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Value of intracoronary ultrasound and Doppler in the differentiation of angiographically normal coronary arteries: a prospective study in patients with angina pectoris

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Background A substantial proportion of patients undergoing heart catheterization for suspected coronary artery disease have normal angiograms. Coronary morphology and blood flow velocity can be assessed very accurately with intracoronary ultrasound and Doppler. The purpose of this study was to use both methods to classify further patients with suspected coronary artery disease but with coronary angiograms adjudged normal at the time.

Methods and results In forty-four patients with suspected coronary artery disease and normal coronary angiograms, intracoronary ultrasound and intracoronary Doppler were performed in the left anterior descending and left main coronary arteries. Coronary flow reserve was obtained by calculating the ratio of the maximal coronary flow mean velocity after the intracoronary administration of 10 mg papaverine to the coronary flow mean velocity at rest. Of 44 patients, 16 (36%) (group I) were found to have normal coronary morphology by intracoronary ultrasound and normal (>3·0) coronary flow reserve (5·3 ± 1·8). In seven patients (16%) (group II) there were normal intracoronary ultrasonic findings but a reduced coronary flow reserve (2·1 ± 0·4). Plaque formation was found in a total of 21 (48%) of the 44 patients; mean plaque sizes were 3·6 ± 1·6 mm^2 for those in group III (normal coronary flow reserve) and 5·0 ± 2·3 mm^2 for those in group IV (reduced coronary flow reserve). Vessel area in both of these groups (16·3 ± 8·0 mm^2 and 19·2 ± 6·1 mm^2) was significantly larger than that of group I (14·6 ± 5·7 mm^2, $P<0·01$). Plaque calcification was found in 25% of those in group III and 44% of those in group IV. Thus, only 36% of the patients with normal angiograms were true normal, 48% exhibited early stage of coronary atherosclerosis, and the other 16% might be considered as syndrome X.

Conclusion Intracoronary ultrasound and Doppler can be used to differentiate further heart disease in patients with normal coronary angiograms. Only a minority were true normal. Early signs of atherosclerosis cannot be detected by coronary angiography. This may have important therapeutic and prognostic implications.
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Key Words: Intracoronary ultrasound, intracoronary Doppler, syndrome X, coronary arteries, coronary angiography, coronary atherosclerosis.

Introduction

As many as 10–30% of patients with chest pain who undergo diagnostic coronary angiography for suspected coronary artery disease have normal or near normal coronary arteries[1]. In the case of anginal chest pain, normal angiography, and ST-segment depression on exercise testing or atrial pacing, the situation is termed 'syndrome X'[2,3]. Considerable discrepancies have been found between cine-angiography and postmortem examinations. Complex and eccentric coronary atherosclerosis lesions are frequently not identified by angiography[4,5], particularly in left main coronary artery disease[6,7]. Even when no signs of atherosclerosis are found in epicardial vessels, in some cases chest pain might be caused by microvascular abnormalities in the distal vessel[8,9].

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Intracoronary ultrasound imaging is a new technique which provides morphological and functional information on the coronary arteries[10–15]. Studies have shown that intracoronary ultrasound demonstrates atherosclerotic plaques which remain angiographically undetected[16,17] and can separate both calcified from non-calcified lesions and eccentric from concentric lesions with high accuracy[7,18]. Differentiation of fibrous and lipid-containing plaques may also be possible[18]. Intracoronary Doppler flow mapping, a method of placing a Doppler flow probe into the coronary artery and measuring coronary blood flow, can be used to evaluate coronary function[8,9,14]. Coronary flow reserve is obtained by calculating the ratio of maximal (through the administration of vasodilator drugs, such as papaverine, dipyridamole, adenosine etc.) and resting flow velocities.

The purpose of this study was to evaluate coronary morphology and blood flow with intracoronary ultrasound and intracoronary Doppler in order to differentiate patients with angiographically normal coronary arteries from those who are true normal, those who represent syndrome X, and those with coronary artery disease with or without reduced coronary flow reserve.

Methods

Patients

Forty-four (22 male, 22 female) consecutive patients who had undergone diagnostic coronary angiography for suspected ischaemic heart disease and had been found to have angiographically normal right and left coronary arteries, i.e. coronary arteries with an angiographically smooth silhouette, were selected for intracoronary ultrasound imaging and intracoronary Doppler examination on an immediate on-line decision by two experienced cardiologists. Informed consents were obtained from all patients. This procedure was selected in order to avoid a second heart catheterization procedure. The patients ranged in age from 42 to 69 years (56 ± 7 years). Conventional 12-lead electrocardiogram and exercise electrocardiogram had been performed before catheterization. Risk factors (triglyceride >160 mg . dl^{-1}, cholesterol >200 mg . dl^{-1}, high density lipoprotein >45 mg . dl^{-1}, blood pressure >160/90 mmHg, and body weight >15% or the normal body weight) were also analysed.

