THE EVALUATION OF ANGINA PECTORIS

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"The dangers of lack of skill, and of incorrect interpretation, cannot be emphasized enough. Inept performance, inadequate instrumentation and overimaginative or undiscerning interpretation provide the means of opening a Pandora's box of misinformation which may plague the physician, harm his patients and retard evaluation of a better understanding of human coronary artery disease."

T. Mason Sones (1962)

The father of modern coronary arteriography

INTRODUCTION

Chest pain is one of the most frequent complaints for which patients seek medical attention. Accurate assessment of the etiology for this pain has tremendous implications for the patient. Incorrectly determining that a patient has angina pectoris is likely to have harmful psychological and economic consequences and may lead to unnecessary complex procedures or inappropriate treatment. However, failure to recognize this serious disorder may result in a dangerous delay of much-needed and potentially life-saving therapy. Surprisingly, there is little relationship between the severity of chest discomfort and the seriousness its cause, thus a frequent problem in patients who complain of chest pain is distinguishing minor disorders from ischemic cardiac pain or other serious illnesses.

Although angina pectoris is a clinical diagnosis, there now exists an impressive list of diagnostic procedures for the evaluation of the patient suspected of having coronary artery disease (CAD). (TABLE 1) Despite this, the evalua-

A. CLINICAL METHODS

1. History
2. Physical Examination

B. NON-INVASIVE METHODS

1. Routine Laboratory
2. Radiologic
   a) Chest X-Ray
   b) Flouroscopy
3. Electrocardiography
4. Echocardiography
5. Stress Testing
6. Nuclear Imaging
   a) Radionuclide Ventriculography
   b) Thallium - 201 Imaging

C. INVASIVE METHODS

1. Cardiac Catheterization and Coronary Angiography

TABLE 1

tion of the patient with angina has not become easier. In fact, because of the many factors to be considered, the evaluation has become quite complex. As our diagnostic methods have improved, we have been able to characterize better the severity of disease, determine prognosis and, thereby develop more effective

treatments. No longer is it adequate simply to determine if the chest pain is caused by CAD. The physician must stratify the patient into "high" or "low" risk subgroups and identify those in whom surgical therapy is known to be of significant benefit. The clinician must realize that the diagnosis, prognosis and management of the patient with CAD are all interrelated and must be considered together. (FIGURE 1) For example, we now know that patients with

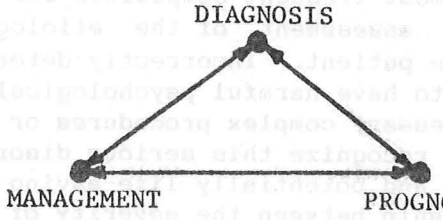


FIGURE 1

significant disease of the left main coronary artery have a poor prognosis, but survival is improved with surgical therapy. Therefore in this instance, the diagnosis of left main stenosis has profound prognostic and management implications. Many of the tests available currently have not only diagnostic capabilities, but also prognostic power. The best diagnostic test for one patient may be of little help or misleading in another. Furthermore in some patients, a test with little diagnostic value may yield important prognostic information. In an attempt to provide some insight into a contemporary approach to the evaluation of chest pain suspected to be angina , this review will: a) examine the utility of the diagnostic methods available for the evaluation of chest pain, b) highlight the prognostic significance of some of these findings, and c) hopefully, provide some insight to how these various modalities should be integrated and used to evaluate patients with angina pectoris. Although this review will not address the evaluation of the patient who has suffered a recent myocardial infarction, many of the techniques discussed would be applicable to these individuals.

DIAGNOSTIC METHODS TO EVALUATE CHEST PAIN

A. HISTORY

1. The Characteristics Of Angina Pectoris

Angina pectoris is a clinical syndrome resulting from transient myocardial ischemia. Heberden's initial description of this syndrome as conveying a sense of "strangling or anxiety" is still pertinent today. (1) Other adjectives used

> *But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare which deserves to be mentioned more at length. The seat of it, and the sense of strangling, and anxiety with which it is attended, may make it not improperly to be called angina pectoris.*

Those who are afflicted with it are seized while they are walking (more especially if it be up hill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.

In all other respects the patients are at the beginning of this disorder, perfectly well, and in particular have no shortness of breath from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are most liable to this disease, especially such as have passed their fiftieth year. After it has continued a year or more, it will not cease as instantaneously upon standing still, and it will come on not only when persons are walking, but when they are lying down. . . . Some have been seized while they were standing still or sitting, also upon first waking out of sleep. . . . The termination of the angina pectoris is remarkable. For if no accident intervenes, but the disease go on to its height, the patients all suddenly fall down, and perish almost immediately.

Dr. William Heberden 1772 (1)

to describe this discomfort include constricting, squeezing, viselike, heaviness, strangling or crushing and only rarely is angina characterized as actual "pain". In some patients, the quality of the sensation is quite vague and may be described as a mild pressure-like feeling or any uncomfortable numb or burning sensation. Sharp, fleeting chest pains or prolonged dull aches localized to the left submammary area are rarely caused by myocardial ischemia. Unfortunately, in some patients myocardial ischemia can produce very atypical symptoms and in others it can be asymptomatic.(2) When asked to localize the sensation, patients will typically press on their sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal site of discomfort. Angina seldom starts abruptly; usually it has a crescendo-decrescendo quality lasting from 1 to 30 minutes. Angina can radiate to the left shoulder and to both arms especially the ulnar surface of the forearms and hands, but can also arise or radiate to the back, neck, jaw, teeth, legs or epigastrium.(3) Other characteristics of angina are listed in Table 2.

Quality
Sensation of pressure or heavy weight on the chest
Burning sensation
Feeling of tightness
Shortness of breath with feeling of constriction about the larynx or upper trachea
Visceral quality (deep, heavy, squeezing, aching)
Gradual increase in intensity followed by gradual fading away
Location
Over the sternum or very near to it
Anywhere between epigastrium and pharynx
Occasionally limited to left shoulder and left arm
Rarely limited to right arm
Limited to lower jaw
Lower cervical or upper thoracic spine
Left interscapular or suprascapular area
Duration
0.5 to 30 minutes
Precipitating Factors
Relationship to exercise
Effort which involves use of arms above the head
Cold environment
Walking against the wind
Walking after a large meal
Emotional factors involved with physical exercise
Fright, anger
Coitus
Nitroglycerin Relief
Relief of pain occurring within 45 seconds to 5 minutes of taking nitroglycerin
Radiation
Medial aspect of left arm
Left shoulder
Jaw
Occasionally right arm

TABLE 2

2. Three Myths Regarding Angina

Myth #1: Angina is reproducable

As recent as 5-10 years ago it was generally felt that myocardial ischemia provoked by exertion occurred in a highly reproducible pattern. Therefore, an individual who experienced angina after climbing 2 flights of stairs would do so every time this were attempted. When such patients are tested on a treadmill, the rate-pressure product at which angina and/or ECG changes occur is nearly constant. This type of angina is due to fixed atherosclerotic lesions within the coronary arterial tree and is now commonly called fixed-threshold angina. (4)

However, a careful historical assessment in many patients reveals some variability in the amount of exertion required to provoke angina. For example, a certain activity may cause angina one day and not the next. Often, even in the course of a single day there may be pronounced variability in the exertion necessary to cause angina. Multiple exercise tests in such patients document a variability in the rate-pressure product required to cause angina and EKG changes. (5) Patients with this variable-threshold angina typically complain of

occasional angina at rest, some nocturnal angina and angina precipitated by emotion, cold exposure and/or meals. The variability of the threshold for angina is caused by alterations in coronary arterial tone usually at the site of an atherosclerotic lesion. This phenomenon can occur at rest (6) and during dynamic (7) or isometric exercise. (8) In these individuals angina threshold tends to be lower in the morning hours perhaps correlating with the finding that coronary arterial lumina are smaller at that time of day. (9) All of these factors combined will cause patients with this syndrome to state that they have "good days" and "bad days." This relatively new syndrome of angina is termed mixed angina or variable - threshold angina. (4)

