Relation between single tomographic intravascular ultrasound image parameters and intracoronary Doppler flow velocity in patients with intermediately severe coronary stenoses

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Background Intravascular ultrasound (IVUS) imaging parameters have been suggested as criteria to determine coronary lesion significance before intervention. However, there has not been a systematic examination of combined anatomic and physiologic data in the same patients with coronary artery disease.

Methods and Results To examine the relation between coronary flow reserve and IVUS parameters, 41 patients with intermediately severe coronary artery stenoses had measurements of coronary flow velocity (0.014-inch Doppler flow wire), coronary flow velocity reserve (CVR) (hyperemic/basal mean flow), IVUS imaging (2.9F, Cardiovascular Imaging Systems, Inc.), and quantitative coronary angiography before intervention. Correlations between physiologic and anatomic parameters were performed by simple regression. Results were also examined by patient subgroups with CVR >1.8 or <1.8 to assess differences in IVUS parameters. The angiographic percent diameter stenosis was 52% ± 17% (range 18% to 95%). Mean CVR was 1.88 ± 0.56 (range 0.9 to 3.18). IVUS minimal luminal diameter ($r = 0.312$, $p = 0.047$) and angiographic percent stenosis ($r = 3.05$, $p = 0.052$) were weakly related to poststenotic CVR. Comparing patients with CVR <1.8, IVUS reference segment area, IVUS lumen area, and angiographic percent diameter stenosis was higher (17.7 ± 0.3 vs 12.9 ± 4.4 mm^2, $p < 0.05$; 6.20 ± 3.76 vs 4.34 ± 2.00 mm^2, $p < 0.05$; and 60% ± 14% vs 46% ± 17%, $p < 0.01$, respectively) than in the group with CVR >1.8.

Conclusions Despite a precise determination of cross-sectional vessel areas and absolute dimensions by IVUS, single tomographic measurements did not correlate well with coronary physiologic responses. These data suggest that the physiologic data may be complementary to anatomic quantitative IVUS, enhancing information for coronary interventional decision making. (Am Heart J 1998;135:988-94.)

Two-dimensional intravascular ultrasound (IVUS) imaging techniques can accurately measure vessel lumen of both diseased and adjacent angiographically normal reference arterial segments during serial interventions in the same patient.[1-3] Various IVUS imaging parameters have been suggested as criteria to determine coronary lesion significance before intervention.[4-6] Recently, intravascular Doppler guide wire velocimetry has also been simplified and permits measurement of poststenotic flow velocity continuously during interventions,[7,8] thus providing information not previously available from earlier studies with larger Doppler catheters.[9,10]

However, unlike direct translesion pressure or flow velocity studies,[11,12] there have been no IVUS studies comparing proposed anatomic parameters with objective evidence of clinical lesion significance by using stress testing or other physiologic tests. Therefore, the purpose of this study was to examine the relation between coronary flow (velocity) reserve (CVR) and IVUS parameters in patients with coronary artery disease. We postulated that a systematic examination of combined anatomic and physiologic data in the same patients with coronary artery disease would establish an anatomic [IVUS or quantitative coronary angiographic (QCA)] criteria associated with impaired physiologic responses.

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Methods

Study population

Stable patients undergoing routine coronary angiography and angioplasty were considered eligible. Patients with recent myocardial infarction in the target vessel territory, severe multivessel disease, or thrombus in the target site were excluded from the study. Patients with clinical conditions (e.g., diabetes, hypertension) that may be associated with impaired CVR were not excluded from the study. Oral and written consent for the Institutional Review Board–approved study was obtained.

Catheterization procedure

Medications were continued to the time of study as clinically indicated. All patients received routine precatheterization medications of diphenhydramine (25 mg orally) and diazepam (5 mg intramuscularly) before the procedure. Heparin (10,000 unit intravenous bolus with 1000 U/hr intravenous infusion) was administered before target lesion assessment. Routine 8F Judkins-style guiding catheters without side holes and the femoral vascular access technique were used. The angioplasty guide wire used to place the IVUS catheter was the 0.014-inch Doppler-tipped FloWire (Cardiometrics, Inc., Mountain View, Calif.). Nitroglycerin (200 μg intracoronary) was given at least 2 to 5 minutes before measurements.

QCA technique

Coronary angiography was performed with the Philips DCA-ACA imaging system. The percent diameter stenosis was computed in a standard fashion by using the proximal normal reference vessel segment. The contrast-filled guiding catheter was used as calibration for vessel dimension calculation. The variability for two observers was as follows: interobserver, $p = 0.022$, $r = 0.90$ and intraobserver, $p = 0.0104$, $r = 0.95$.