Intracoronary ultrasound device

The intracoronary ultrasound catheter used in this study consisted of a 3·5F or 4·8F catheter sheath and a 20 MHz ultrasound transducer inside the catheter (Sonicath, Boston Scientific Corporation, Watertown, MA). The coronary artery could be studied to a diameter as small as 1·8–2·0 mm. The transducer was mechanically rotated within the catheter at 900 rpm to provide cross-sectional images via a 512 × 512 pixel ultrasound diagnostic imaging console that discriminated 64 grey levels (Diasonics, Milpitas, CA). A simultaneous electrocardiogram was recorded in order to differentiate systole (end of T wave) and diastole (peak of R wave). The axial resolution of the catheter was about 150 μm, and the lateral resolution was about 300 μm. The images were recorded on 1/2 inch S-VHS videotape for off-line analysis.

Intracoronary Doppler device

A commercially available 3F catheter with an end-mounted transducer was used for intracoronary Doppler measurement (model DC-201, Millar Instrument Inc., Houston, TX). The signal was generated by a pulsed transmitter-receiver (model MDV-20, Millar Instruments Inc., Houston, TX). The operating frequency was 20 MHz, and the pulse repetition rate 62·5 kHz. The sample volume was 0·46 mm and was movable between 1 and 10 mm from the tip. In this study, the range of motion was 1–4 mm. Phasic and mean signals proportional to a Doppler frequency shift were recorded.

Myocardial perfusion imaging with Technetium-99m-MIBI and employing single photon emission computed tomography (SPECT)

For myocardial perfusion imaging, 370 MBq technetium-99m-MIBI (Cardiolite, DuPont) were injected intravenously at maximum stress (using a bicycle ergometer) and under rest conditions on different days (2 day protocol). About 10 min after injection, the patient was asked to eat in order to stimulate bile excretion.

Scintigraphy was performed by single photon emission computed tomography employing a single head gamma camera (Siemens Orbiter), 30 projections were acquired every 6° covering 180° starting from 45° right anterior oblique to left posterior oblique. The total acquisition time was 30 min. Data were processed as a routine basis using filtered back projection with a modified ramp filter and without attenuation correction. The investigation was interpreted visually by two experienced readers who were blinded to the coronary angiography using the complete data sets of the rest and stress investigations (short axis, coronal oblique and sagittal oblique slices). The final results were based on the visual interpretations and numerical analysis in bull eye technique, comparing the results to that of a normal population.

Techniques

Each patient received 20 mg of isosorbide dinitrate and 10 mg nifedipine orally before catheterization. Before

each intracoronary ultrasound examination, the patient received 3000 IU of intracoronary heparin. An 8F or 9F giant lumen guiding catheter (Medtronic, U.S.A.) was used to position the ultrasound catheter for intracoronary ultrasound imaging. A 3 m, 0·014 inch guidewire was placed in the left anterior descending coronary artery, and the intracoronary ultrasound catheter was advanced as far as possible in the distal portion of the vessel using a monorail technique to obtain coaxial images of the left anterior descending and left main coronary arteries. This decision was chosen as the proximal part of the former artery is predominantly involved in the early stage of atherosclerosis as described by Montenegro and Eggen[19] and again underlined by Stary *et al.*[20]. The intracoronary ultrasound catheter was then drawn back slowly while the images were recorded in real time and stop frames[7]. The cross-sectional images of the proximal, mid and distal sections of the vessel were obtained. The position of the intracoronary ultrasound probe was documented and numbered on 35 mm cine film with numbers referring to the subsequent stop frame of the intracoronary ultrasound. During pull back, stop frames were taken every 5–8 mm of the vessel if no plaque was visualized. If plaque formation was found, stop frames every 1–3 mm were recorded. Each stop frame was regarded as one section of the vessel and additionally documented on hard copy. For better visualization, contrast was injected via the guiding catheter. Flow in the ultrasound images was thus documented as microcavitation. After intracoronary ultrasound examination, the catheter was removed but the guidewire left in situ in the coronary artery. The Doppler catheter was then advanced over the wire in the proximal part of the left anterior descending artery where no side branches were found by angiography. The position chosen was dependent on obtaining a high quality phasic signal of blood flow velocity. After the resting velocity was recorded, 10 mg papaverine was administered into the left coronary artery via the guiding catheter within 20 s during continuous recording. An estimation of the coronary flow reserve was obtained by calculating the ratio between the maximal mean flow velocity after the administration of intracoronary papaverine and the resting mean flow velocity[14]. In addition, heart rate and blood pressure before and 2 min after infusing papaverine were documented.

