Comparison of Quantitative Coronary Angiography, Intravascular Ultrasound, and Coronary Pressure Measurement to Assess Optimum Stent Deployment

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Background—Although intravascular ultrasound (IVUS) is the present standard for the evaluation of optimum stent deployment, this technique is expensive and not routinely feasible in most catheterization laboratories. Coronary pressure–derived myocardial fractional flow reserve (FFR\textsubscript{myo}) is an easy, cheap, and rapidly obtainable index that is specific for the conductance of the epicardial coronary artery. In this study, we investigated the usefulness of coronary pressure measurement to predict optimum and suboptimum stent deployment.

Methods and Results—In 30 patients, a Wiktor-i stent was implanted at different inflation pressures, starting at 6 atm and increasing step by step to 8, 10, 12, and 14 atm, if necessary. After every step, stent deployment was evaluated by quantitative coronary angiography (QCA), IVUS, and coronary pressure measurement. If any of the 3 techniques did not yield an optimum result, the next inflation was performed, and all 3 investigational modalities were repeated until optimum stent deployment was present by all of them or until the treating physician decided to accept the result.

Optimum deployment according to QCA was finally achieved in 24 patients, according to IVUS in 17 patients, and also according to coronary pressure measurement in 17 patients. During the step-up, a total of 81 paired IVUS and coronary pressure measurements were performed, of which 91% yielded concordant results (ie, either an optimum or a suboptimum expansion of the stent by both techniques, \(P<0.00001\)). On the contrary, QCA showed a low concordance rate with IVUS and FFR\textsubscript{myo} (48% and 46%, respectively).

Conclusions—In this study, using a coil stent, both IVUS and coronary pressure measurement were of similar value with respect to the assessment of optimum stent deployment. Therefore, coronary pressure measurement can be used as a cheap and rapid alternative to IVUS for that purpose. (Circulation. 1999;99:1015-1021.)

Key Words: pressure \(\blacklozenge\) ultrasonics \(\blacklozenge\) stents \(\blacklozenge\) angiography

Notwithstanding the benefits of coronary stenting during coronary intervention in terms of a better initial result and lower restenosis rate, the use of coronary stents has also been associated with some major concerns, ie, the risk of (sub)acute stent closure despite optimum anticoagulation and in-stent restenosis that can be difficult to treat.\(^1\)\(^-\)\(^4\) Studies with intracoronary ultrasound (IVUS) have shown that despite an apparently satisfying angiographic result, stents are often insufficiently deployed, and high-pressure balloon inflation may be necessary to achieve complete stent expansion.\(^5\)

However, unnecessary high-pressure inflation bears the risk of damaging the adjacent wall, disturbing the configuration of the stent, protruding the plaque remnants through the stent struts, and inducing inappropriate intimal hyperplasia.\(^6\)

Therefore, the importance of methods to guide optimum stent deployment is indisputable, and the usefulness of IVUS in this respect is so far unsurpassed. However, IVUS is expensive, requires exchange of the balloon for the IVUS catheter, and can be time consuming.\(^6\)\(^-\)\(^7\) It would be useful to have available a cheaper and more simple alternative method of evaluating optimum stent deployment.

During the past years, pressure-derived myocardial fractional flow reserve (FFR\textsubscript{myo}) has emerged as an easily obtainable, accurate, and lesion-specific index of the functional severity of a coronary stenosis that is not affected by hemodynamic variability such as changes in heart rate and blood pressure.\(^8\)\(^-\)\(^10\) FFR\textsubscript{myo} has an unequivocal normal value of 1.0 for every patient and every coronary artery and is a specific index of the conductance of the epicardial coronary artery.\(^9\)\(^,\)\(^11\) During percutaneous transluminal coronary angioplasty, FFR\textsubscript{myo} quantifies subsequent changes in maximum achievable blood flow.\(^11\) Because the purpose of coronary stenting is normalization of the conductance of the stented epicardial segment, it has been hypothesized that FFR\textsubscript{myo} after coronary stenting should return to normal, or at least that if disease is present elsewhere in the same coronary artery, no

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hyperemic gradient should persist across a well-stented segment. The opposite (ie, the question of whether the absence of a hyperemic gradient is always associated with complete stent deployment) has not been investigated so far. Therefore, the purpose of this study was to compare in a side-by-side manner the values of QCA, IVUS, and coronary pressure measurement in the assessment of optimum stent deployment.