MYTH #2: Pain in the left arm is usually angina

The lay public and many physicians are frequently convinced that pain in the left arm, especially in conjunction with chest discomfort is pathognomonic of ischemic heart disease. This association has neither theoretic nor clinical foundation. The exact neural pathways and mediators of cardiac pain are complex and not fully understood. Cardiac nociception is believed to be subserved mainly by primary sympathetic afferents. (10) Nerve endings in the ventricles and around coronary arteries are excited by a variety of chemical and mechanical stimuli that may be produced during ischemia. The specific substance that actually stimulates these sympathetic afferents and begins this series of interactions is not known, but mechanical stimuli (i.e. stretching) (11), bradykinin (11,12), serotonin (13), histamine (13), potassium (14), and acidosis (15) have all been suggested. Modulation of the sensory input may also occur at a spinal segmental level by both local and descending inputs (16,17) and by vagal afferents (11). (FIGURE 2) The discomfort of myocardial ischemia is perceived in

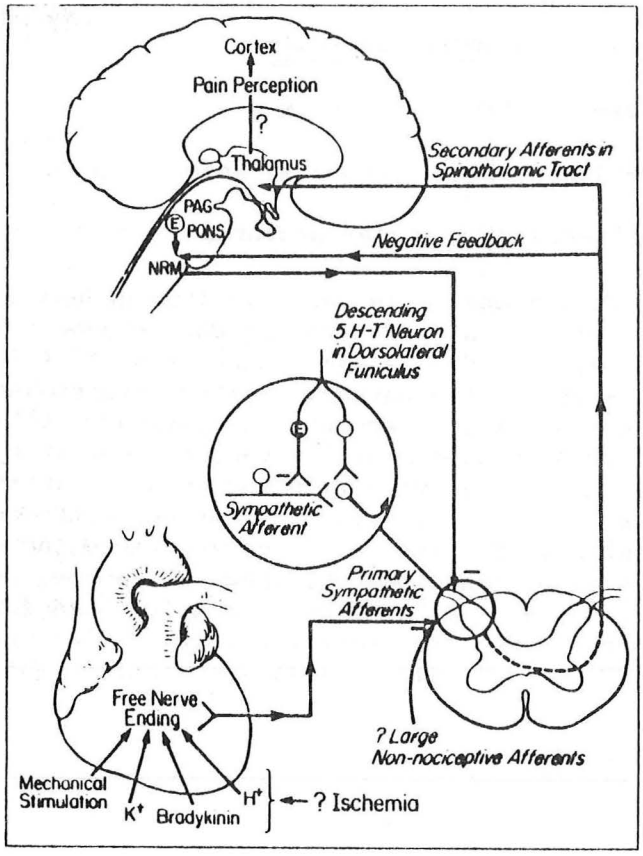


FIGURE 2

Schematic diagram of pathways that are likely to participate in cardiac nociception. Free nerve endings of ventricular sympathetic afferents are excited by a variety of chemical and mechanical stimuli that may be produced during ischemia. Modulation of the sensory input may then occur at a spinal segmental level by both local and descending inputs. The latter may involve a system that is proposed to descend from the periaqueductal gray (PAG) of the midbrain via the nucleus raphe magnus (NRM) of the medulla and involve enkephalin (E) and serotonergic (5H-T) neurons. This system would act to inhibit the primary nociceptive afferents and may be stimulated by secondary afferent fibers via the reticular formation and nucleus raphe magnus, thus forming a negative feedback loop for modulation of pain sensation.

various regions of the chest because it can be "referred" to the corresponding peripheral dermatomes that supply afferent nerves to the same segment of the spinal cord as the heart. One possible explanation for this phenomenon is that a common pool of secondary neurons can be stimulated both by somatic and visceral afferent impulses. (18) If the visceral impulses are excessive, the nearby intermediate neurons that are receptors for somatic impulses may be excited and the discomfort will be perceived as cutaneous in origin. With the various sites of stimulation and neuronal relationships within the cord, the origin of these various impulses may be confused by the cerebral cortex. Therefore, the potential for modulation of cardiac pain exists at many levels and, for that reason it is not surprising its description may vary widely among individuals. From a theoretic standpoint, any disorder involving the deep afferent fibers of the left upper thoracic region should be capable of causing discomfort in the chest, either arm or both areas. Such localization is common not only in patients with myocardial ischemia, but also in those with other visceral thoracic disorders. Although angina most frequently is substernal, radiates down the ulnar aspect of the left arm and is squeezing or constricting in description, the location, radiation and quality of the discomfort are of less diagnostic significance than its behavior in terms of the conditions which induce and relieve it.

MYTH #3: Silent myocardial ischemia is rare and usually occurs in diabetics

At some point in training, nearly every physician is told that diabetic patients may not develop angina with significant myocardial ischemia or infarction, presumably because of a diabetic - induced neuropathy. (19,20) Although this is true, it is now recognized that silent myocardial ischemia may be a very frequent occurrence in patients with CAD. Cohn has classified patients with silent myocardial ischemia into 3 types (21).

Classification of Silent Myocardial Ischemia

TYPE 1: Silent ischemia in asymptomatic individuals

TYPE 2: Silent ischemia in patients after myocardial infarction

TYPE 3: Silent ischemia in patients with angina pectoris

The exact prevalence of silent myocardial ischemia in these various groups is now being examined more closely. Early studies suggest that silent myocardial ischemia occurs in 2.5 to 10% of asymptomatic, middle-aged males (type 1) (22-24) and may occur in as many as 50% of asymptomatic patients after myocardial infarction (type 2).(25) The prevalence of silent ischemia in patients with angina (type 3) has been characterized more precisely by the use of ambulatory monitoring. Deanfield et. al. collected 446 days of monitoring in 30 patients who had documented coronary artery disease for more than 18 months, chronic stable angina and abnormal exercise test results.(26) Their observations indicate that only 470 (24%) of 1,934 episodes of transient ST-segment depression (0.1 mV or greater) were accompanied by angina. Other studies confirm that for each episode of symptomatic ischemia there are approximately 3 silent ones.(27,28) Thallium - 201 defects (29), increases in left ventricular end-

diastolic pressure (30) and increased myocardial oxygen extraction (31) have all been documented during silent episodes of myocardial ischemia. Episodes associated with angina tend to have more prolonged ST-segment depression (26), but there is considerable overlap. (FIGURE 3) Moreover, it is not just the mild

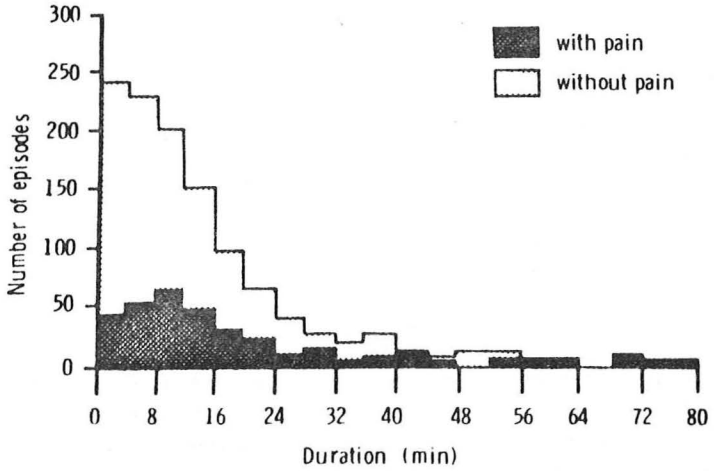


Fig 1—Histogram showing duration of symptomatic and asymptomatic episodes of ST depression.

Duration of episodes varied from 1 to 90 min and there was wide overlap between two groups.

FIGURE 3

episodes that are asymptomatic; more than 60% of the severe episodes (ST-segment depression 0.3mV or greater) were silent.(26)

The overall physiological importance and prognosis of asymptomatic myocardial ischemia remains to be determined, but it is now clear that symptomatic myocar dial ischemia represents only "the tip of the iceburg."

