High probability of disease in angina pectoris patients: Is clinical estimation reliable?

Poul F Højlund-Carlsen MD DMSc¹, Allan Johansen MD¹, Werner Vach PhD³,
Henrik Wulff Christensen MD DC PhD⁴, Mette Møldrup MLT¹, Torben Haghefelt MD DMSc²

PF Højlund-Carlsen, A Johansen, W Vach, HW Christensen, M Møldrup, T Haghefelt. High probability of disease in angina pectoris patients: Is clinical estimation reliable? *Can J Cardiol* 2007;23(8):641-647.

BACKGROUND: According to most current guidelines, stable angina pectoris patients with a high probability of having coronary artery disease can be reliably identified clinically.

OBJECTIVES: To examine the reliability of clinical evaluation with or without an at-rest electrocardiogram (ECG) in patients with a high probability of coronary artery disease.

PATIENTS AND METHODS: A prospective series of 357 patients referred for coronary angiography (CA) for suspected stable angina pectoris were examined by a trained physician who judged their type of pain and Canadian Cardiovascular Society grade of pain. Pretest likelihood of disease was estimated, and all patients underwent myocardial perfusion scintigraphy (MPS) followed by CA an average of 78 days later. For analysis, the investigators focused on the approximate groups of patients with more severe disease, ie, typical angina (n=187), Canadian Cardiovascular Society grade 2 pain or higher (n=176) or high (higher than 85%) estimated pretest likelihood of disease (n=142).

RESULTS: In the three groups, 34% to 39% of male patients and 65% to 69% of female patients had normal MPS, while 37% to 38% and 60% to 71%, respectively, had insignificant findings on CA. Of the patients who had also an abnormal at-rest ECG, 14% to 21% of men and 42% to 57% of women had normal MPS. Sex-related differences were statistically significant.

CONCLUSIONS: Clinical prediction appears to be unreliable. Addition of at-rest ECG data results in some improvement, particularly in male patients, but it makes the high probability groups so small that the addition appears to be of limited clinical relevance.

Key Words: Angina; Angiography; Coronary artery disease; Diagnosis; Ischemia; Perfusion; Scintigraphy

La forte probabilité de maladie chez des patients atteints d'angine de poitrine : L'évaluation clinique est-elle fiable ?

HISTORIQUE : D'après les lignes directrices les plus récentes, il est possible de repérer avec fiabilité en clinique les patients atteints d'une angine de poitrine stable présentant une forte probabilité de coronaropathie.

OBJECTIFS : Examiner la fiabilité de l'évaluation clinique avec ou sans électrocardiogramme (ÉCG) au repos chez les patients présentant une forte probabilité de coronaropathie.

PATIENTS ET MÉTHODOLOGIE : Une série prospective de 357 patients aiguillés pour subir une coronarographie en raison d'une angine de poitrine présumée a été examinée par un médecin formé qui a évalué leur type de douleur et l'intensité de la douleur d'après la Société canadienne de cardiologie. On a évalué la probabilité de maladie avant l'examen, et tous les patients ont subi une scintigraphie myocardique de perfusion (SMP) suivie d'une coronarographie 78 jours plus tard, en moyenne. Pour des besoins d'analyse, les chercheurs se sont concentrés sur les groupes approximatifs de patients atteints d'une maladie plus grave, comme une angine classique (n=187), une douleur d'intensité minimale de 2 d'après la Société canadienne de cardiologie (n=176) ou une probabilité estimative élevée de maladie (supérieure à 85 %) avant l'examen (n=142).

RÉSULTATS : Dans les trois groupes, de 34 % à 39 % des patients et de 65 % à 69 % des patientes avaient une SMP normale, tandis que de 37 % à 38 % des patients et de 60 % à 71 % des patientes, respectivement, avaient obtenu des constatations négligeables à la coronarographie. Chez les patients dont l'ÉCG au repos était également anormal, de 14 % à 21 % des hommes et de 42 % à 57 % des femmes avaient une SMP normale. Les différences selon les sexes étaient significatives d'un point de vue statistique.