Methods

Study Population
Thirty patients who were scheduled for elective coronary angioplasty and primary stenting of a de novo lesion in the proximal part of a native coronary artery with a reference diameter of ≥3.0 mm were selected for inclusion in the study. After written informed consent had been obtained, these patients were treated and underwent implantation of a Wiktor-i stent (Medtronic) according to the procedure described below. The study protocol was approved by the institutional ethical review board.

Angioplasty and Stent Implantation
After the introduction of a 6F to an 8F guiding catheter into the left femoral artery and the introduction of a 5F sheath into the femoral vein, 10 000 IU heparin IV was administered, repeated by an additional 5000 IU every hour. The guiding catheter was advanced into the coronary artery, and after the intracoronary administration of 300 μg nitroglycerin, angiograms were made from 2 orthogonal projections at an acquisition rate of 25 frames/s. Determination of the appropriate stent size was performed with the use of online quantitative coronary angiography (QCA) measurement. After appropriate predilatation, a Wiktor-i stent was implanted using an inflation pressure of 6 atm, after which deployment was assessed consecutively with QCA, IVUS, and pressure measurement. For these 3 investigational modalities, criteria for optimum stent deployment were defined in advance. If optimum stent deployment was not achieved with any of these 3 methods, inflation pressure was increased with steps of 2 atm and stent deployment was reassessed by the use of all 3 investigational modalities after every step, until all criteria for optimum stent deployment were met by all methods (Figure 1) or until the treating cardiologist decided to accept the result. If no optimum result could be achieved, a larger balloon size could be chosen to repeat the sequence above. After stent implantation, all patients were treated with ticlopidine 250 mg/day for 28 days and aspirin 80 mg indefinitely.

Quantitative Coronary Angiography
Coronary angiograms were made preferably from 2 orthogonal views before the procedure, after predilatation, and after every step of stent deployment. For all angiograms, 10 mL (right coronary artery) or 12 mL (left coronary artery) of the contrast agent iomeprol (Iomeron) with an iodine content of 350 mg/mL was injected with the use of a power injector at an injection rate of 4 mL/s. QCA was both performed online and repeated offline with the QCA-CMS 3.0 system (CMS-MEDIS). For automated edge detection, the gradient field transform algorithm of this system for complex lesion analysis was used. It has also been shown that with radiopaque stents, like the Wiktor stent, accurate edge detection can be performed in this way, provided that a high iodine contrast agent is used with rapid and complete filling of the epicardial segment, as was the case in this study. Reference diameter, minimal luminal diameter, and percentage diameter stenosis were calculated as the average value of the 2 views analyzed offline. Optimum stent deployment according to QCA was defined as a residual diameter stenosis of <10%.

IVUS Imaging
IVUS imaging was performed using a 2.9F, single-element, 30-MHz beveled transducer imaging catheter (Cardiovascular Imaging Systems Inc) or a 3.0F, phased-array transducer (Endosonics). At every step of evaluation, the catheter was withdrawn at a speed of 0.5 mm/s by using a motorized automatic pull-back device. Stent deployment was assessed online and defined as optimum if, and only if, all of the following criteria were fulfilled: (1) complete apposition of all stent struts against the vessel wall; (2) symmetry index of ≥0.7, that is, the ratio of the minimal in-stent luminal diameter to the maximal in-stent luminal diameter; and (3) in-stent minimal cross-sectional area (CSA) of ≥90% of the average reference CSA or ≥100% of the smallest reference segment CSA. All studies were recorded on videotape and reanalyzed offline.