Data analysis

Intracoronary ultrasound image analysis

The intracoronary ultrasound images of each section were digitized into a 512 × 512 pixel matrix using an image processing computer (ECHO-COM, PPG HELLIGE, Germany) that enables digitization of a series of 32 frames of intracoronary ultrasound images. The images were stored on 1 gigabyte of an erasable optical disk (Maxtor, The Netherlands). These images were reviewed; the optimal frame was magnified using the built-in zoom function for measurement[7]. A section of artery was considered normal when it met the criteria proposed by Nissen *et al.*[21]. Intimal thickening increases with age but can be detected only when it exceeds the resolution of the catheter. Therefore, up to an intimal thickening of about 150–200 μm, a three-layer appearance could not be visualized[22]. Apart from the above recommended criteria, a normal wall has a monolayer with a circular smooth surface[7]. Plaques were defined as echo-dense structures within the vessel lumen with sharp demarcation and separated by an echolucent zone from the adjacent structures[21]. Calcium deposits were regarded as areas of bright reflections of ultrasound with shadowing beyond[18]. Lesions were divided into eccentric and concentric plaques according to the previous reported criteria[17,18,21]. The minimal lumen diameter and cross-sectional area at end-diastole of each analysed segment were measured. The values were then compared with the measurements derived from angiography. The cross-sectional plaque area was determined by outlining the area of the lumen and the area of the plaque at the boundary of the media-plaque interface. Subtraction of the lumen area from the total area yielded the cross-sectional area of the plaque[23].

Angiographic measurement

A third experienced cardiologist who was blind to the intracoronary ultrasound findings did an off-line analysis from cine films. The cineangiograms were projected onto a 20 × 28 cm screen using an angiogram projection system (CAB-35B, Weinberger, Zürich, Switzerland). The left anterior descending artery was magnified and drawn. The positions where the intracoronary ultrasound images had been taken were then traced onto the drawing[7]. The diameter of the contrast-free guiding catheter (8F = 2·67 mm, 9F = 3 mm) was used for calibration; the luminal diameter of the vessel was measured using an image processing computer (Kontron, Cardio-500, Germany) at end-diastole. The luminal area was calculated according to the following model: $A = (\pi D^2)/4$, where A is the luminal area and D the luminal diameter.

Patients classification

According to intracoronary ultrasound and intracoronary Doppler findings, patients were divided into four groups. Group I, no plaque formation/normal coronary flow reserve; group II, no plaque formation/reduced coronary flow reserve; group III, plaque formation/normal coronary flow reserve; and group IV, plaque formation/reduced coronary flow reserve. We took coronary flow reserve >3·0 as normal, with reference to previous publications[1,24,25] and our own experiences[47]. Patients with normal coronary arteries but with reduced coronary flow reserve were regarded as syndrome X[26].

Statistics and calculations

The lumen dimensions from the stop frames in each individual patient were given as mean ± standard

Table 1 Demographic characteristics of the 44 patients

Patient	Age	Sex	Risk factors						ECG	Exercise ECG	SPECT
			TG	CHOL	HDL	Smoking	Hypertension	Obesity			
1	54	m	−	−	+	+	+	+	−	+	+
2	49	m	−	+	+	+	−	+	−	−	+
3	61	f	+	−	+	−	+	−	+	+	−
4	50	f	+	+	+	+	+	−	+	−	−
5	52	m	−	−	+	+	−	+	+		
6	51	m	−	−	−	−	−	+	−	+	
7	50	f	−	+	−	+	−	−	−	−	+
8	61	m	−	+	−	−	+	−	−	+	+
9	51	m	−	+	−	−	+	−	−	−	−
10	58	m	−	−	+	−	−	−	+	+	+
11	57	m	+	−	+	−	+	−	−	+	−
12	49	f	−	+	−	−	+	+	−	+	−
13	61	f	−	+	−	−	+	−	+	−	
14	68	f	−	+	−	−	−	−	−	−	−
15	63	m	−	+	−	−	−	−	−	−	−
16	68	f	+	−	+	+	+	+	+	+	+
17	58	f	−	−	−	−	−	−	+	+	
18	55	m	+	−	+	+	+	+	−	+	+
19	46	f	−	+	−	−	−	+	−	+	+
20	66	f	+	+	+	−	+	−	+	+	
21	66	m	−	+	+	+	−	+	−	−	
22	61	f	−	−	−	−	+	+	+		
23	63	m				−	−	−	+	+	+
24	66	m	−	−	+	−	+	+	+		
25	65	m				+	+	+	−	−	
26	48	f	−	+	−	−	−	+	−	−	
27	42	m	−	+	−	+	+	+	−	−	+
28	52	f	−	+	−	+	+	+	−	−	−
29	54	f	−	+	−	−	+	−	−	−	+
30	51	f	−	+	−	+	−	−	−	+	+
31	70	f	+	+	−	−	+	+	+	−	
32	54	f	−	+	−	−	−	−	−	+	−
33	64	f	−	−	−	−	+	−	−	−	+
34	66	f				−	−	+	+		
35	53	m	−	−	+	−	+	−	+	−	+
36	43	m				+	+	+	−	+	
37	48	m	+	+	+	+	−	+	−	−	+
38	51	f	−	−	−	+	−	+	−	+	+
39	66	f	+	+	−	−	−	−	+	+	+
40	40	m	−	−	−	−	−	+	−	−	
41	57	f	−	−	−	+	+	+	−	+	−
42	38	m	+	+	+	−	−	+	+	+	
43	37	m	+	+	+	+	+	−	−	+	+
44	49	m	−	+	−	+	+	+	−	−	−