CONCLUSIONS : La prédiction clinique ne semble pas fiable. L'ajout des données de l'ÉCG au repos apporte une certaine amélioration, notamment chez les patients de sexe masculin, mais il rend les groupes à forte probabilité tellement minimes que cet ajout semble avoir une pertinence clinique limitée.

With few exceptions (1,2), current guidelines, reviews and editorials advocate rather unanimously that angina pectoris patients who have a high probability of coronary artery disease should be referred directly for catheterization without preceding stress test imaging, because these procedures add little to the work-up in this particular category of patients (3-7). However, coronary angiography (CA) is not without risk (8,9); therefore, for this guidance to be justified, it should be possible to identify subsets of patients with a high degree of accuracy.

In many studies on the effects of coronary revascularization, the type of chest pain is determined clinically according to principles originally proposed by Diamond (10), while the severity of pain is graded as suggested by the Canadian Cardiovascular Society (CCS) (11). The pretest likelihood of coronary artery disease is often estimated from the type of angina, as well as by age and sex (12); alternatively, it may be determined by more elaborate systems, such as the Duke Treadmill Score (13) or probability estimates based on a series of important risk factors (14,15). In daily practice, however, the use of

Departments of ¹Nuclear Medicine and ²Cardiology, Odense University Hospital; ³Department of Statistics, Institute of Public Health, University of Southern Denmark; ⁴Nordic Institute of Chiropractic and Clinical Biomechanics, Odense, Denmark

Correspondence: Dr Poul F Højlund-Carlsen, Department of Nuclear Medicine, Odense University Hospital, DK-5000 Odense C, Denmark.

Telephone 45-6541-1396, fax 45-6590-6192, e-mail pfhc@ouh.fyns-amt.dk

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TABLE 1
Comparison of the results of myocardial perfusion scintigraphy and coronary angiography by patient sex and disease variables

Variable	Patients with suspected stable angina pectoris (n=357)		
	Men (n=192)	Women (n=165)	P
Age ± SD, years	56.3±9.5	58.2±9.2	NS
History of hypertension, n (%)	123 (64)	104 (63)	NS
Hypercholesterolemia, n (%)	80 (42)	70 (42)	NS
Symptoms, n (%)			
Typical angina	104 (54)	83 (50)	NS
Atypical angina	55 (29)	49 (30)	NS
Noncardiac chest pain	23 (12)	23 (14)	NS
No chest pain	10 (5)	10 (6)	NS
Anti-ischemic treatment, n (%)			
Beta-blocker	90 (47)	67 (41)	NS
Calcium antagonist	42 (22)	46 (28)	NS
Long-acting nitrate	27 (14)	18 (11)	NS
Acetylsalicylic acid	113 (59)	83 (50)	NS
Statin	38 (20)	35 (21)	NS
ACE inhibitor	28 (15)	27 (16)	NS
Myocardial perfusion scintigraphy results, n (%)			0.0004
Normal perfusion	97 (50)	118 (71)	
Reversible defects	58 (30)	27 (16)	
Mixed defects	24 (13)	9 (6)	
Fixed defects	13 (7)	11 (7)	
Coronary angiography results, n (%)			<0.0001
0-vessel disease	102 (53)	129 (78)	
1-vessel disease	32 (17)	24 (15)	
2-vessel disease	37 (19)	5 (3)	
3-vessel disease	21 (11)	7 (4)	

ACE Angiotensin-converting enzyme; NS Not significant

these systems may be hampered by insufficient information regarding risk factors or lack of relevant test data, whereas the at-rest electrocardiogram (ECG) is almost always available. Therefore, the aim of the present study was to examine the reliability of clinical assessment with or without the at-rest ECG for categorizing stable angina pectoris patients.