3. The Diagnostic Power Of The History And Other Clinical Factors

Despite the difficulties many patients have in describing their chest pain symptom complex, the history alone is an extremely powerful diagnostic tool. Simply being able to classify the symptoms as "typical angina", "atypical angina" or "noncardiac chest pain" allows one to develop a reasonable estimate of the likelihood of CAD. The largest study of the predictors of CAD severity is the Coronary Artery Surgery Study (CASS).(32) In this multicenter study, 20,391 patients underwent coronary arteriography after their chest pain had been classified as typical angina, atypical angina or nonanginal chest pain. Typical angina was defined as a substernal pain relieved within 10 minutes by rest or nitroglycerin. Most patients with typical angina had pain that radiated to the arms or jaw. Patients were classified as having atypical angina when their pain lacked a few of these features, had atypical radiation or took longer to resolve after rest or nitroglycerin. Nonanginal pain did not conform to either of the above descriptions. In the men of the entire study population, the prevalence of CAD was 0.14 in those with nonanginal chest pain, 0.66 in those with atypical chest pain and 0.93 in those with typical angina. A similar relationship

was observed in women, but age and gender modified the prevalence somewhat. (TABLE 3) In general, the prevalence of CAD in women was lower than in men,

PREVALENCE OF CAD IN SUBGROUPS OF PATIENTS

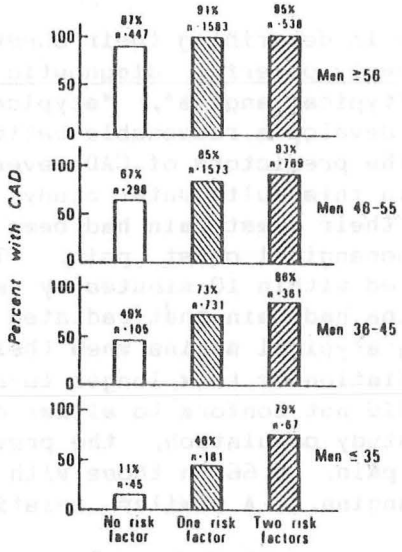
HISTORY TYPE	AGE < 50 yr MEN	AGE < 50 yr WOMEN	AGE > 50 yr MEN	AGE > 50 yr WOMEN	AGE < 70 yr MEN	AGE < 70 yr WOMEN
TYPICAL ANGINA	.87	.59	.95	.74	.93	.72
ATYPICAL ANGINA	.54	.30	.73	.37	.66	.36
NONANGINAL PAIN	.08	.04	.20	.07	.14	.04

Adapted from Chaitman et al (32)

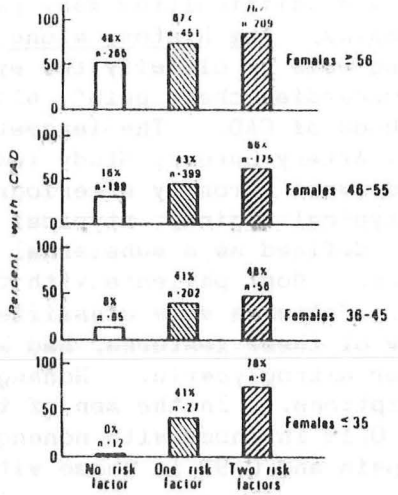
TABLE 3

even when those with similar chest pain syndromes were compared. The explanation for this is not known, but the history may be inherently less predictive in women. Alternatively, since these data were derived from arteriography, the relatively low prevalence of CAD in women with typical angina may simply reflect the low overall prevalence of CAD in women who are referred for coronary arteriography. In the CASS patients, age, sex and the history also predicted the severity of CAD.(32) Typical angina, male gender and increasing age tended to predict left main and/or multivessel CAD. In this publication, the CASS investigators did not evaluate the effect of other known cardiac risk factors on the prevalence of CAD. In a separate study derived from the CASS data, the effect of 14 separate risk variables on the likelihood of CAD was determined by a discriminant function analysis.(33) Age, sex, cigarette smoking and blood cholesterol level best distinguished between the groups with and without CAD. A family history of CAD and the presence of hypertension or diabetes were of additional, but less discriminating value. Figure 4 shows the effect of smoking

FIGURE 4



Percentage of males with coronary artery disease (CAD) by age group, with no risk factors, one risk factor and both risk factors (smoking and high cholesterol level).



Percentage of females with coronary artery disease (CAD) by age group, with no risk factors, one risk factor and both risk factors (smoking and high cholesterol level).

and elevated cholesterol on the likelihood of coronary artery disease for men and women in different age groups. Unfortunately in this study, the type of chest pain history was not considered in the determination of the likelihood of CAD. Generally, the effects of risk factors are more notable in younger individuals.

A more comprehensive approach involves utilization of multivariable statistical methods. These methods identify independent predictors of disease, weight each according to its predictive power and specify how the predictors are used to estimate the probability of disease in an individual patient.(34,35) Goldman et. al. (34) found that typical angina, significant Q-waves on a resting ECG, male gender, clinical history of acute myocardial infarction, cigarette smoking, hypercholesterolemia and age were all independent predictors. The prediction formula these investigators developed is depicted below.

CLINICAL PREDICTOR	ASSIGNED WEIGHT
1. Is the chest pain typical for angina?	1.79
2. Does the ECG have Q-waves thought to be diagnostic of an old MI?	1.50
3. Is the patient male?	1.54
4. Does the patient have a clinical history of acute MI?	1.60
5. Has the patient smoked at least 1/2 pack/day in the past 5 years?	0.75
6. Serum cholesterol level	0.009mg/dl
7. Age	0.067/yr

To estimate the prevalence of CAD, take the sum of the weights of any of the first five factors that are present. Add this sum to the serum cholesterol level times its weight plus the patient's age times its weight. Subtract 7.6234. Call this number A.

$$\text{Prevalence of CAD} = \frac{1}{1 + e^{-A}},$$

where e is the base of the natural logarithm.
An example of this computation is given below:

Suppose the patient is a 60-year-old man with typical angina who has smoked at least half a pack of cigarettes daily for the past five years and has a serum cholesterol level of 250mg/dl. There is no evidence of myocardial infarction by history or on the resting ECG. Calculate the sum of the weights as follows:

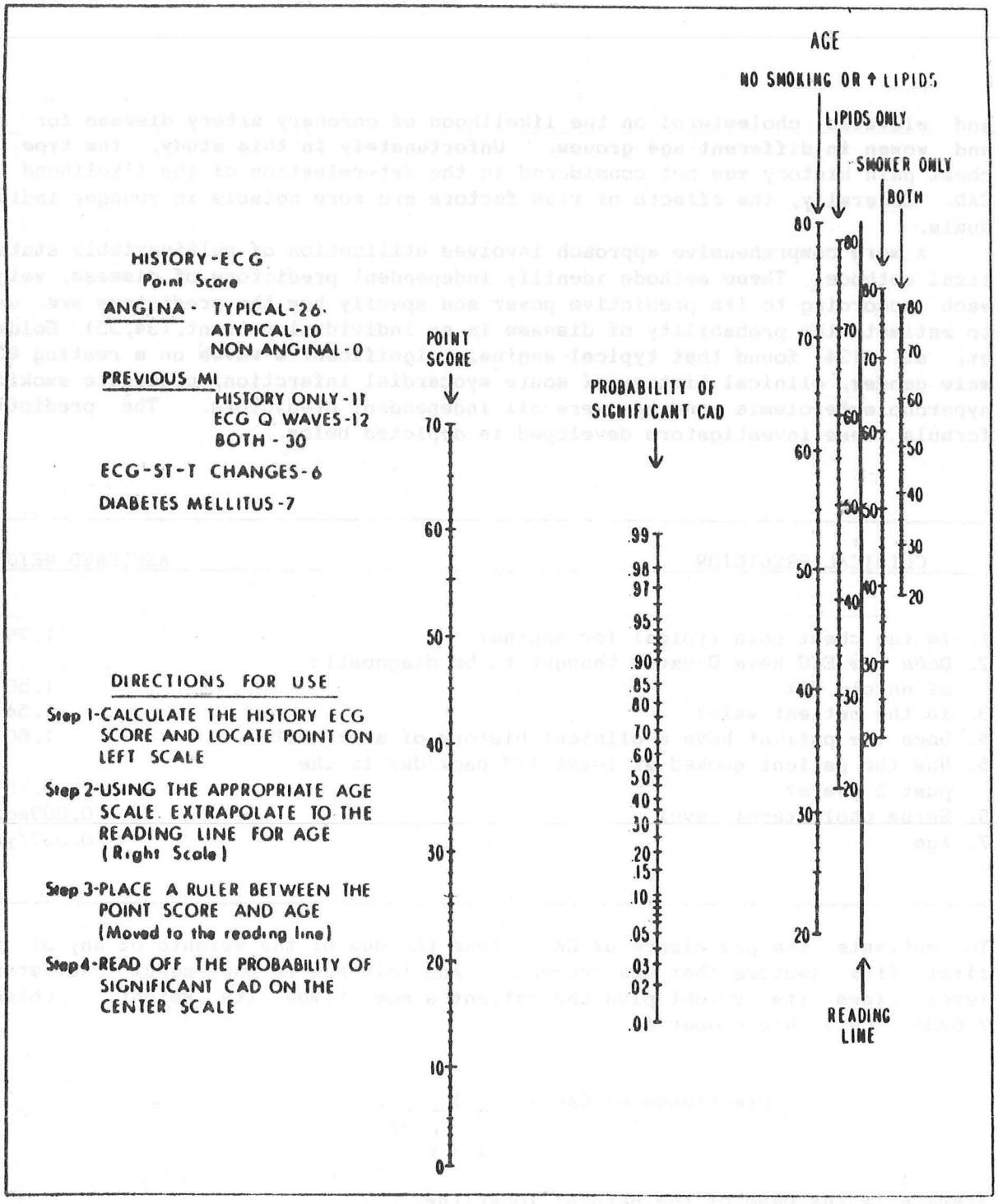


FIGURE 5: A nomogram for estimating the likelihood of significant CAD in men.

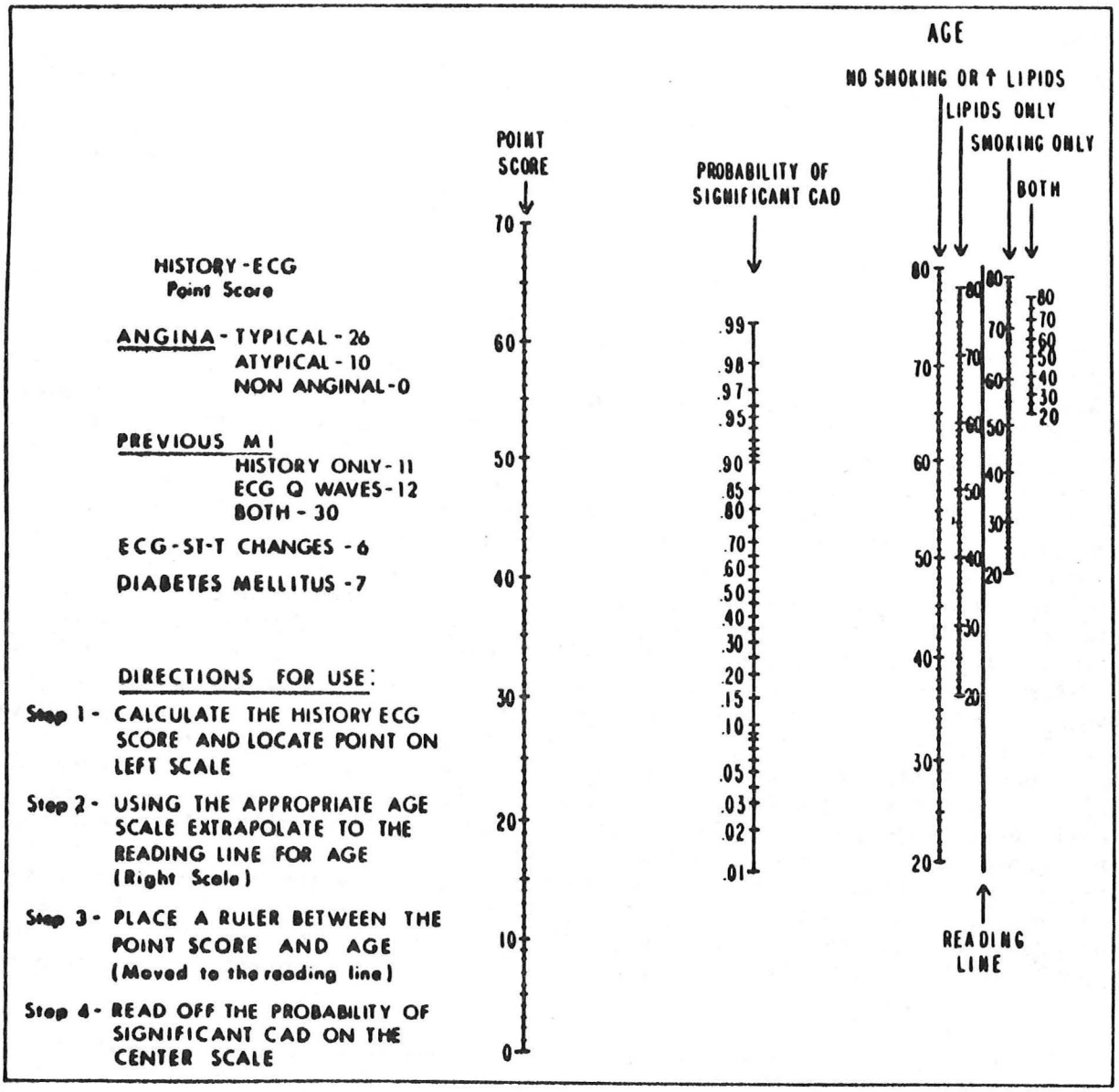


FIGURE 6: A nomogram for estimating the likelihood of significant CAD in women

CLINICAL FINDING			ASSIGNED WEIGHT
Typical angina			1.79
Male gender			1.54
Cigarette smoking			0.75
	Serum cholesterol, 250mg/dl x 009/mg/dl	=	2.25
Age, 60 years	60 years x 0.067/yr	=	4.02
	Sum of weights	=	10.35

Subtract 7.6234 from the sum of weights = 2.72 = A

$$\text{Prevalence of CAD} = \frac{1}{1 + e^{-A}} = \frac{1}{1 + e^{-2.72}} = 0.938$$

Thus, in this patient the likelihood of CAD based on these clinical factors is 94%. More recently, Pryor et. al. have developed a nomogram for estimating the likelihood of CAD based not only on the type of chest pain (i.e. typical, atypical or noncardiac), but also evidences of a previous myocardial infarction and the presence or absence of certain coronary risk factors.(35) These nomograms (FIGURES 5 and 6) were developed from the clinical and arteriographic findings in 3627 consecutive symptomatic patients and subsequently tested prospectively in another 1811 patients. Diamond and Forrester took a different approach to using multiple predictors.(36) They treated each predictor as a test with its own sensitivity and specificity. Starting with the prevalence of disease in patients with one finding (e.g. type of chest pain history) as the pretest likelihood of disease, they used Bayes' theorem (to be discussed later) to calculate the probability of disease corresponding to a second finding (e.g. gender). Then, using the probability of disease with these two findings as the pretest likelihood, they again used Bayes' formula to calculate the probability of disease related to a third finding (e.g. age). In this way, they were able to calculate the probability of disease in patients according to age, gender, chest pain history and certain other findings. Specifically, they determined the prevalence of angiographically proven coronary artery disease in 4952 patients collected from 17 earlier studies. The prevalence of coronary artery disease in patients with "typical angina" was approximately 90%, whereas in "atypical angina" it was about 50% and in "nonanginal chest pain" it was 16%. (TABLE 4) These data were combined with pathological information regarding the

TABLE 4

Prevalence of Angiographic Coronary-Artery Disease in Symptomatic Patients.

SYMPTOM	PROPORTION OF PATIENTS AFFECTED	POOLED MEAN ± SEP* (%)
Nonanginal chest pain	146/913	16.0±1.2
Atypical angina	963/1931	49.9±1.1
Typical angina	1874/2108	88.9±0.7

*Standard error of the per cent (see the Appendix). These values establish statistical levels of error but do not include errors due to sampling bias & other factors, which are probably of greater magnitude.

TABLE 5

Prevalence of Coronary-Artery Stenosis at Autopsy.

AGE	MEN		WOMEN	
YR	PROPORTION AFFECTED	POOLED MEAN ± SEP* (%)	PROPORTION AFFECTED	POOLED MEAN ± SEP (%)
30–39	57/2,954	1.9±0.3	5/1,545	0.3±0.1
40–49	234/4,407	5.5±0.3	18/1,778	1.0±0.2
50–59	488/5,011	9.7±0.4	62/1,934	3.2±0.4
60–69	569/4,641	12.3±0.5	130/1,726	7.5±0.6
Totals	1,348/17,013		215/6,983	
Population-weighted mean†		6.4±0.2		2.6±0.2

*Standard error of the per cent (see the Appendix).