deviation. The lumen dimensions measured from intracoronary ultrasound images were correlated with those measured from angiography. Linear regression and correlation coefficients were calculated. The inter- and intraobserver variabilities were also calculated from 30 intracoronary ultrasound images. For vessel diameter, the intraobserver variability was $2{\cdot}3 \pm 2{\cdot}3\%$, interobserver variability was $2{\cdot}7 \pm 1{\cdot}7\%$. For vessel area, the intraobserver variability was $4{\cdot}1 \pm 4{\cdot}2\%$, and interobserver was $6{\cdot}5 \pm 5{\cdot}9\%$.

The values of different groups were compared by analysis of variance. If significant differences were found, a two tailed t-test was applied to pairs of data. Quantitative data were compared using chi-square test. A statistical probability $P<0{\cdot}05$ was considered significant. A linear regression analysis was used to assess the relationship between two appropriate variables. All statistical procedures were performed on the SAS (SAS Institute Inc., Cary, NC) and Primer statistical package (McGraw-Hill).

Results

Clinical data for the 44 patients included in the study are listed in Table 1. A total of 321 coronary segments were analysed, i.e. about seven segments during continuous pull-back were evaluated in each patient. In 21 (48%) of the patients, atherosclerotic plaques were found in the left coronary artery in 93 (29%) of the 321 segments

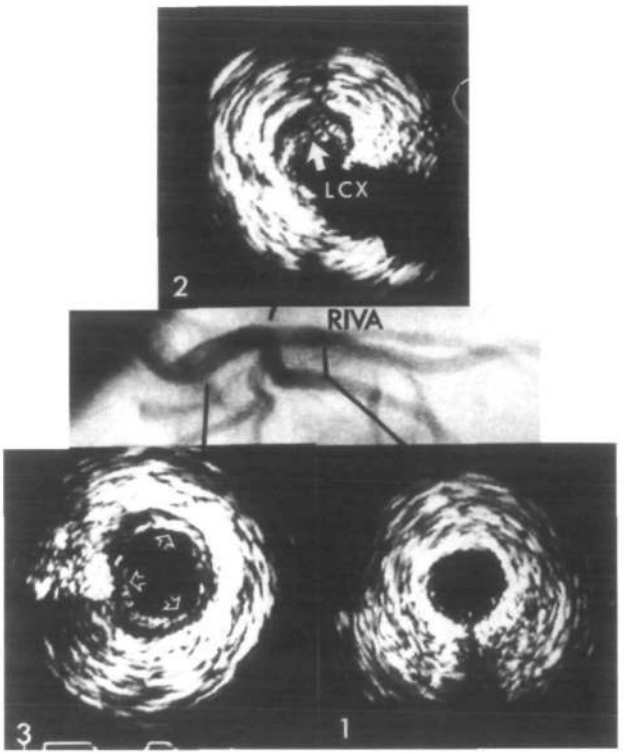

Figure 1 **Angiogram and intravascular ultrasound images at corresponding sites of the left coronary artery. No abnormalities are detected by angiography. An eccentric plaque at the bifurcation of the circumflex coronary artery and a concentric plaque in the left main coronary artery are clearly visualized by intracoronary ultrasound.**

(Fig. 1). Plaque size ranged from 2·0 to 10·6 mm^2 which yields a percent stenosis of 6–50% (26 ± 10%). The plaques were eccentric in 80 (86%) of 93 segments and concentric in 13 (14%) of the 93 segments. Plaque calcification was found in 15 (16%) of the 93 segments in seven (33%) of the 21 patients. The calcification was found in nine (60%) in eccentric and six (40%) in concentric plaques. It was superficial in 87% and deep in 13%. Off-line analysis from cine films by an independent observer revealed wall irregularities in two of the 44 patients in whom on-line evaluation was judged as smooth.

Intracoronary Doppler demonstrated that in 28 (64%) of the patients coronary flow reserve was not reduced (Fig. 2). In patients with a coronary flow reserve greater than 3·0, the values ranged up to eight, meaning that the coronary flow velocity increased eight-fold after the injection of papaverine (Fig. 3). No significant differences were found regarding the heart rates and blood pressure before and after papaverine infusion (Fig. 4).