METHODS

Patients

The present study was part of a larger prospective trial (16) on primary myocardial perfusion scintigraphy (MPS) as a gatekeeper for CA in patients referred for catheterization due to known or suspected stable angina pectoris. Patients with acute myocardial infarction or unstable angina were not eligible. In the larger study, 507 patients without diabetes mellitus or recent myocardial infarction underwent MPS. Because MPS in Denmark is not part of the routine work-up in these patients, the results could be kept secret. CA was performed in 476 of these patients, on average two months post-MPS, and was omitted in 31 patients, primarily because of patient refusal. From these 476 patients, three patient groups with a higher-than-average probability of having coronary artery disease were to be selected. However, the focus on patients without 'known' coronary artery disease needed to be retained, because this category of patients, according to guidelines, is clinically the most relevant to undergo MPS (3,5,6). Therefore, all patients with prior myocardial infarction and/or prior revascularization (n=119) were excluded, leaving a population of 357 eligible patients with only 'suspected' disease. Their

TABLE 2
Demographic data of the three focus populations

Variable	Patients fulfilling various the selection criteria		
	Typical angina (n=187)	CCS pain grade ≥2 (n=176)	HPL (n=142)
Sex (men/women)	104/83	87/89	99/43
Age ± SD, years	58.7±8.9	58.4±8.8	61.3±7.9
History of hypertension, n (%)	142 (76)	136 (77)	112 (79)
Hypercholesterolemia, n (%)	88 (47)	83 (47)	67 (47)
Symptoms, n (%)			
Typical angina	187 (100)	151 (86)	142 (100)
Atypical angina	–	22 (13)	–
Noncardiac chest pain	–	3 (2)	–
No chest pain	–	0 (0)	–
Anti-ischemic treatment, n (%)			
Beta-blocker	107 (57)	101 (57)	67 (47)
Calcium antagonist	54 (29)	54 (31)	46 (32)
Long-acting nitrate	38 (20)	39 (22)	18 (13)
Acetylsalicylic acid	118 (63)	117 (66)	83 (58)
Statin	41 (22)	41 (23)	35 (25)
ACE inhibitor	35 (19)	35 (20)	27 (19)
Myocardial perfusion scintigraphy results, n (%)			
Normal perfusion	98 (52)	88 (50)	118 (83)
Reversible defects	60 (32)	58 (33)	27 (19)
Mixed defects	16 (9)	17 (10)	9 (6)
Fixed defects	13 (7)	13 (7)	11 (8)
Computed tomography results, n (%)			
0-vessel disease	98 (52)	95 (54)	129 (91)
1-vessel disease	38 (20)	38 (15)	24 (17)
2-vessel disease	31 (16)	24 (22)	5 (4)
3-vessel disease	20 (11)	19 (11)	7 (5)

ACE Angiotensin-converting enzyme; CCS Canadian Cardiovascular Society; HPL High pretest likelihood of coronary artery disease

characteristics and medication use data are presented in Table 1. All patients were clinically evaluated by the same observer before rest and stress MPS, which were carried out later on the same day. The study received approval from the local ethics committee and complied with the Declaration of Helsinki (www.wma.net/e/policy/b3.htm), and all patients gave their written, informed consent. Three subgroups with a rather high probability of disease were studied, ie, patients characterized by typical angina pectoris (n=187), chest pain of CCS grade 2 or higher (n=176) or a high (higher than 85%) pretest likelihood of coronary artery disease (n=142). For details, see the text below, Table 2 and Figure 1.

Clinical evaluation

On the day of MPS, a single physician (HWC) recorded each patient's medical history and performed a physical examination before judging the pain type (typical angina, atypical angina, noncardiac chest pain or no pain) (10), as well as the CCS grade of pain (0 to 4) (11). Patient pretest likelihood of coronary artery disease was estimated based on type of pain, age and sex, according to the guidelines outlined by Diamond and Forrester (12). The physician had access to referral letters and history, but not to the results of MPS and CA. His clinical judgment had been tested against that of a professor in cardiology (TH) in a prospective sample of the original study. In a blinded design, they agreed 100% on the presence of angina, and 93% and 86% on the type of pain and the CCS grade, respectively (17).