†Population weighting was performed by use of the 1970 U.S. Census figures.

prevalence of CAD from 23,996 autopsy studies (TABLE 5) to determine the likelihood of CAD for any patient (according to age, sex and symptoms). (TABLE 6)

Pretest Likelihood of Coronary-Artery Disease in Symptomatic Patients According to Age and Sex.*

Age	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
yr	men	women	men	women	men	women
30–39	5.2±0.8	0.8±0.3	21.8±2.4	4.2±1.3	69.7±3.2	25.8±6.6
40–49	14.1±1.3	2.8±0.7	46.1±1.8	13.3±2.9	87.3±1.0	55.2±6.5
50–59	21.5±1.7	8.4±1.2	58.9±1.5	32.4±3.0	92.0±0.6	79.4±2.4
60–69	28.1±1.9	18.6±1.9	67.1±1.3	54.4±2.4	94.3±0.4	90.6±1.0

*Each value represents the per cent ±1 standard error of the per cent, calculated from the data in Tables 1 & 2 as described in the Appendix.

TABLE 6

For example based on these historical factors alone, the likelihood of CAD in a 55 year old man with typical angina is 92%. In contrast, the likelihood of CAD in a 45 year old woman with atypical angina is only 13%. To use this approach, it must be assumed that the frequency of each finding in diseased and non-diseased patients is the same regardless of which other findings are present. The assumption that these predictors are always independent of each other is probably incorrect, although the effects of this error are probably small.

Although predictive rules or tables of disease prevalence in various clinical subsets may be useful there are several unresolved issues. First, the definitions employed have not been standardized. Different investigators have not used a consistent definition of typical angina and atypical or nonanginal chest pain has been defined inadequately or not at all. Hickman et. al. (37) found that certain of these findings were present much more often in high-risk patients and from this inferred that sometimes they biased the judgment clinicians. A second potential error derives from the comparison of a given patient to the population from which the prevalence estimates were obtained. For example, referral patients may differ in many ways from patients seen in a primary care setting where the evaluation of chest pain usually begins. In general, prevalence figures are derived from patients referred for coronary arteriography. Therefore, in unselected patients, the value of the history may be lower. Nevertheless, based on the history alone one can develop a reasonable estimate of the likelihood of CAD and this will help define the proper course for further evaluation. Despite its small price tag, a careful historical assessment is the foundation upon which all other decisions should be made.

B. PHYSICAL EXAMINATION

Although the general physical examination of the patient with chronic ischemic heart disease is often completely normal, it may reveal findings that are helpful in assessing associated risk factors. The presence of systemic hypertension, xanthomas, arcus senilis (in patients less than 50) and other peripheral vascular findings all should be noted. A diagonal ear lobe crease has been reported to be more prevalent in patients with coronary artery disease (38),

however this finding is not universally accepted.(39) Retinal arteriolar changes are common in patients with CAD even in the absence of hypertension and diabetes. An abnormal light reflex is the most sensitive sign, while increased vessel tortuosity and diminished vessel caliber are more specific.(40)

The cardiac examination usually has been considered to be of little help in the diagnosis of chronic CAD, especially in the patient with only a history of angina pectoris. However, the examination can, in fact, provide useful clues to both the diagnosis of CAD and the functional state of the myocardium. The assessment of left ventricular function is of major prognostic importance and frequently is a key step in determining the direction of further evaluations.

1. Examination Of The Patient At Rest.

It is important to realize that chest pain characteristic of myocardial ischemia can occur in several other cardiac diseases. Therefore, findings indicating the presence of hypertrophic cardiomyopathy, pulmonary hypertension and aortic or pulmonic stenosis are noteworthy. Moreover, patients with severe congestive cardiomyopathies (41), mitral valve prolapse syndrome (42) and severe hypertension can have chest pain, but its description is usually somewhat atypical. In the absence of other obvious cardiac diseases, certain findings can suggest that ischemia is the basis for the chest pain. First, the presence of a papable ectopic impulse suggests anterior left ventricular dyskinesis, thus implying previous infarction. Second, a third or fourth heart sound is suggestive of ischemic heart disease, (43,44) especially if it is accentuated during a provocative maneuver like hand-grip exercise. (45) Since these sounds are related to the diastolic properties of the left ventricle, their absence does not exclude CAD, but rather suggests that the function of the LV is preserved. The specificity of a S_4 has been questioned because it is heard frequently in individuals >45 years of age (46,47). Nevertheless, many experts still believe that an unequivocal S_4 is abnormal. (43,44,48) Third, certain murmurs may be suggestive of CAD. Transient or persistent apical systolic murmurs may be present and are usually related to papillary muscle dysfunction.(44) These murmurs may be early, late or holosystolic and are more prevalent in patients with extensive CAD. Although characteristic of mitral valve prolapse, a mid-systolic click followed by a late systolic murmur can develop in patients with CAD.(49,50) Rarely, a diastolic or continuous murmur is heard and can be attributed to turbulent flow through a proximal coronary stenosis.(51)

2. Examination Of The Patient During Pain

Although it is frequently not possible to examine a patient during pain, when the opportunity does arise, it can be very enlighting. During angina, the face may appear pale or flushed and mild diaphoresis and dyspnea are common. Usually the individual prefers to be immobile, either standing still or sitting down. Gripping or rubbing the chest and arms is common. (FIGURE 7) A third or fourth heart sound may develop or be accentuated during angina (52) and the second heart sound may split paradoxically.(53) The appearance of an apical systolic murmur during angina probably represents papillary muscle dysfunction due to ischemia. Characteristically, this murmur has an "ejection" quality rather than being pansystolic. During an episode of chest pain, two diagnostic

FIGURE 7

maneuvers may be helpful in distinguishing angina from other noncardiac causes. Both a valsalva maneuver and carotid sinus pressure may result in the rapid relief of angina.(54) These maneuvers slow heart rate and reduce blood pressure as a result of increased vagal tone, diminished sympathetic tone and also may act by a central mechanism. However, both maneuvers should be performed with caution because they could contribute to bradycardia and hypotension in some patients.

C. ROUTINE LABORATORY STUDIES

Although the diagnosis of CAD cannot be confirmed by blood or urine analyses, simple laboratory tests can confirm the presence of associated risk factors. Diabetes mellitus, renal insufficiency and hyperlipidemia can be assessed easily with routine laboratory methods and are all unequivocally linked to the atherosclerotic process.(55 - 58) The prevalence of hyperlipidemia and carbohydrate intolerance are impressive, especially in younger patients. Over 90% of those under age 50 with angiographically-proven CAD have either glucose intolerance or Type II or IV hyperlipoproteinemia.(59,60) Accordingly, when evaluating a young patient with angina, great emphasis should be placed on risk factor evaluation and modification.

D. CHEST RADIOGRAPHY

1. Standard Chest Radiograph

Although the standard chest x-ray is not one of the more helpful tools for evaluating myocardial ischemia, it seldom is used to its full advantage. The most important use of the chest roentgenogram is in the evaluation of left ventricular failure. This judgment should be made primarily on the basis of the pulmonary vascularity rather than any feature of the cardiac silhouette. The plain chest film is of limited value in excluding other cardiac causes of chest

pain such as pericardial disease and aortic dissection since signs specific of these diseases are present far too seldom to be of any help. The chest film may be helpful when aortic stenosis is suspected since many patients with significant stenosis will have calcium present on a standard film.(61) Finally, the chest x-ray may reveal the cause of chest pain by suggesting the diagnosis of hiatal hernia, gallstones, pleural disease or pneumonia.