CVR technique

All CVR measurements were made at least 10 artery diameters distal to the lesion without the presence of the IVUS catheter. CVR was measured with a 0.014-inch Doppler FloWire as previously described.[13,14] CVR was computed as the ratio of hyperemic to basal average peak velocity. Coronary hyperemia was induced with intracoronary adenosine (8 μg for the right coronary artery and 18 to 24 μg for the left coronary artery) as previously reported.[15] In all patients, CVR was measured at least 2 cm distal to the stenosis, 3 to 5 minutes after administration of intracoronary nitroglycerin (200 μg). The average peak velocity was obtained from the spectral signals averaged over two cardiac cycles. In previous studies, duplicate velocity measurements had a variation of 15% ± 9% in both the control and postangioplasty states.[7,14]

IVUS technique

Coronary luminal dimensions were measured with a 2.9F imaging catheter (Cardiovascular Imaging Systems, Mountain View, Calif.).[16-18] Intracoronary nitroglycerin (200 μg) was given before catheter placement. IVUS measurements of vessel cross-sectional areas were acquired in a standard fashion.[18] A slow manual pullback (approximately 1 mm/sec) from the distal to proximal vessel was recorded on half-inch SVHS videotape. The most narrowed cross-sectional area was selected as the target location. An angiographically normal segment >0.5 cm distal to the target lesion was selected as the reference location.

After the procedure, off-line analysis of the dimensions within the target and reference vessel segments was made by using the integrated manual digitizing features of the IVUS imaging system.

All ultrasound measurements were made from end-diastolic images. The adventitial-medial border (external elastic lamina) was traced manually to obtain vessel area. In a similar manner, the lumen-intimal interface was traced, yielding lumen area. The distal reference segment vessel area was determined as the integrated area central to the medial-adventitia border.

IVUS minimal lumen diameter was computed as the minimal diameter within the target stenosis. IVUS reference diameter was defined as the lumen diameter at the site of the most normal reference vessel segment >0.5 cm distal to the target lesion. IVUS percent diameter stenosis was the ratio of the [(IVUS minimal lumen diameter – Reference diameter) /Reference diameter] × 100. The IVUS reference vessel area was defined as the area circumscribed by the adventitial-medial border (external elastic lamina). The IVUS vessel diameter was defined as the largest diameter across the area used for the IVUS area reference. The IVUS percent area stenosis was computed as the [(IVUS target lumen area – IVUS reference lumen area)/IVUS lumen reference area] × 100. The IVUS plaque area was computed as the difference between the IVUS vessel area and the IVUS lumen area. The QCA percent diameter was measured as the [(Minimal lumen diameter – Reference diameter)/Reference diameter] × 100.

Statistical analysis

Comparisons of CVR and IVUS parameters were performed by simple linear regression to establish the relation between IVUS and flow data. Comparisons between CVR subgroups (>1.8 or <1.8 and >2.0 and <2.0) were made with the Student's unpaired *t* test. Statistically significant results were accepted when the probability value was <0.05. Results are presented as mean ± 1 SD.

Results

Patient characteristics

The clinical characteristics of the 41 patients are listed in Table I. There were 25 men and 16 women,

Table I.

Clinical data	*n*
M/F	25/16
Age (yr, mean ± SD)	59 ± 11
Left ventricular ejection fraction (%)	57 ± 8
Hypertension	28 (68%)
Diabetes mellitus	10 (24%)
Hypercholesterolemia (>220 mg/dl)	24 (56%)
Family history coronary artery disease	29 (71%)
Cigarette usage	19 (46%)
Positive/negative stress test in target region	14/4
≥2-Vessel coronary artery disease	16 (39%)

with a mean age of 59 years. Left ventricular function was normal. Sixty-eight percent of patients had hypertension, 24% had diabetes mellitus, and 46% had a history of recent cigarette use. Thirty-nine percent of patients had two or more diseased vessels. Thirteen patients had a myocardial infarction remote from the target vessel at the time of study. The target vessels were the left main artery (n = 8), left anterior descending artery (n = 22), right coronary artery (n = 6), and circumflex artery (n = 5).

Systemic hemodynamic data

During the measurement period, the blood pressure (143 ± 26/71 ± 14), mean arterial pressure (100 ± 18 mm Hg), and heart rate (69 ± 14 beats/min) were stable.