MPS

Gated single-photon emission computed tomography was performed using a same-day rest/stress dual-isotope protocol originally described by Berman et al (18). Details on the method and its reproducibility have been described elsewhere (19). The interobserver agreement with regard to normal or abnormal MPS was 95%, with a kappa value of 0.89, which was considered to be excellent (19). In short, thallium-201 (95 MBq + 1 MBq/kg above 70 kg) was applied for rest and technetium-99m sestamibi (925 MBq + 10 MBq/kg above 70 kg) was applied for stress imaging using a rotating dual-head gamma camera and ECG-gated acquisition, with eight frames per cycle and 100% beat acceptance. The data sets were smoothed, reconstructed using filtered (ramp) back projection and postfiltered before being Fourier-transformed, reoriented and made ungated by summing the eight intervals. Patients were stressed either on a bicycle ergometer (n=177), according to guidelines of the Danish Society of Cardiology (20), until they reached target heart rate, or pharmacologically (n=180), almost exclusively by adenosine using standard procedures.

Image interpretation included a review of all scans by two independent observers (PFHC, AJ), who were blinded to all other data. A semi-quantitative visual interpretation was made using short-axis, horizontal and vertical long-axis myocardial tomograms, and a 20-segment model (18,19). Four perfusion patterns were distinguished: normal; reversible defects (the appearance of new defects during stress); mixed defects (the appearance of worsening defects during stress, or the presence of reversible and fixed defects); and fixed defects (defects that were present at rest and remained unchanged during stress). Final interpretation and overall diagnosis were determined by consensus. The diagnostic accuracy of this approach has been reported elsewhere (21). The MPS results were not revealed to the referring physician.

ECG

The at-rest ECGs were recorded in all patients immediately before MPS and were interpreted by a single observer (AJ) as previously described (22). The at-rest ECGs were categorized as either normal or abnormal, according to general principles. In the case of doubt, the final diagnosis was reached by consensus (AJ, PFHC).

CA

Selective CA was undertaken, on average, 78 ± 54 days after MPS at the discretion of the Department of Cardiology (Odense University Hospital, Odense, Denmark) using standard techniques in multiple views, with 50% or greater luminal diameter narrowing indicating significant coronary artery disease. The CA results were interpreted by the physicians on duty in the catheterization laboratory, who were unaware of the MPS results, and if necessary, the results were reviewed and corrected at the 'Heart Conference'.

Statistical analysis

Descriptive statistics were generated using percentages for discrete variables and means $\pm$ SD for continuous variables. Differences in frequency distribution were compared by Fisher's exact test or the χ^2 test. $P < 0.05$ (two-tailed) was considered significant.

RESULTS

The distributions of the outcomes of MPS and CA in the whole population are included in Table 1, and the distributions in the above-defined subsets of patients with an assumed rather high probability of disease are described in Table 2. The data in Table 3 indicate that 34%–39% of male patients and

Figure 1 A Venn diagram demonstrating the overlaps among clinical groups in patients with suspected disease (n=357). By definition, all patients with an estimated high pretest likelihood of coronary artery disease (HPL) have typical angina pectoris. Note that several patients did not belong to any of the three groups. CCS 2-3 Canadian Cardiovascular Society pain grade 2 or 3

65%–69% of female patients had normal findings on MPS. Similarly, 37%–38% of male patients and 60%–71% of female patients had normal CA. In all subsets, the sex-related differences were statistically significant ($P < 0.05$ for all). Using CA as the reference, the diagnostic values of the various disease criteria and combinations of these are compared in Table 4.

Only 76 male patients fulfilled all three 'high probability' criteria. Of these, 25 (33%) had normal MPS and 28 (37%) had insignificant coronary artery disease, while 19 (24%) had both normal MPS and normal CA. Corresponding figures for the 41 female patients fulfilling all three criteria were 27 (66%), 24 (59%), and 21 (51%) patients, respectively.