Coronary Pressure Measurement and Calculation of FFR
During the procedure, aortic pressure (P a) and distal (transstenotic) coronary pressure (P d) were measured continuously with use of the guiding catheter and a 0.014-in pressure guide wire (PressureWire; RADI Medical Systems, respectively). Before angioplasty and after every step of in-stent balloon inflation, steady-state maximum hyperemia was induced by the intravenous infusion of adenosine 140 μg·kg⁻¹·min⁻¹ through the femoral venous sheath, and FFR was calculated by use of the following equation:

\[
\text{FFR} = \frac{P_{\text{d}}}{P_{\text{a}}}
\]

where \(P_d\) and \(P_a\) are recorded simultaneously at maximum hyperemia. Before the predilatation, a pull-back pressure curve was made to detect disease elsewhere in the artery. In case of unexpected coronary artery disease elsewhere in the vessel, which was the case in 3 patients, FFR was replaced by the ratio of the hyperemic pressure just distal to the stent to the hyperemic pressure just proximal to the stent. Because FFR in true normal coronary arteries equals 0.94 to 1.00 and because normalization of epicardial conductance is expected by optimum stent implantation, optimum stent deployment according to coronary pressure measurement was defined as a value of FFR (or a distal-to-proximal hyperemic pressure ratio) of ≥0.94.

Statistical Analysis
The values of angiographic and pressure indexes are given as mean ± SD. All data for QCA and IVUS refer to the offline analysis. The relations between IVUS and FFR, QCA and IVUS, and QCA and FFR were analyzed with use of the \(x^2\) test. The inflation pressures necessary to obtain optimum results were compared with use of the unpaired \(t\) test. Receiver operating characteristic curve (ROC) analysis was performed to establish the value of FFR most predictive for optimum stent deployment according to the combined IVUS criteria. Statistical significance was considered to be present at \(P < 0.05\).

Figure 1. Coronary angiograms, simultaneously obtained aortic (P a) and distal coronary (P d) pressures, and IVUS images during successive steps of protocol in a 49-year-old man. Top row. Angiogram and pressure tracings before intervention. Identical pressures are obtained to proximal pressure and equals 0.43. Three bottom rows, Coronary angiogram, IVUS images, and pressure recordings after stent inflation with 8, 10, and 12 atm, respectively. At 8 atm, although residual stenosis by QCA is <10%, IVUS image shows incomplete apposition of several stent struts, and there still is considerable pressure drop provicable across the stented segment, resulting in FFR value of 0.78. At 12 atm, both IVUS image and pressure recordings have improved, but they are still suboptimum.
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Results

Baseline Characteristics and Procedural Results
In our study population (mean age, 60 ± 8 years; 24 men and 6 women), 30 Wiktor-i stents with a diameter of 3.5 ± 0.3 mm were successfully implanted: 10 in the left anterior descending artery, 11 in the left circumflex artery, and 9 in the right coronary artery.

A total of 93 balloon inflations for stent deployment at inflation pressures of 6 to 14 atm were performed, according to the study protocol. Ultimately, optimum stent deployment was obtained in 24 patients according to QCA criteria, in 17 patients according to IVUS criteria, in 17 patients according to FFRmyo criteria, and in 13 patients according to all 3 investigation modalities. In other words, optimization of stent deployment according to QCA was achieved in 24 of the 93 balloon inflations used for stent deployment. Optimum stent deployment according to IVUS was obtained in 17 patients, as specified in Table 1.

Quantitative Coronary Angiography
Reliable QCA measurements were performed after 92 of the 93 balloon inflations used for stent deployment. Optimum stent deployment according to QCA was achieved in 24 of the 30 patients at a mean inflation pressure of 8.4 ± 2.0 atm. The distribution of inflation pressures and the results of QCA are presented in Table 1.