Quantitative angiographic results

The mean percent diameter stenosis was 52% ± 17% for the group, ranging from 18% to 95%. When patients were examined by subgroups on the basis of coronary vasodilatory reserve >1.8 or <1.8 and >2.0 or <2.0 (Table II), 18 patients with coronary vasodilatory reserve <1.8 had more severe percent stenosis than those with CVR >1.8 (60% ± 14% vs 46% ± 17%; p < 0.007) (Fig. 1).

IVUS imaging data

Total vessel cross-sectional area was similar between subgroups with CVR <1.8 or >1.8 (16.1 ± 3.4 and 16.2 ± 4.6 mm^2, respectively; p = 0.9143). However, lumen area was smaller 5.10 ± 2.03 to 8.39 ± 2.09 mm^2 (p < 0.001) in the low CVR group (Fig. 1).

Coronary flow velocity data

For the entire group, basal poststenotic average peak velocity increased from 24 ± 12 to 43 ± 17 cm/sec during hyperemia, resulting in a mean CVR of 1.88 ± 0.56 (range 0.9 to 3.18). There was no difference in basal average peak velocity between CVR subgroups.

Table II. Anatomic data

Coronary flow reserve groups	*n*	IVUS MLD (mm)	IVUS ref diameter (mm)	IVUS %D
>2.0	18	2.20 ± 0.63	4.0 ± 0.63	45 ± 12
<2.0	23	2.37 ± 0.77	4.32 ± 1.03	46 ± 13
>1.8	23	2.14 ± 0.59	3.97 ± 0.63	46 ± 11
<1.8	18	2.48 ± 0.89	4.45 ± 1.09	44 ± 14
		IVUS ref area (mm^2)	**IVUS vessel diameter (mm)**	**IVUS %Area**
>2.0	18	13.1 ± 4.50	4.40 ± 2.08	66 ± 12
<2.0	23	16.5 ± 9.56	5.75 ± 3.50	63 ± 16
>1.8	23	12.9 ± 4.4	4.34 ± 2.00	66 ± 11
<1.8	18	17.7 ± 10.3	6.20 ± 3.76	62 ± 18
		IVUS plaque area	**QCA %D**	
>2.0	18	8.7 ± 3.7	49 ± 17	
<2.0	23	9.7 ± 6.1	54 ± 17	
>1.8	23	8.5 ± 3.6	46 ± 17	
<1.8	18	10.1 ± 6.6	60 ± 14	

p < 0.05 vs group >1.8.
MLD, Minimal lumen diameter; *ref*, reference; *%D*, percent diameter stenosis; *%area*, percent area stenosis; *QCA*, quantitative coronary angiography.