Also requiring an abnormal at-rest ECG caused a drop in the rate of normal MPS among the four groups (Table 5), from 34%–39% to 14%–21% in male patients and from 65%–69% to 42%–57% in female patients. The same drop was not present in the rates of normal CA, in that the rates stayed quite high in male patients (from 37%–38% to 43%) and in female patients (from 60%–71% to 57%–73%). However, one should note that by also requiring an abnormal at-rest ECG, the high probability groups decrease substantially. Thus, by doing so in the present study, fewer than 7% of male patients and fewer than 9% of female patients would remain for evaluation. Of course, higher rates of abnormal MPS or significant coronary artery disease can also be obtained by requiring more extreme values of CCS grade or pretest likelihood, but again, there would be a substantial decrease in the high probability groups. Actually, by requiring more extreme values, the investigators failed to identify subgroups with a frequency above 80% of abnormal MPS or abnormal CA that included more than 15% of patients.

DISCUSSION

According to the American College of Cardiology and the American Heart Association guideline update on the management of patients with chronic stable angina (23), patients should be examined clinically and directly referred for catheterization, and eventually coronary revascularization if history, physical and estimation of pretest likelihood of coronary artery disease indicate a high probability of disease. A similar recommendation regarding patients with typical and

TABLE 3

Clinical classification compared with the results of myocardial perfusion scintigraphy and coronary angiography in patients with suspected stable angina pectoris (n=357)

	Myocardial perfusion scintigraphy				Coronary angiography				Both normal*
	Normal	Reversible	Mixed	Fixed	0-VD	1-VD	2-VD	3-VD	
Men, n (%)									
Typical angina (n=104)	41 (39)	42 (40)	13 (13)	8 (8)	40 (38)	21 (20)	28 (27)	15 (14)	30 (29)
CCS pain grade ≥2 (n=87)	30 (34)	36 (41)	13 (15)	8 (9)	32 (37)	22 (25)	21 (24)	13 (15)	22 (25)
High pretest likelihood of coronary artery disease (n=99)	39 (39)	16 (16)	12 (12)	8 (8)	38 (38)	19 (19)	27 (27)	15 (15)	28 (28)
Women, n (%)									
Typical angina (n=83)	57 (69)	18 (22)	3 (4)	5 (6)	58 (70)	17 (20)	3 (4)	5 (6)	48 (58)
CCS pain grade ≥2 (n=89)	58 (65)	22 (25)	4 (4)	5 (6)	63 (71)	17 (19)	3 (3)	6 (7)	50 (56)
High pretest likelihood of coronary artery disease (n=43)	28 (65)	12 (28)	1 (2)	2 (5)	26 (60)	10 (23)	3 (7)	4 (9)	22 (51)

*Indicates patients in whom both examinations were normal. CCS Canadian Cardiovascular Society; VD Vessel disease

TABLE 4

Comparison of noninvasive criteria and combinations of these with regard to the identification of coronary artery disease (ie, with coronary angiography as reference) when applied in the original population of 357 patients with only suspected stable angina pectoris

Criterion	Sensitivity	Specificity	Accuracy	PPV	NPV
Typical angina (n=187)	71%	58%	62%	48%	78%
Typical angina + HPL (n=142)	62%	72%	69%	55%	78%
Typical angina + HPL + CCS pain grade 2-3 (n=117)	52%	77%	68%	52%	78%
Exercise test (n=177)	69%	90%	85%	76%	86%

CCS Canadian Cardiovascular Society; HPL High pretest likelihood of coronary artery disease; NPV Negative predictive value; PPV Positive predictive value

severe symptoms was given in the updated European guidelines (3), which advocated Diamond and Forrester's estimation of the pretest likelihood of disease, whereas the American update recommended a combination of this with data from the Coronary Artery Surgery Study (CASS) (23). In contrast, statements from the 1997 Canadian Cardiovascular Society Consensus Conference, as well as the recent American College of Cardiology Foundation and the American Society of Nuclear Cardiology guidelines (2), were less stringent. The Canadian consensus was that MPS is useful when stress exercise testing or 24 h ambulatory ECG recording has left doubt about the diagnosis, or when a more detailed or accurate definition of myocardial ischemia is needed (1). The American College of Cardiology Foundation and the American Society of Nuclear Cardiology guidelines found MPS to be 'appropriate' for this category of patients, without further explanation (2). However, the prognosis of patients with normal MPS is so favourable (2-4) that invasive procedures mean a stepping-up in risk, which tends to increase with age, comorbidities and the number of previous interventions (8,9,24-26). Therefore, the clinical evaluation of an individual patient should be sufficiently accurate as to justify direct referral for catheterization and potential revascularization by reliably sorting out most patients with normal myocardial perfusion and insignificant coronary artery disease.