Table 2 gives the quantitative analysis of intracoronary ultrasound and intracoronary Doppler values of the four groups. A significant difference in vessel area was found between group I and group IV (Fig. 5, $P<0·001$). No significant differences were found for luminal area. Plaque formation in group IV was more

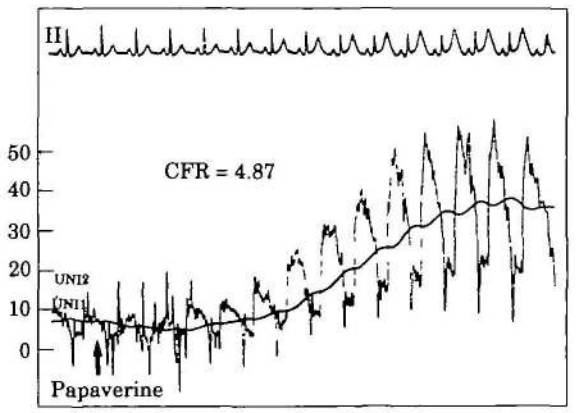

Figure 2 **Intracoronary Doppler flow recording of a patient with normal coronary flow reserve. The mean coronary flow velocity (CFR) increased nearly five-fold after the injection of 10 mg papaverine intracoronarily.**

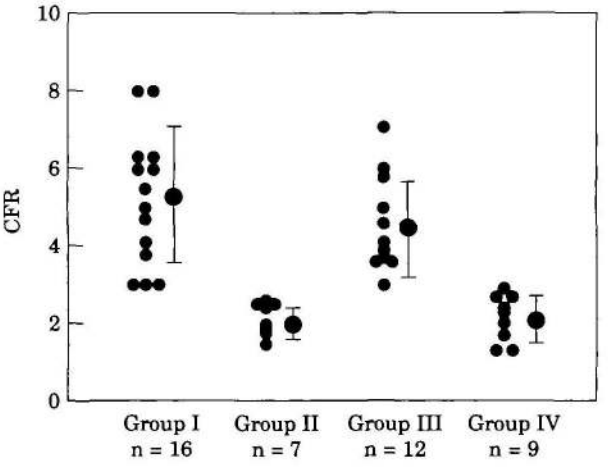

Figure 3 **Coronary flow reserve (CFR) in different groups. Group I=true normals, group II=syndrome X (reduced CFR, normal intracoronary ultrasound), groups III and IV=coronary atherosclerosis without reduced CFR (group III) or with reduced CFR (group IV).**

extended than in the other groups and the plaque area in group IV was larger than that of group III ($P=0·003$). In addition, calcium deposits were more frequent in group IV (44%) than in group III (25%). Vessel size in group IV (19·2 ± 6·1 mm^2) was larger than in group III (16·3 ± 8·0 mm^2) but was not statistically significant ($P=0·06$). Correlation of plaque area to coronary flow reserve yielded a r value of −0·38 ($P=0·09$).

Of all the patients studied, SPECT was available in 29 patients, of which one out of 10 in group I, three out of four in group II, seven out of eight in group III and seven out of seven in group IV were positive. The positive results in groups III and IV were significantly more frequent than in group I (both $P<0·01$).

The distribution of the risk factors in the different groups is listed in Fig. 6. No significant differences between the groups regarding age and body weight was found. The triglyceride level was higher in groups III

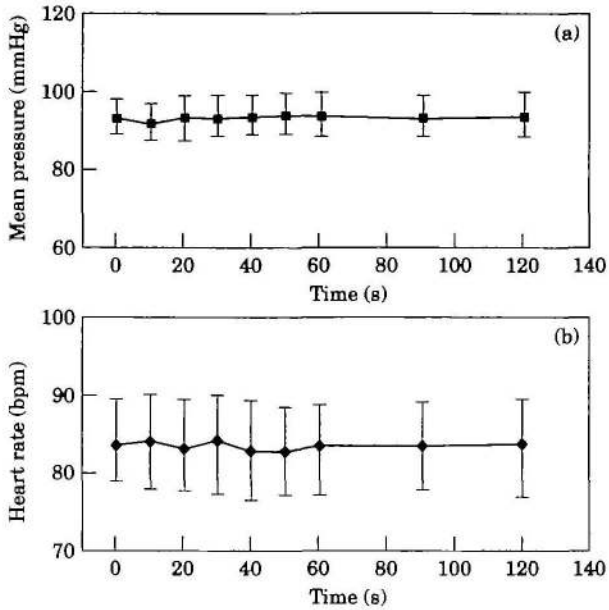

Figure 4 **Blood pressure (a) and heart rate (b) before and 2 min after papaverine infusion.**

