingsreserve in detail beschreven, en wordt een eerste poging ondernomen de coronaire doorstromingsreserve te relateren aan kwantitatief bepaalde afmetingen van de kransslagaderen. Afbeelding van de hartspier middels thallium-201 tijdens en na inspanning is een belangrijke, niet-bloedige manier om de fysiologische betekenis van een vernauwing in een kransslagader te bepalen. In hoofdstuk 6 worden de resultaten van de toepassing van deze techniek bij 38 patiënten vergeleken met de gemeten coronaire doorstromingsreserve en kwantitatief bepaalde afmetingen van de kransslagaderen. In hoofdstuk 7 worden de relaties tussen de kwantitatief bepaalde afmetingen van de kransslagaderen en de coronaire doorstromingsreserve beschreven bij 81 patiënten. Tevens wordt een poging gedaan de resultaten van deze invasieve methoden te relateren aan de klinische uitingen van vernauwingen van de kransslagaderen, namelijk angina pectoris en niet-invasief verkregen aanwijzingen voor het bestaan van een tekortschietende doorstroming van de hartspier.

Sinds de introductie van ballondilatatie van de kransslagaderen in 1977, is deze behandeling uitgegroeid tot een van de belangrijkste behandelingsmogelijkheden voor patiënten met vernauwingen van de kransslagaderen. Geslaagde ballondilatatie, gedefinieerd als een residuele vernauwing van minder dan 50%

van de diameter van de kransslagader, leidt tot duidelijke verbetering in de klinische toestand van de patiënt. Of deze behandeling de doorbloeding van de hartspier echter geheel kan normaliseren werd aanvankelijk betwijfeld. Dit probleem komt aan de orde in de hoofdstukken 8,9 en 10. In hoofdstuk 8 wordt de doorstromingsreserve voor en onmiddellijk na ballondilatatie gemeten met 2 technieken: de radiologische techniek en intracoronaire stroomsnelheidsmeting middels het Dopplereffekt. In hoofdstuk 9 wordt aangetoond dat bij geselecteerde patiënten de coronaire doorstromingsreserve na ballondilatatie op langere termijn normaal kan worden. In hoofdstuk 10 worden de functionele resultaten van ballondilatatie op korte en lange termijn bij 25 patiënten in detail beschreven. Tevens wordt de variabiliteit van de radiologische techniek om de coronaire doorstromingsreserve te meten, beschreven.

Dit proefschrift beschrijft de implementatie en validatie van een radiologische techniek die, gebruikmakend van selectieve coronairangiografie, de meting van de coronaire doorstromingsreserve mogenlijk maakt tijdens een hartcatheterisatie. Deze techniek is een praktische en waardevolle toevoeging aan de angiografische visualisatie van de kransslagaderen.

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