The presence of non-valvular cardiac calcification can be an extremely helpful sign. Calcium within the left ventricular wall is pathognomonic of previous myocardial infarction and need not be associated with an aneurysm.(62) Calcification may occur within the coronary arteries, but usually is not seen on the plain film unless exceptionally heavy.(63) On the standard film, the most productive area to examine is the coronary artery calcification (CAC) triangle where the left main, left anterior descending and left circumflex arteries all overlap. (FIGURE 8) Using this method, Souza et. al. were able to identify

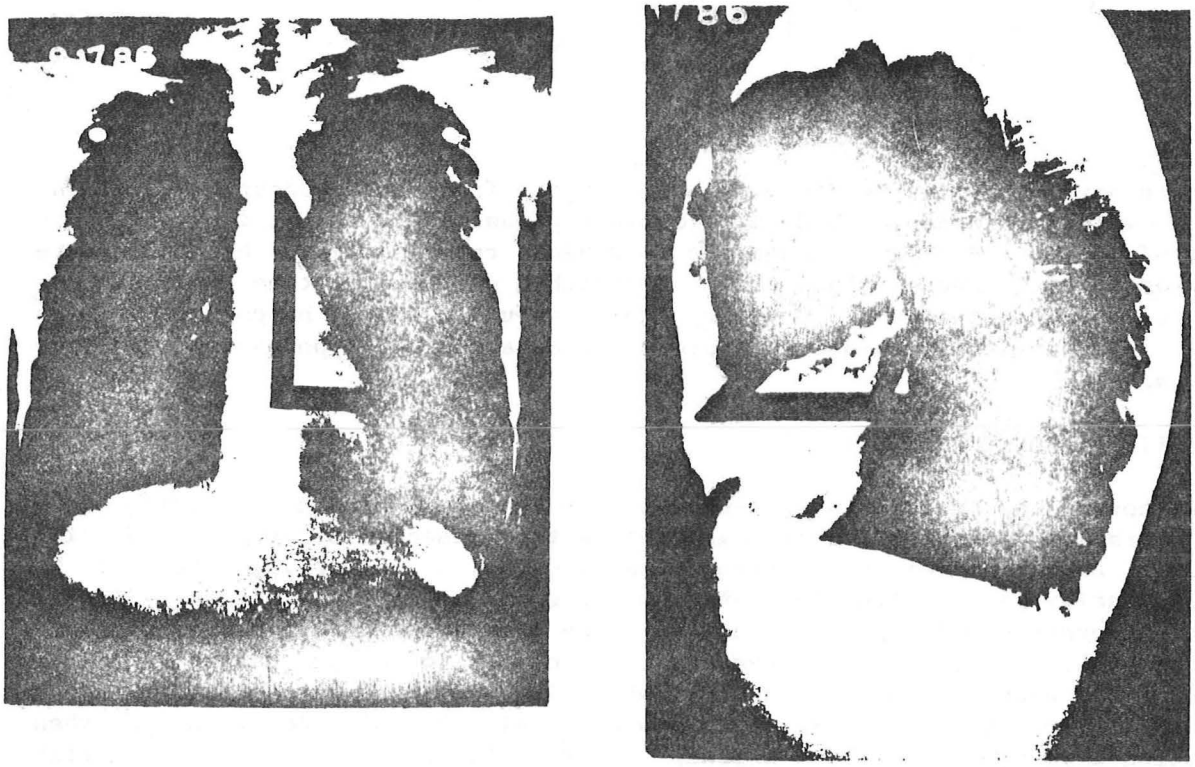


FIGURE 8

coronary artery calcification on the plain film in 42% of those with calcification detected by fluoroscopy.(64)

2. Cardiac Fluoroscopy

In contrast to the plain chest x-ray which is frequently obtained, but of limited value, cardiac fluoroscopy may be of considerable value, but is seldom used. The greatest utility of cardiac fluoroscopy lies in the detection of

coronary artery calcification. Arterial calcification can occur in two different pathological situations. In small and medium-sized muscular arteries (i.e. iliac and femoral arteries) calcification may develop in association with Monckeberg's medial sclerosis, whereas in the coronary arteries, calcification usually develops as a result of atherosclerosis. (65,66) The distinction between these two causes of vascular calcification is important because Monckeberg's medial sclerosis affects the media exclusively and never results in luminal narrowing. In contrast, calcification associated with atherosclerosis often compromises the lumen. It is not possible to distinguish these 2 forms of vascular calcification radiographically, but Monckeberg's medial sclerosis is rare in coronary arteries (67) thus, coronary calcification always implies atherosclerosis.(65) When present, coronary calcification can be located anywhere within the coronary distribution, but has a peak density between 2 and 4cm from the origin of both coronary arteries.(68) The left anterior descending artery is involved most frequently.(69)

Despite considerable evidence linking coronary calcification to the presence of coronary atherosclerosis, relatively few studies have correlated fluoroscopic with arteriographic findings.(70-73) The results of 4 such studies are summarized in Table 7. There are 2 major observations that can be made from

Sensitivity and Specificity of Coronary Artery Calcification

Study	n	Definition of Significant CAD*	Sensitivity	Specificity
Hamby (70)	500	$\geq$50%	0.76	0.78
Bartel (71)	360	$\geq$70%	0.56	0.95
Margolis (72)	800	$\geq$75%	0.40	0.93
Detrano (73)	297	$\geq$50%	0.67	0.81

*all luminal diameter narrowing

TABLE 7

these data. First, although calcification detected by fluoroscopy has a nearly perfect correlation with atherosclerosis detected pathologically, it is not a sensitive indicator of lesions that are hemodynamically important. Second, the absence of coronary calcification is a fairly good indicator of the absence of severe disease. Like any other diagnostic test, cardiac fluoroscopy requires adequate equipment and some expertise in interpretation; these obviously impact greatly on the sensitivity and specificity. When other factors such as age, sex and symptomatic status are considered the following generalizations can be made: 1) coronary calcification has a greater likelihood of indicating a significant coronary stenosis in younger age groups for both men and women; 2) coronary calcification in women is more likely to indicate a coronary stenosis than in men of the same age group; and 3) the importance of the finding of coronary calcification is greatly influenced by the symptomatic status. This latter point was emphasized by Aldrich et. al. who evaluated the utility of coronary

calcification as a screening test for CAD in patients enrolled in the NHLBI's Type II Coronary Intervention Study.(74) Table 8 lists the predictive accuracy

PREDICTIVE ACCURACY OF CORONARY CALCIFICATION*

Patient Symptoms	for a $\geq$ 50% coronary stenosis	for any degree of coronary stenosis
Asymptomatic	46%	86%
Atypical	69%	69%
Typical	96%	100%
All patients	61%	87%

*All patients had coronary arteriography

TABLE 8

(the percent of subjects with a positive test who actually had the disease) of coronary calcification in relationship to symptomatic status. Perhaps the greatest utility of cardiac fluoroscopy is when it is combined with exercise testing in asymptomatic subjects.(24,74,75) In these studies, the predictive accuracy of the combined tests for the detection of significant CAD ranged from 92-100%. Finally, the finding of coronary calcification may have some prognostic significance since Margolis et. al. (72) found a diminished survival in patients with coronary calcification even when the extent of coronary artery disease, abnormal left ventricular function and hemodynamic abnormalities also were considered.

Therefore, the fluoroscopic detection of coronary calcification can be a useful noninvasive tool in the evaluation of chest pain. Altough it is not always an accurate indicator of hemodynamically significant disease, it may be especially useful in combination with exercise testing as screening procedure in patients with few or no symptoms.

E. ELECTROCARDIOGRAM

1. The ECG at rest.

The resting electrocardiogram is normal in 25-50% of the patients with chronic stable angina, depending on the incidence of previous myocardial infarction in the group sampled.(76) Obviously, when the ECG shows evidence of a prior MI, the likelihood of obstructive CAD is extremely high, although not 100%. The correlation between the electrocardiographic pattern of myocardial infarction and obstruction of the coronary artery perfusing that segment of the ventricle is excellent.(77) When patients with a <u>known</u> prior myocardial in-

farction are excluded, the ECG is normal in approximately 60% at the time of presentation with angina.(78) The spectrum of ECG abnormalities typically present are displayed in Table 9. Patients with normal ECGs may have severe

ECG Abnormalities Present in Patients with Angina

Electrocardiographic Abnormality	% of Patients
Left ventricular hypertrophy only	3.6%
Left axis deviation only	3.1%
Prior silent MI only	4.0%
Repolarization changes only	18.4%
LBBB only	4.6%
Other single abnormality	2.0%
More than one abnormality	4.9%
Normal ECG	59%

TABLE 9

angina, but they usually have not suffered large infarctions. There are some ECG findings that may have importance with regard to the direction for additional evaluation. For example, the presence of findings suggestive of prior extensive infarction not only confirm the diagnosis of CAD, but also define the patient in whom angiography may be necessary because of a high likelihood of depressed LV function. Moreover, the presence of conduction or ST-T-wave abnormalities identify those in whom the standard exercise electrocardiogram may be impossible to interpret.