Table 2 Coronary dimensions derived from intravascular ultrasound and CFR derived from intracoronary Doppler in different groups

	Group I (n=16)	Group II (n=7)	Group III (n=12)	Group IV (n=9)
Lumen area (mm^2)	14·6 ± 5·7	16·3 ± 7·9	12·7 ± 7·6	14 3 ± 5·4
Vessel area (mm^2)	14·6 ± 5·7	16·3 ± 7·9	16·3 ± 8·0	19·2 ± 6·1
Plaque area (mm^2)	—	—	3·6 ± 1·6	5·0 ± 2·3
CFR	5·3 ± 1·8	2·1 ± 0·4	4·6 ± 1·3	2·1 ± 0·6

CFR=coronary flow reserve. Values are mean ± standard deviation.

and IV than in the groups I and II ($P<0·05$). Group II had the highest cholesterol level. There were significant differences regarding smoking between group I and the other three groups. No significant differences were noticed concerning hypertension. Figure 7 gives the distribution of findings for electrocardiogram and exercise electrocardiogram.

Of the 321 coronary sites measured, the luminal diameter ranged from 2·3 to 6·7 mm as measured by intracoronary ultrasound, and from 2·2 to 7·1 mm as measured by angiography. The following correlations were obtained between intracoronary ultrasound and angiography for luminal diameter and area ($y=0·77x+1·12$, r=0·79, SEE= ± 0·55 mm, $P<0·001$ for luminal diameter and $y=0·73x+4·9$, r=0·73, SEE= ± 4·12 mm^2, $P<0·001$ for luminal area).

Discussion

This study demonstrates the clinical value of a combined use of intracoronary ultrasound and Doppler in patients

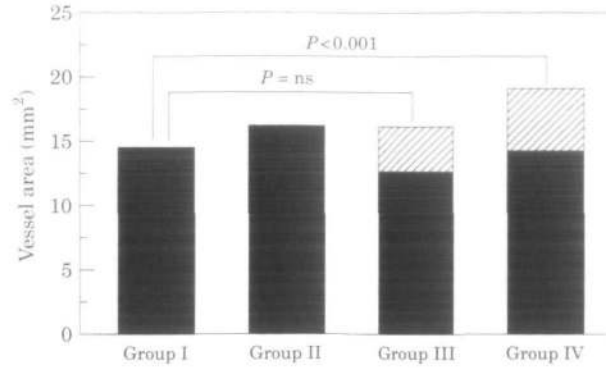

Figure 5 **Coronary cross-sectional areas of different groups. Significant difference regarding the vessel area was found between group I and group IV ($P<0·001$) indicating compensatory enlargement of the coronary artery in the presence of atherosclerosis. ▨, plaque area; ■, lumen area.**

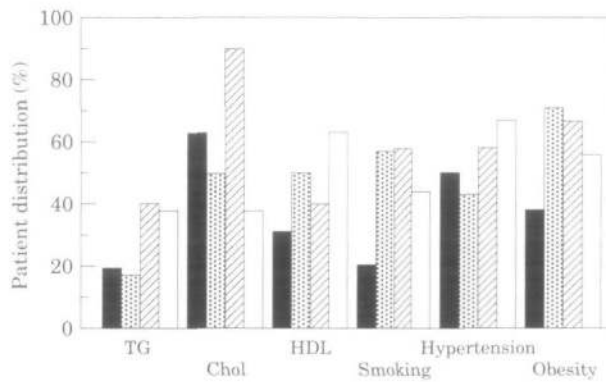

Figure 6 **Distribution of risk factors in the four different groups. TG=triglyceride; Chol=Cholesterol; HDL=high density lipoprotein. ■, group I (n=16); □, group II (n=7); ▨, group III (n=12); □, group IV (n=9).**

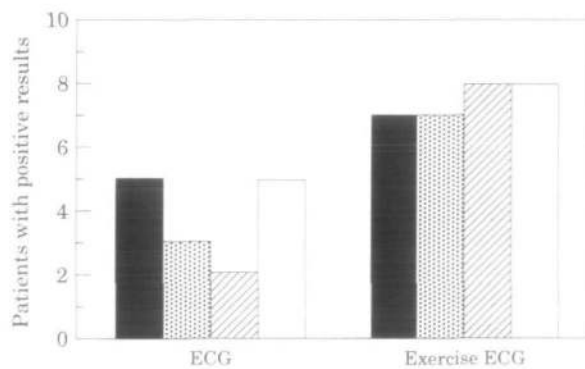

Figure 7 **Positive electrocardiogram and exercise electrocardiogram findings in different groups. ■, group I (n=16); □, group II (n=7); ▨, group III (n=12); □, group IV (n=9).**