The main finding of our study was that approximately one-third of our male patients and approximately two-thirds of our

TABLE 5

Clinical classification and at-rest electrocardiogram (ECG) compared with results of myocardial perfusion scintigraphy (MPS) and coronary angiography (CA)

Patients with suspected stable angina pectoris (n=357)				
	ECG	Number of patients	Normal MPS, n (%)	Normal CA, n (%)
Men				
Typical angina	Abnormal	14	3 (21)	6 (43)
	Normal	90	38 (42)	34 (38)
CCS pain grade ≥ 2	Abnormal	14	2 (14)	6 (43)
	Normal	73	28 (38)	26 (36)
High pretest likelihood of CAD	Abnormal	14	3 (21)	6 (43)
	Normal	85	36 (42)	32 (38)
Women				
Typical angina	Abnormal	12	5 (42)	7 (58)
	Normal	71	52 (73)	51 (72)
CCS pain grade ≥ 2	Abnormal	11	6 (55)	8 (73)
	Normal	78	52 (67)	55 (71)
High pretest likelihood of CAD	Abnormal	7	4 (57)	4 (57)

CAD Coronary artery disease; CCS Canadian Cardiovascular Society

female patients with a more severe degree of disease or a high likelihood of coronary artery disease had normal MPS and insignificant coronary artery disease (Table 3). This suggests that standard clinical evaluation and a commonly used system for estimation of the pretest likelihood of coronary artery disease cannot reliably identify patients with ischemic and/or coronary artery disease. Even if one requires the presence of several indicators, the fractions of patients with normal MPS and insignificant coronary artery disease remain high.

In line with current recommendations, we focused deliberately on study groups with a higher-than-average probability of disease. We did this because recommendations have unanimously emphasized typical angina and severe chest pain as indications for catheterization, and in severe cases, some guidelines have found them sufficient as stand-alone criteria (3,5-7,23). Therefore, in our analysis, we considered not only the type of angina, but also its severity by CCS grading. For estimating the pretest likelihood of coronary artery disease, we applied the original Diamond and Forrester approach (12), which was based exclusively on age, sex and the type of chest

pain; however, it was not based on other risk factors such as smoking, hyperlipidemia and hypertension, or the results of exercise ECG testing and/or stress thallium imaging, which are included in more elaborate systems (12-15). We did this because in Denmark, it is not a routine to use any of these systems. The simple Diamond and Forrester method we applied was recommended by the Danish Society of Cardiology, but it is not in general use in Denmark.

What are the reasons for the discrepancy between our results and those of Diamond et al (12,15)? Despite several cross-tabulations, we did not find any evident clues. When their systems were tested prospectively, they worked quite well (12,14,27-29). The studies were similar to ours, in that they were university-based and patients were largely referred; however, the large cohorts were more heterogeneous by often including several patients with a previous myocardial infarction and by using clinical evaluation by several physicians in the routine without blinding. However, a few reported data are not far from our findings. Thus, defining significant disease as 75% luminal diameter narrowing, compared with our 50%, Pryor et al (14) found, in similar patients older than 40 years of age and without a history or ECG evidence of previous infarction, that approximately 21% of patients with typical angina had insignificant coronary artery disease, compared with 38% and 70% in our male and female patients, respectively, when applying a limit of only 50% diameter reduction. Unfortunately, the lack of actually observed and predicted data relating age, sex and typical angina to the results of CA in these previous studies prevents a meaningful comparison. However, the relatively low disease prevalence in our study groups may explain some of the discrepancy, because Sox et al (29) have demonstrated that the prevalence of disease is lower in the low disease prevalence population than in the high disease prevalence population, even when patients with similar logistic scores, and thus similar clinical histories, are compared (29).