IVUS Imaging
Reliable IVUS imaging could be performed after 87 of the 93 balloon inflations. Reasons for not having performed IVUS imaging after 6 inflations were stent deformation (n = 2), length of the procedure (n = 3), and technical failure of the equipment (n = 1). All 3 IVUS criteria for optimum stent deployment were met after 19 inflations in 17 patients, at an average inflation pressure of 11.8 ± 0.7 atm. After the last inflation, complete apposition of all stent struts against the vessel wall, symmetric stent expansion, and sufficient CSA surface were obtained in 18, 30, and 22 of the 30 patients, respectively. IVUS data are summarized in Table 1.

Myocardial Fractional Flow Reserve
Reliable hyperemic pressure measurements and calculation of FFRmyo were performed after 87 of the 93 inflations. Reasons for not having obtained pressure measurements after the remaining 6 inflations were technical problems with the signal in 3 patients and doubt about the presence of sufficient hyperemia in 3 other patients. FFRmyo increased from 0.49 ± 0.17 before intervention to 0.93 ± 0.07 at the final measurement. Finally, complete normalization of FFRmyo (ie, a value ≤ 0.94) was obtained in 17 patients at an average inflation pressure of 11.5 ± 0.9 atm. In those patients, in whom an hyperemic pressure gradient was still present after the last balloon inflation, a slow pull-back curve across the stent at steady-state hyperemia was always performed to confirm the presence of a pressure drop within the stented segment. In a few patients, it was even possible to correlate a discrete pressure drop to the site of incomplete apposition of 1 of the struts. An interesting observation was deterioration of FFRmyo in 2 patients, after initial improvement, when inflation pressure was increased further. FFRmyo data are summarized in Table 1.

Relation Among QCA, IVUS, and FFRmyo
In Table 2, QCA, IVUS, and FFRmyo are compared on a side-by-side basis with respect to optimum stent deployment. Concordance between IVUS and FFRmyo was found in 91% of

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**Table 1. QCA Measurements, IVUS Results, and Coronary Pressure–Derived FFRmyo After Successive Stent Inflations**

<table>
<thead>
<tr>
<th>No. of Dillations</th>
<th>QCA</th>
<th>IVUS</th>
<th>FFRmyo</th>
<th>QCA, IVUS, FFRmyo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% DS</td>
<td>Apposition</td>
<td>S &gt;0.7*</td>
<td>CSA*</td>
</tr>
<tr>
<td>Preintervention</td>
<td>30</td>
<td>78.93±8.60</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6 atm</td>
<td>30</td>
<td>10.83±8.93</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>8 atm</td>
<td>25</td>
<td>9.73±10.11</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>10 atm</td>
<td>21</td>
<td>5.84±8.93</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>12 atm</td>
<td>14</td>
<td>4.26±10.93</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>14 atm</td>
<td>3</td>
<td>8.42±1.81</td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>

% DS indicates percentage diameter stenosis; SI, symmetry index; CSA, cross-sectional area; and asterisk, cumulative number of patients fulfilling the respective criteria.

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**Table 2. Relations Among QCA, IVUS, and Pressure-Derived FFR**

<table>
<thead>
<tr>
<th>FFR+</th>
<th>FFR−</th>
<th>QCA+</th>
<th>QCA−</th>
<th>QCA+</th>
<th>QCA−</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUS+</td>
<td>14</td>
<td>2</td>
<td>15</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>MUS−</td>
<td>5</td>
<td>60</td>
<td>42</td>
<td>27</td>
<td>42</td>
</tr>
</tbody>
</table>

Concordance 91% 48% 46%

P<0.00001 P=NS P=NS

+ indicates optimum stent deployment according to the respective criteria; −, suboptimum stent deployment.