with angiographically normal coronary arteries. Only one-third of the patients studied could be classified as true normal regarding the part of the coronary vessel studied. This may have important therapeutic or prognostic implications. Instead of discharging a patient and concluding that he does not have coronary artery disease, we determined there was coronary artery disease without significant narrowing of epicardial vessels but with a reduction in flow reserve in 50% of the patients in this group. The impact of such a diagnosis on lifestyle can be anticipated to be very great. Patients may be more willing to control risk factors. Follow-up studies, however, have to be undertaken in order to provide verifications that our findings have a prognostic value, for example by demonstrating that patients who have normal coronary angiograms and in whom signs of atherosclerosis have been ruled out by intracoronary ultrasound and in whom there is normal coronary flow reserve, as demonstrated by Doppler flow, actually do have a good prognosis. We succeeded in demonstrating signs of atherosclerosis in 48% of the patients which were not detected by coronary angiography, as previously reported[7,16,19]. The present study demonstrated that most (86%) of the lesions were focal and eccentric, which means that we detected an early stage of coronary atherosclerosis. This is in agreement with pathological observations that atherosclerosis first develops as a focal lesion with lipid deposits and foam cell formation by macrophage[27]. Within the studied part of the left coronary artery, focal lesions were mainly found in the proximal segment of the left anterior descending coronary artery. This part is known to be involved predominantly in the early stage of the disease. The number of lesions per patient and the percentage of calcified lesions (13%) also supports the hypothesis that an early stage of the disease was present in our patients. Furthermore, calcium deposits were more frequent (44%) in group IV with additional reduction of flow reserve; calcium deposits are usually found in more advanced stages of the disease, according to Stary[27].

Intracoronary Doppler was able to clarify further the disease in patients with angiographically normal coronary arteries and plaque formation. In 36% of our patients coronary flow reserve was reduced, suggesting additional, more distal microvascular abnormalities[8]. This reduction could not be explained by the extent of the disease. In the vessels studied by intracoronary ultrasound, luminal narrowing was not more than 70%, the threshold of coronary flow limitation[28]. But interestingly, a correlation trend was noticed between the extent of plaque formation and the values of coronary flow reserve. Thus, there may be a weak relation between the extent of coronary artery stenosis in epicardial arteries and microvascular involvement.

Pathohistological, epicardial echocardiographic, and intracoronary ultrasound studies have shown that coronary arteries undergo compensatory enlargement in the presence of atherosclerosis[29–31]. In the present study, a significant difference in total vessel area was found between patients with and without signs of atherosclerosis ($P<0{\cdot}001$) although no difference in the luminal cross-sectional area was found between the two groups with plaque formation. This suggests that compensatory enlargement of the vessel occurred in order to maintain luminal size. Coronary artery luminal narrowing may only occur when the compensatory mechanism is exhausted. The point at which this occurs is 40% according to Glagov *et al.*[29] in a pathological study, and 45% according to an intracoronary ultrasound study by Ge *et al.*[31]. Because of this compensation, coronary angiography cannot detect the early signs of atherosclerosis, which explains the discrepancies between contrast angiography and postmortem observation and our findings with intracoronary ultrasound[32–34]. Coronary angiography is a contour imaging technique, while intracoronary ultrasound is a cross-sectional method enabling imaging of the vessel wall.

This study demonstrated that even in patients with angiographically normal coronary arteries, coronary flow reserve can be reduced, either with or without plaque formation. Thus, symptoms or signs of coronary insufficiency — positive exercise-electrocardiogram or thallium single photon emission computed tomography (SPECT) — in our patients can now be regarded as true-positive, whereas previously (by angiographic criteria) they would have been regarded as false-positive. False-positive electrocardiograms and SPECT tests are found in 10–25%[35] and 5–10%[36], respectively, of patients studied. Coronary angiography is used as a gold standard. This practice should now be reconsidered. The use of more sophisticated approaches, such as quantitative coronary angiography and calculation of pressure gradient and coronary flow reserve, as suggested by Gould *et al.*[37], might have provided different results. Further studies have to address this problem in more detail.

Patients included in previous studies might not have been carefully characterized, and syndrome X is likely to be very heterogeneous[3,26]. Discrepancies might be related to the differences in patient groups, as suggested by Maseri[38]. Our study demonstrated that 36% of the patients with angiographically normal coronary arteries had reduced coronary flow reserve, fulfilling the criteria established by others[1,38,39]. Yet, intracoronary ultrasound showed that 48% of these patients had coronary plaque formation. Only 16% of the total population studied had to be included in the category of syndrome X according to the criteria proposed by Kaski *et al.*[26]. Both groups represent different populations. The disease in patients with plaque formation was even more pronounced than in those with plaque formation but normal coronary flow reserve. That means that studies in the future on syndrome X may first have to rule out atherosclerosis by employing intracoronary ultrasound. This may in turn lead to a better selection of patients and possibly eliminate striking discrepancies in the results of clinical, haemodynamic, metabolic, and prognostic studies.