Other reasons should be considered. Both left ventricular hypertrophy (more than 75% of our study population had a history of hypertension) and microvascular disease may be associated with perfusion abnormalities in the presence of normal coronary arteries (21,30,31). The precise impact of these confounders remains unknown; however, hypertension does not degrade the diagnostic value of MPS for diagnosing coronary artery disease (32), and none of the factors can explain the high rate of insignificant angiographic disease in these patients. Also possible are differences in practice and assessment of symptoms. It is difficult to evaluate this, because previous articles have rarely described local practice, and have seldomly stated how the clinical manifestations were judged and recorded. In general, it was simply stated that the patients had angina and that this was the reason for referral to catheterization. In contrast, all our patients were systematically assessed by a single trained clinician whose judgment was in line with that of a professor in cardiology (17). Danish and American stable angina patients are perhaps not directly comparable, but importantly, patient characteristics have probably changed over the years (23,33-35), with differences from country to country (35-37). Referral patterns may differ too. Thus, in a consecutive series of 972 patients referred for CA for known or stable angina, 40% had normal angiograms (16), ie, approximately twice the rate reported in Canada (38) but lower than the 44% reported a few years earlier in the United States (39).

We have previously shown that the exercise ECG alone may not reliably diagnose ischemic or coronary artery disease (22). However, integrating clinical data with stress ECG results from elaborate and predominately prognostic systems, such as the Duke Treadmill Score, may improve prediction (40), although it appears this cannot replace MPS (13). In our sample population, the inclusion of at-rest ECG data did improve prediction somewhat, especially in male patients, whereas the reduction in the rate of normal CA was much smaller. In fact, in female patients, there was almost no reduction (Table 5). After also requiring an abnormal at-rest ECG, 14%–21% of male patients had normal MPS, whereas the rate of normal CA remained too high (43%) to allow the reliable exclusion of coronary artery disease. In female patients, the rates of normal MPS and normal CA were much too high for reliable prediction (Table 4). Thus, our data support the belief that both clinical history and exercise testing are of little value in female patients with chest pain.

The traditional criteria did not define groups with a frequency of abnormal MPS or CA, which justifies regarding these as high-probability groups warranting direct referral to CA. Such groups may be achieved by requiring rather extreme values, such as higher than CCS grade 2 pain or a pretest likelihood of greater than 95%, or by also requiring an abnormal at-rest ECG. However, the resulting groups typically include fewer than 10% of all patients, thus limiting the clinical relevance of this approach, because the majority of patients remain unsatisfactorily classified. Nevertheless, typical angina alone is not a criterion that allows the definition of a true high-likelihood group. However, likelihood of disease should not be confused with risk of later events and judgment of outcome. Recently, it has been shown that a higher CCS class is linearly related with angiographic findings and higher revascularization rates, as well as lower all-cause mortality and nonfatal infarction, although not closely enough to allow reliable prediction in individual patients (41).

It would be interesting to examine whether the exercise ECG can improve prediction beyond that gained from the at-rest ECG. However, the exercise ECG was only available in a subset of patients ($n=177$), and we could not regard this subset as a random sample. Therefore, such an investigation is beyond the scope of the present study and will form the basis of future work. We might have tried identifying other discriminators than sex, age and the type of chest pain. This, however, would have required another design with larger subgroups. Our sample was not consecutive and, consequently, perhaps not representative of the entire population of stable angina pectoris patients without known disease. Nevertheless, even among patients selected to have a higher-than-average probability of disease, we found a substantial portion with normal myocardial perfusion and/or insignificant coronary artery disease.

CONCLUSIONS

Our data suggest that standard clinical evaluation and a commonly used system for estimating the pretest likelihood of coronary artery disease are unreliable for predicting the presence of myocardial ischemia or coronary artery disease. Prediction was less reliable in female patients than in male patients. The inclusion of an abnormal at-rest ECG in the high probability definition caused some improvement in predictability in predominantly male patients, but at the expense of a reduction of the high probability groups, limiting the clinical relevance of this approach.

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