2. The ECG at rest during pain

The ability to record an ECG during pain could best be characterized by the old cliche: "One picture is worth 1000 words." The sequence of events during angina at rest have now been characterized well and, for the most part, are triggered by a primary reduction in coronary flow rather than an increase in demand.(79,80) The absolute sensitivity and specificity of ECG changes at rest for myocardial ischemia are not known primarily because there is no clear "gold standard" for the presence of myocardial ischemia. For example, in the National Cooperative Study of Unstable Angina, ECG changes were required to establish the diagnosis of unstable angina; 87% of the patients had transient ST changes and the remainder T-wave inversions. (81) While the presence of such ECG changes greatly increases the certainty of the diagnosis, their absence does not exclude ischemia as a cause for the chest pain. Patients can experience myocardial ischemia without ECG abnormalities if: a) the involved amount of myocardium is small, b) there are substantial resting ECG abnormalities, c) an inadequate number of leads are sampled, or d) ischemia in multiple areas causes a canceling of electrical forces. However, when detected, ECG abnormalities have important diagnostic and prognostic implications.

Elevation of the ST-segment during pain is caused by transmural myocardial ischemia. This may occur with or without an atherosclerotic lesion of a coronary vessel and is the hallmark of Prinzmetal's angina only when the coronary

anatomy is known or strongly implied by the clinical situation. ST-segment depression is the electrocardiographic manifestion of subendocardial ischemia and is the usual finding during pain at rest in those with chronic CAD. However, it may also occur in those with coronary artery spasm. (82) During exercise, ST-segment elevation or depression may occur. When patients with these two different findings were compared there were no differences in age, sex, history of previous myocardial infarction or angiographic features. (83)

3. The Diagnostic and Prognostic Value of the ECG

The detection of transient ST-segment deviations is highly suggestive of myocardial ischemia, but because of the variability of coronary anatomy it is not possible to predict accurately the coronary artery involved. However, two ECG findings have been found to correlate with disease of the left anterior descending or left main coronary artery. Gerson et. al. found that inversion of the U-wave was a significant predictor of severe disease in the left anterior descending or left main coronary artery (84) while others have found that the development of new anterior T-wave inversions during the course of unstable angina strongly suggest left anterior descending disease. (85,86)

Of greater importance is the prognostic significance of ST and T-wave changes during pain. Table 10 presents the results from 3 such studies. In general, those with chest pain and associated ECG changes were twice as likely to suffer a subsequent cardiac event as those with no associated ECG changes and, at least in some studies, less likely to respond to medical treatment. (88) Moreover, when treated aggressively (i.e. early coronary artery bypass surgery), the trend toward more cardiac events in those with ECG changes was abolished.

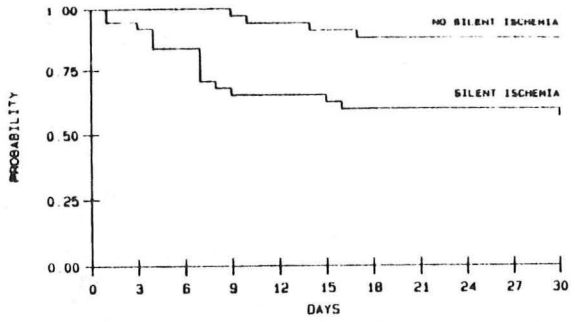
TABLE 10

PROGNOSTIC SIGNIFICANCE OF EKG ABNORMALITIES

STUDY	n	Follow-up (months)	ECG Abnormalities		Outcome			
Haines (85)	118	16	T-wave inversion	+	38% had an event			*
				-	16% had an event			
					AMI	DEATH	EITHER	
Granborg (86)	127	31	T-wave inversion	+	17%	24%	31%	
				-	8%	12%	19%	
					*	*	*	
Lindberg (87)	81	12	ST $\geq$ 0.1mV	+	26% had an event			*
				-	26% had an event			
			ST + T $\geq$ 0.1mV	+	56% had an event			*
				-	11% had an event			

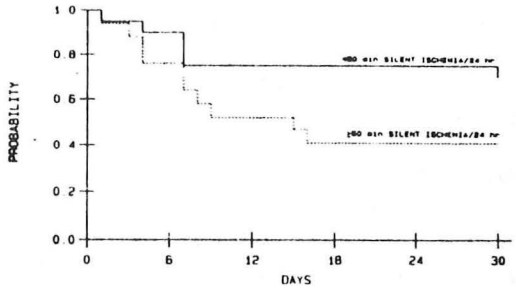
Abbreviations: AMI = acute myocardial infarction; ST = ST-segment depression; T = T-wave inversion. * = significant difference at least $p < 0.05$

(85) The potential importance of ST-segment changes even in the absence of chest pain was highlighted recently by Gottlieb et. al. (89) Seventy patients with unstable angina had continuous ECG monitoring (i.e. Holter monitors) and subsequently were separated into those with or without silent ECG changes. Those with changes were more likely to suffer a MI or required coronary revascularization by either surgery or angioplasty. (FIGURES 9 and 10) In summary, an ECG, especially if it is obtained during pain, can be extremely useful not only for diagnosis, but also for prognosis.



Kaplan–Meier Curves Comparing the Cumulative Probabilities of Not Experiencing Myocardial Infarction or Revascularization for Recurrent Angina during a Period of 30 Days for the 37 Patients with Silent Ischemia (Group 1) and the 33 Patients without It (Group 2), as Detected by Continuous Electrocardiographic Monitoring (P<0.002).

FIGURE 9



Kaplan–Meier Curves Showing the Cumulative Probabilities of Not Experiencing Myocardial Infarction or Revascularization for Recurrent Angina during a Period of 30 Days in the Patients with Silent Ischemia, Comparing the Patients with Less Than 60 Minutes of Silent Ischemia per 24 Hours and Those with More Than 60 Minutes per 24 Hours during the Two Days of Electrocardiographic Monitoring (P = 0.04).

FIGURE 10

F. ECHOCARDIOGRAPHY

Although the echocardiogram is generally not considered the primary test to evaluate patients with chest pain, it can provide useful ancillary information and occasionally confirm the diagnosis. Echocardiography is an excellent noninvasive method to evaluate valve motion, thus in the patient with chest pain and a murmur, the echocardiogram may confirm the presence of aortic stenosis or hypertrophic cardiomyopathy. When a mitral regurgitant murmur is present, the echocardiogram, coupled with a doppler study, can assess mitral valve motion, left atrial size, left ventricular function and provide a semiquantitative evaluation of the severity of regurgitation.

The principal value of echocardiography in patients with ischemic heart disease is determining the consequences of coronary stenoses. The presence of diseased coronary arteries is determined indirectly by the motion of various segments of the left ventricle. (90) For example, abnormal motion of the interventricular septum suggests an obstruction of the left anterior descending coronary artery. (91) Obviously, such indirect evidence is relatively insensitive, since the interventricular septum may move normally despite obstruction of this artery. The ischemic segment may be hypokinetic, akinetic or dyskinetic and the involved wall may exhibit diminished systolic thickening. (92) This latter finding may be a more accurate indicator of ischemic damage than a wall motion abnormality. (93) Myocardial scars resulting from old infarcts tend to be thinner and denser (more echo-producing) than nonscarred muscle; they do not thicken during systole, as normal tissue does nor do they become thinner during

systole as is the case for acutely ischemic myocardium (94,95) In this respect, echocardiography may be particularly helpful when there is an undocumented history of MI or the ECG cannot corroborate the diagnosis. In this circumstance, the demonstration of a segmental wall motion abnormality is strongly suggestive of coexistant coronary artery disease. Two-dimensional echocardiography can provide an assessment of LV volumes and function and, thus provide information that has prognostic importance. (96-98) Occasionally, obstructive lesions in the left main coronary artery and very proximal right coronary can be detected with 2D-echocardiography, but these techniques are tedious, requiring a frame-by-frame analysis of the study. (99-101) The use of echocardiography to detect coronary artery lesions has not achieved widespread acceptance and its proper role in the management of patients has not been defined. More recently, several investigators have attempted exercise echocardiography as a diagnostic technique, but experience with this methodology is still too limited to recognize its full utility. (102)