Side effects, possibly due to premedication with additional heparin and nitroglycerin, were not observed.

A multicentre study has shown that intracoronary ultrasound is a safe method with few side effects, particularly in patients undergoing intracoronary ultrasound studies not linked to interventions[40,41]. A potential risk of intracoronary ultrasound is endothelial damage induced by the catheter, which may accelerate atherosclerosis in the vessel examined. Chenzbraun *et al.*[42] however, demonstrated that intracoronary ultrasound can be used safely in patients not undergoing interventions, as no significant change in luminal size of the imaged and non-imaged vessels, as measured on coronary angiography, was observed. These results confirm our data from 6 months follow-up examinations of the proximal coronary segment in patients undergoing interventions[43]. In these patients, furthermore, no intimal thickening was demonstrated by intracoronary ultrasound. The higher incidence of coronary spasm in transplant recipients has to be taken into account[51], but it posed no problem in this study possibly due to premedication with nitroglycerin.

Critique of the study

The calculation of coronary flow reserve should take into consideration the criteria previously proposed by Gould *et al.*[28]. Intracoronary Doppler can only permit coronary flow reserve estimated from coronary blood flow velocity using a 3F end-mounted crystal tip catheter. Both simultaneous measurement of intracoronary Doppler and ultrasound are possible, which may become generally available in the future when Doppler guidewires or imaging guidewires are produced.

The Doppler catheter we used has been validated previously[14]. In normal volunteers the ratio of maximal to resting flow velocity has been reported to be 3–5[1], $5{\cdot}0 \pm 0{\cdot}6$[24], $3{\cdot}4 \pm 1{\cdot}2$[44], $2{\cdot}94 \pm 1{\cdot}00$[45], and $4{\cdot}0 \pm 1{\cdot}1$[25]. The varied results may be due partly to the use of different medication to bring about vasodilation, since the value of the coronary flow reserve derived by Doppler flow measurement depends on the pharmacological stimulus[46]. We have taken 3·0 as normal under papaverine stimulation[47]. Thus, in group I, a mean coronary flow reserve of $5{\cdot}3 \pm 1{\cdot}8$ was found which is similar to $5{\cdot}0 \pm 0{\cdot}6$ reported by Wilson *et al.*[24]. Our results demonstrate that the use of a different threshold would have reduced further the number of true normals and increased the number with syndrome X. The implications of our study, however, would not have been different.

A premedication of nifedipine and nitroglycerin was used to avoid coronary spasm caused by placing an intracoronary ultrasound catheter into the coronary artery[1]. This may have influenced the coronary flow reserve. However, the increase of blood flow after nifedipine was only 11%[48] and the premedication was identical for all patients. Thus, the influence was similar in all groups.

The recently introduced Doppler flow wire allows rapid spectral analysis using the fast Fourier transform (FFT) algorithm[49]. It has the advantage of being able to record the maximal and spectral mean blood velocity. The use of the maximal flow velocity also overcomes the dependency on the positioning of the sampling volume[50]. The results were comparable to flow measurements obtained in the coronary sinus by thermodilation[51]. The calculation of coronary blood flow velocity was based in our study on the zero crossing detection method measuring the Doppler shift from the interval between each pair of adjacent zero crossings of the same velocity[50]. The catheter must be well positioned, i.e. able to measure continuous flow and be in a stable catheter position without any vessel wall artifacts because: (1) misalignment of the catheter with the non-axial flow velocity, (2) inclusion of a limited area of the velocity profile in the sample volume, and (3) presence of non-flow related disturbing signals can influence the Doppler recordings. As significant coronary artery stenosis was not present, impaired accuracy of the zero crossing method by disturbed flow or turbulence could be ruled out[51]. The zero crossing technique may be of limited use in severe coronary artery disease and for controlling interventions[50]. It seems, however, to be reliable for assessing relative flow changes, as determined experimentally by Tadaoka *et al.*[53]. The technique was used as a standard method in recent reports for analysing the coronary response to acetylcholine and other drugs[54–56]. Further studies will be performed using the fast Fourier analysis and Doppler flow wires in order to be able also to assess more distal vessels and side branches.

Clinical implications

Our study in patients with chest pain and normal coronary angiograms demonstrated that intracoronary ultrasound and Doppler are useful for further differentiation of patients who otherwise would have been regarded as normal, although only a minority of the patients were true normals. Studies on syndrome X may in the future, have to rule out signs of coronary atherosclerosis by intracoronary ultrasound. Signs of atherosclerosis (plaque formation) will influence a patient's response to the advice of his physician to control the risk factors. Whether these findings have therapeutic or prognostic implications must be determined

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