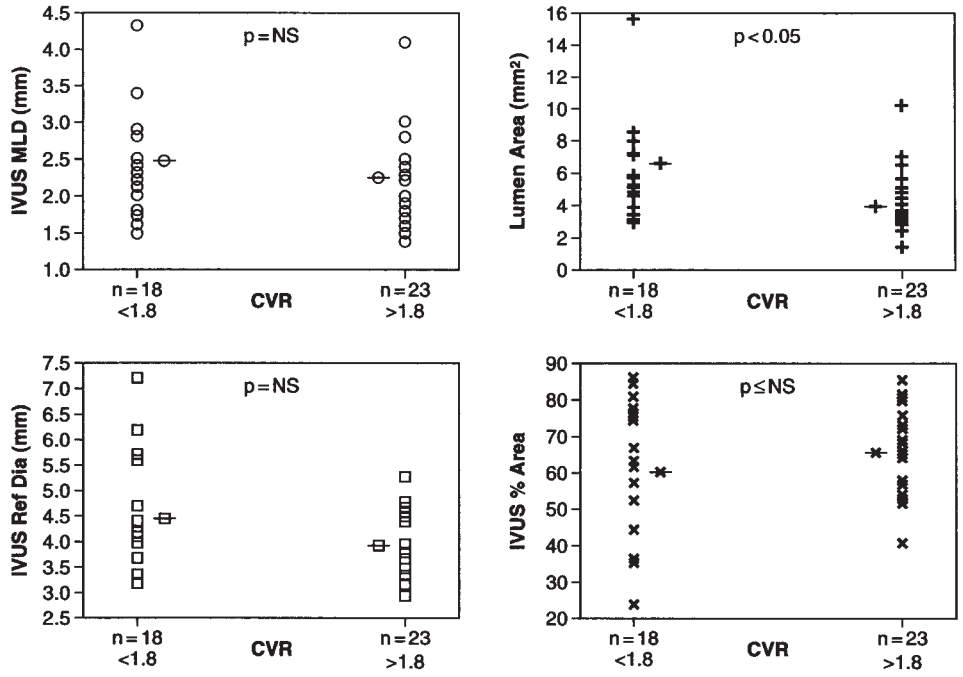
Anatomic and physiologic relations

QCA percent diameter stenosis and IVUS reference vessel diameter were weakly related to increasing CVR (angiographic percent diameter stenosis, r = 0.305, p = 0.0524; IVUS reference vessel area, r = 0.312, p = 0.474) (Fig. 2). Analysis of other IVUS parameters failed to identify statistically significant relations (Table III).

Discussion

The findings of this study show that single cross-sectional anatomic measurements, either by QCA or by IVUS imaging, have only a weak relation to physiologic responses in the intermediately severe range of stenoses examined in this patient group. This result would be anticipated from the numerous variables relating cross-sectional vessel area to changes in flow and pressure as described by Poiseuille[19] and other studies in fluid dynamics.[20,21] The length of the steno-

Figure 1



Anatomic IVUS and QCA parameters compared by coronary vasodilatory reserve (CVR) for subgroups with CVR <1.8 or >1.8. *MLD,* Minimal lumen diameter; *Ref Dia,* reference vessel segment diameter; *%D,* percent diameter stenosis.

Table III. Correlation between coronary flow reserve and anatomic parameters

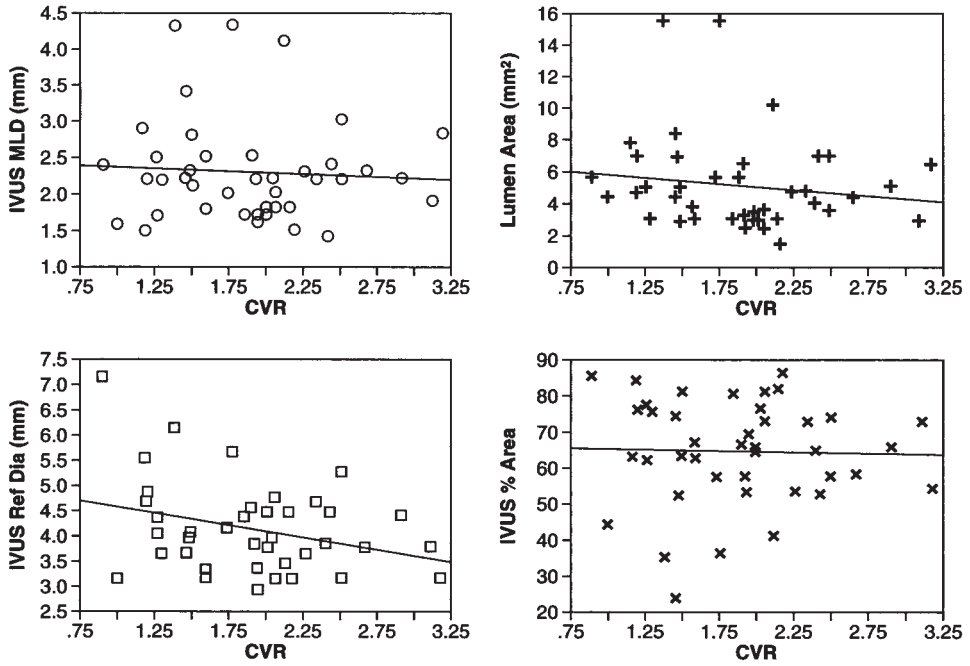
CVR vs	*r*	r^2	SEE	*F*	*p* Value
IVUS					
Reference vessel diameter	0.312	0.097	0.241	4.19	0.0474
Reference vessel area	0.277	0.077	2.175	3.248	0.0792
Plaque volume	0.254	0.065	1.426	2.699	0.1084
Lumen area	0.156	0.024	0.853	0.973	0.3301
%Diameter stenosis	0.146	0.021	3.486	0.855	0.3608
Minimal lumen diameter	0.06	0.004	0.202	0.141	0.7096
%Area stenosis	0.031	0.001	4.156	0.038	0.8467
QCA					
%Diameter stenosis	0.305	0.93	4.64	4.003	0.0524

sis, viscosity of fluid, potential turbulence, and friction, among the many factors, must also be incorporated into the calculation of flow through a stenosis. In addition, the status of the microvascular circulation cannot be incorporated into a strictly anatomic modeling of flow. It should not be expected that a single dimensional measurement would have a strong correlation to CVR given these additional rheologic factors, which cannot be assessed by the tomographic imaging technique.