Note the large number of observations in which the QCA result of stent deployment was already optimum, whereas MUS and FFR still yielded suboptimum stent deployment.
the paired observations. Only after 7 of 81 inflations was discordance present between IVUS and FFRmyo. In 5 of these 7 outliers, FFRmyo had already normalized, whereas IVUS was still suboptimum; in 3 cases, there was incomplete apposition of the struts, and in 2 cases, there was both incomplete strut apposition and insufficient in-stent CSA. However, in 4 of these 5 cases, concordance was still achieved at the next step, after inflation at a 2-atm higher pressure. In the 2 cases with optimum IVUS and suboptimum FFRmyo, the latter value was 0.89 and 0.91, respectively. In these cases, a hyperemic pressure drop of 7 and 9 mm Hg, respectively, was still detectable on the slow pull-back curve across the stent at maximum hyperemia, at a discrete location within the stent, without any visible abnormality at IVUS. By ROC analysis, the most accurate value of FFR to predict optimum stent deployment by IVUS was 0.94, corresponding exactly to the lower limit of the normal range as found in earlier studies (Figure 2).11 The correlations between IVUS and QCA and between FFRmyo and QCA were significantly worse: 48% and 46% concordance rates, respectively.

The majority of the discordant observations were caused by an already optimum QCA result but still suboptimum IVUS or still depressed FFRmyo, respectively.

**Optimum Inflation Pressure**

In Figure 3, the cumulative distribution of observations with optimum stent deployment according to the different evaluation modalities is presented in relation to the inflation pressure. It can be observed how FFR provides information similar to that provided by the most stringent IVUS criteria, being complete apposition of all struts. In patients in whom optimum stent expansion of the Wiktor-i stent was not obtained at 12 atm, it also was not obtained at 14 atm, and in 2 cases, either stent deformation or decrease in FFR occurred at that last step.

**Discussion**

This study demonstrates a high concordance rate of 91% between IVUS and FFRmyo for the purpose of evaluating optimum stent deployment. As shown in this study, QCA alone is obviously insufficient for that purpose. Although the use of a radiopaque stent in this study might have influenced the QCA analysis, it has also been described in former studies that despite an excellent angiographic result, IVUS still reveals insufficient stent deployment in 60% to 80% of cases.19–21 It was confirmed in the present study that in only 15 of 57 situations with optimum QCA an optimum IVUS result was also present (Table 2). Several investigators have shown that with the use of IVUS-guided stent placement, instead of QCA alone, better acute results are obtained and that warfarin anticoagulation can be replaced by antiplatelet therapy without increasing the incidence of stent thrombosis.5,22 It has also been shown that the inflation pressures necessary to obtain optimum stent deployment as assessed with IVUS are higher than the pressures needed for optimum deployment as assessed with QCA only, which was confirmed for the Wiktor-i stent in the present study (Figure 3). However, due to financial constraints, time limitation, and the increasing number of stents used, IVUS-guided stent implantation is not routinely performed in the majority of catheterization laboratories. Therefore, angiography-guided stent implantation with high-pressure balloon inflation without IVUS guidance has been proposed as an alternative.23 Although this has significantly reduced acute stent thrombosis, some negative effects of blind, unnecessarily high-pressure inflation have been suggested, such as adjacent vessel wall damage and augmentation of neointimal proliferation.24,25
 Coronary pressure-derived FFR\textsubscript{myo} is a specific index of the conductance of the epicardial coronary artery. In contrast to other functional methods, such as Doppler velocimetry and videodensitometry, FFR\textsubscript{myo} shows no variation in normal values, is not confounded by distal small vessel disease, and not influenced by hemodynamic variations; therefore, it is a specific measure of the functional state of the stented segment.\textsuperscript{10–12} As demonstrated in the present study, pressure measurements indeed correlate very well with IVUS imaging with respect to suboptimum or optimum stent deployment.