CVR and lumen area

The curvilinear relation between CVR and lesion severity reaches a plateau for stenosis diameters <40%,[20] a common range of intermediate stenoses, especially after coronary interventions. CVR is not sensitive enough to detect small changes in cross-sectional area for minimal to moderate coronary narrowings, a finding supported by the correlation coefficients between IVUS areas and CVR in this and other similar studies.[22,23] Three-dimensional image reconstruction

Figure 2



Correlation of anatomic IVUS parameters with coronary vasodilatory reserve (CVR). *MLD,* Minimal lumen diameter; *Ref Dia,* reference vessel segment diameter; *%D,* percent diameter stenosis.

may improve the relation between the anatomic and physiologic parameters by considering lesion length and plaque eccentricity. This capability was unavailable in the laboratory at the time of this study.

The current findings indicated that no stenosis with a minimal lumen diameter ≤1.4 mm had a CVR >2.0 and that no lumen area <2.6 mm² had a CVR >1.8. These anatomic cutoff values suggest a general criteria for stenoses nearly always associated with impaired CVR. Values above these limits demonstrated considerable overlap. In concert with these data, preliminary reports by Liebergen et al.,[22] Kern et al.,[23] and Di Mario et al.,[24] examining the relation between angioplasty IVUS lumen areas and CVR in the postintervention period, also found weak correlations between anatomy and physiology for moderate to mild stenoses. The current study differs in that no intervention was performed before evaluation and thus the native state of the lesional morphology and undisturbed reference vessel segment is assumed to be a major contributor to CVR. Because CVR is the summed response of the conduit and microvascular bed, an impaired microvascular circulation would also contribute to large disparity between observed CVR and a large and adequate conduit lumen. Use of relative CVR ($CVR_{target}/CVR_{reference}$) may improve the correlation between anatomy and physiology by minimizing the influence of microcirculatory abnormalities on the physiologic response. Recent reports of CVR in angiographically normal vessels in patients with chest pain syndromes have demonstrated that <12% of such patients will have a global impairment (CVR <2.0) of the microcirculation.[25]

Limitations

The limitations of both intracoronary ultrasound imaging and Doppler flow velocity have been described in detail elsewhere.[4,26] There was no adverse interaction between the two ultrasound modalities because serial, not simultaneous, measurements were made. The variability of CVR in patients within the catheterization laboratory remains a confounding factor in this study and for routine use for clinical decision making. Biologic conditions impairing normal microvascular function exist in patients with diabetes mellitus, left ventricular hypertrophy, myocardial infarction, syndrome X, and various hematologic and

rheologic abnormalities[27] in the absence of obstructive atherosclerotic coronary disease.

Despite large conduit cross-sectional areas, microvascular circulatory abnormalities may exist.[25] Microcirculatory disturbances can be confirmed by measuring a lesion-specific index of relative CVR using CVR in an adjacent normal reference vessel. A normal relative CVR ($CVR_{target}/CVR_{reference}$) should exceed 0.8.[28] Although confirmation of which patients had concomitant microvascular disease was not performed, the failure of IVUS lumen dimensions to reflect physiologic responses of intermediate stenoses remains an important limitation in using IVUS to select lesions appropriate for intervention.

Evaluation of QCA lesion subtype was not performed because the patients were considered stable without type B2 or C lesions. Prior correlations with angiographic and IVUS anatomic data have identified the limitations of angiography.

The use of the minimal cross-sectional area of a target region was made by visual examination of several images. Computer reconstruction and automatic edge algorithm to determine the true minimal cross-sectional area was not available. In addition, characterization of the lumen morphology (e.g., eccentricity) was limited to relatively simple but commonly used in laboratory parameters. Errors in the determination of absolute areas may occur because of the IVUS catheter, rotational speed variance, or catheter-vessel malalignment.[29]

Clinical implications

Despite the precise determination of lesion cross-sectional dimensional parameters by IVUS imaging, the correlation with the directly measured physiologic responses is weak, for the most part, attributable to the complex nature of atherosclerotic narrowings and the variability of microcirculatory function in patients with coronary artery disease. These data support the complementary use of physiologic data in combination with anatomic (IVUS and QCA) information to assist in decision making for coronary interventions.

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