The disconnectable pressure wire can be used as a primary guide wire throughout a coronary intervention, facilitating easy, rapid, and safe assessment of the hyperemic pressure gradient across the stented segment. Because the sensor is located 3 cm from the floppy tip, it can be pulled back and advanced across the stented segment repeatedly, without the necessity of crossing the stent with the tip of the wire. This method avoids multiple passages with potential damage or dislocation of the stent.\textsuperscript{26} An interesting observation in this study was the fact that optimum stent deployment according to IVUS or FFR\textsubscript{myo} could be achieved in only \(\approx60\%\) of the patients. Although in early reports it was claimed that optimum deployment could be achieved in the majority of stented patients, reports in recent literature are more doubtful on that point, and our present study supports that position.\textsuperscript{27} It is unclear whether there are differences in that respect between coiled wire stents, as used in this study, and slotted tube stents. In a former study by Vrints et al.,\textsuperscript{28} it was shown that Doppler flow velocity measurements after stenting yielded higher values of coronary flow reserve for slotted tube stents than for coiled wire stents. From our own database, we found that FFR after stent implantation in unselected patients between January 1997 and June 1998 was 0.96±0.03 for slotted tube stents (\(n=33\)) and 0.93±0.06 for coiled wire stents (\(n=45\); NS). In some patients in our present study, stent deployment even deteriorated at higher pressure, suggesting that unlimited high pressure might be deleterious, especially when applied without adequate control. It is unknown whether this problem is specifically related to the Wiktor-i stent used in this study or should be extrapolated to other types of stents. Another interesting observation was that the maximum inflation pressure for optimum inflation of the Wiktor-i stent never exceeded 12 atm in this study, although upsizing of the balloon was necessary in some patients.

It is interesting to observe in the present study that even small abnormalities in stent deployment, such as poor apposition of a few struts, resulted in the majority of cases in hemodynamic consequences reflected by an abnormal FFR.

### Study Limitations

Due to the extensive study protocol, the number of patients in this study was rather small, which was partly compensated for by the stepwise inflation protocol, providing a sufficient number of paired observations of IVUS and pressure, QCA and pressure, and IVUS and QCA, respectively. Only a selective group of patients were investigated with a single stenosis in the proximal part of a large vessel, and only 1 type of stent was investigated. Further studies are necessary before our results can be extrapolated to smaller vessels, distal lesions, or other stents.

In addition, successful IVUS and pressure measurements could be performed in only 94% of the patients versus 99% of the patients for QCA. Furthermore, there are no data relating optimum initial deployment as investigated in this study to long-term outcome. To address this issue, studies with large numbers of patients are required.

The question can be raised regarding the extent to which the use of a radiopaque stent in this study could have influenced the quantitative angiographic analysis. Because we used a high iodine contrast agent at a rather high volume, assuming rapid and complete filling of the stented segment, no problems occurred in automated edge detection of those segments, which is in accordance with earlier studies.\textsuperscript{15} For follow-up studies, in which densitometric analysis of the lesion is important, the use of such a radiopaque stent might be more problematic.\textsuperscript{29} Finally, although coronary pressure measurement seems to be equally effective for the assessment of stent deployment as IVUS, in the case of insufficient deployment, it does not elucidate the cause of the problem. In contrast to IVUS, no data are obtained regarding vessel wall and plaque morphology, malformation of the stent, malapposition of the struts, hidden disease in the adjacent vessel parts, or other morphological parameters.

### Clinical Implications and Conclusions

In this study, the usefulness of coronary pressure measurement to guide optimum stent deployment was comparable to IVUS. Concordance between both techniques was present in 91% of all observations. Because a single-pressure guide wire can be used to perform the interventional procedure and to perform the pressure recordings, coronary pressure measurement can be suggested as a rapid and cheap alternative for IVUS to assess stent deployment without the necessity to use additional equipment, to perform exchange procedures, or to repeatedly cross the stented lesion. Larger studies, using different types of stents, are mandatory to further support these findings.

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### References


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