G. STANDARD EXERCISE TESTING

Exercise tests (ETTs) can be very useful in patients with suspected CAD, but there is no consensus about how they should be used. Some advocate routine testing for stable angina and periodic screening in asymptomatic subjects (103) while others would reserve these tests for subgroups of patients who are most likely to benefit from them. (104,105)

1. Understanding the use of the ETT

The framework for the proper use of exercise testing is based on probability theory. The uncertainty about whether a patient has a disease may be expressed as the probability of disease. When the physician is certain, the probability of disease is either very low or very high. When one is uncertain, the probability of disease is intermediate. To be useful, the results of a diagnostic test should alter the probability of disease, hopefully to the point that the physician is confident of the diagnosis. Probability theory provides a tool, Bayes theorem, for estimating the effect of new information, such as the result of an exercise test, on the probability of CAD. (106) Bayes theorem basically states that, although the reliability of a less than perfect diagnostic test is defined by the tests' sensitivity and specificity, the test cannot be interpreted adequately without reference to the prevalence of the disease in the population under study. (For a complete definition of terms such as sensitivity, specificity, prevalence, etc... see the Appendix) This derives, in part, from the fact that unless the test is perfect, a finite proportion of normal subjects, will manifest an abnormal (false-positive) response and some abnormal subjects will not be identified by the test (false-negative response). Therefore, the predictive value of a positive test is diminished to an extent that is partly related to the proportion of normal subjects in the population to be tested. Table 11 lists the sensitivity and specificity of maximal or near maximal exercise testing for the diagnosis of coronary disease from several early studies (107-114) As evident from the table, the sensitivity is about 0.70 and specificity about 0.90.

TABLE 11

Sensitivity and Specificity of Exercise Testing for CAD

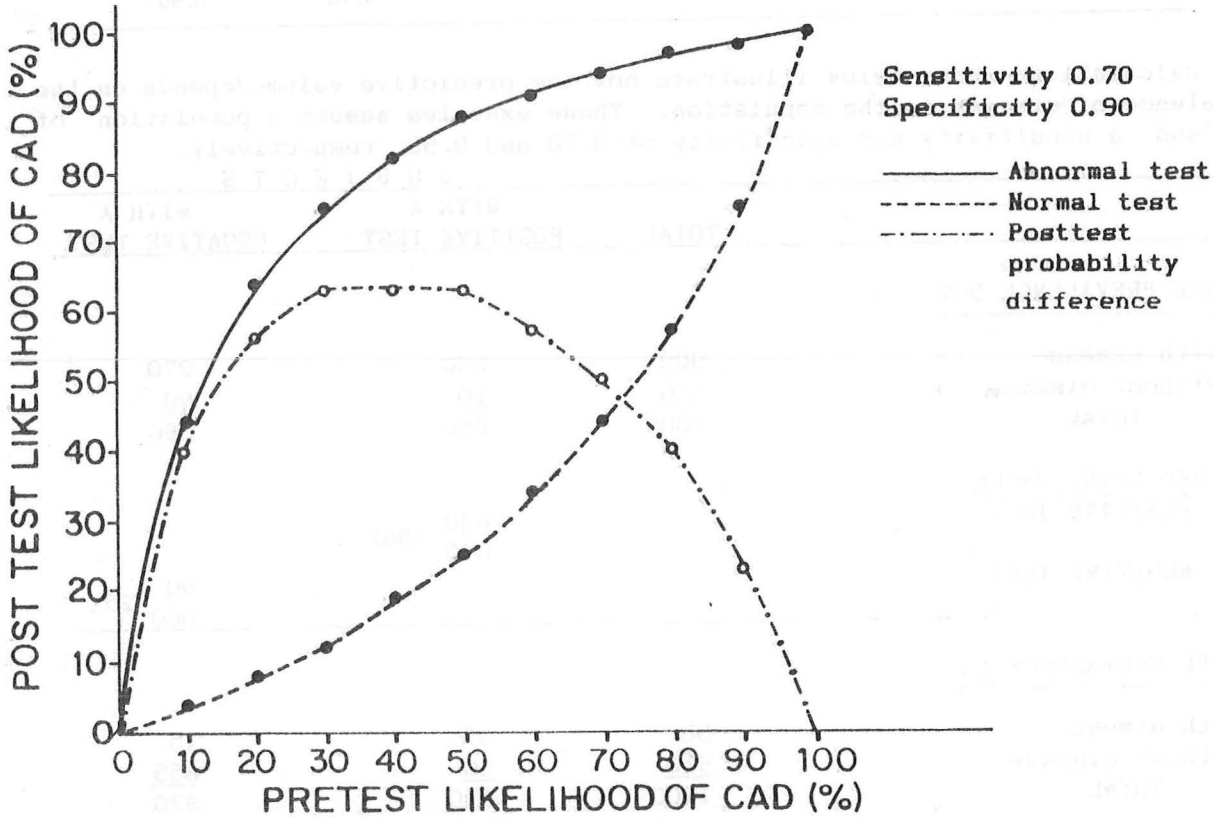
Study	Year	Patients with disease	Patients without disease	SENSITIVITY	SPECIFICITY
Roitman (107)	1970	30	16	.80	.88
Martin (108)	1972	63	37	.62	.89
Keleman (109)	1973	48	24	.54	.96
Bartel (110)	1974	258	123	.64	.91
Linhart (111)	1974	71	47	.80	.89
Rios (112)	1974	29	21	.83	.90
Piessens (113)	1974	40	30	.65	.83
Goldschlager (114)	1976	269	141	.64	.91
Approximate Mean				0.70	0.90

The calculations shown below illustrate how the predictive value depends on the prevalence of disease in the population. These examples assume a population of 1000 and a sensitivity and specificity of 0.70 and 0.90, respectively.

		SUBJECTS	
	TOTAL	WITH A POSITIVE TEST	WITH A NEGATIVE TEST
DISEASE PREVALENCE 90%			
With disease	900	630	270
Without disease	100	10	90
TOTAL	1000	640	360
PREDICTIVE VALUE			
POSITIVE TEST		$\frac{630}{640}$ =98%	
NEGATIVE TEST			$\frac{90}{360}$ =25%
DISEASE PREVALENCE 5%			
With disease	50	35	15
Without disease	950	95	855
TOTAL	1000	130	870
PREDICTIVE VALUE			
POSITIVE TEST	$\frac{35}{130}$ =27%		
NEGATIVE TEST			$\frac{855}{870}$ =98%

As illustrated above, if the ETT is used to evaluate a population (or an individual patient) with a low likelihood of disease, a "positive" test result raises the chance of disease from 5% to only 27%. If the identical test result were found in a person or population with a 90% likelihood of CAD (e.g. a middle-aged male with typical angina), the likelihood of CAD would increase to 98%. Likewise, the predictive value of a negative test is related to the disease prevalence, but this relationship is the inverse of that seen with a positive test. Therefore, in the patient who has a high or low likelihood of CAD a "positive" or "negative" treadmill test result will add little to the prediction derived from the history above. Comparing highly symptomatic to asymptomatic subjects is an extreme example of Bayes theorem. Figure 11 illustrates the complete spectrum of the effects that disease prevalence has on the usefulness of the ETT. As illustrated by this figure, the greatest utility of the ETT occurs in patients with intermediate likelihoods of CAD (i.e. pretest probabilities from 0.20 to 0.70)

FIGURE 11



The modern era of ETT interpretation began with Rifkin and Hood.(115) They used Bayes theorem to demonstrate that the usefulness of the stress ECG depends on the pretest risk of the disease. They proved their hypothesis by showing that the calculated and observed posttest risks were in close agreement. Subsequently, Diamond and Forrester amplified this concept by incorporating age,

gender, chest pain history and cardiac risk factors into the assessment of the pretest risk of CAD.(36) Using this conceptual framework it becomes clear that the results of an ETT are not properly expressed as a "yes or no" diagnostic statement, but rather as a probability estimate of the likelihood of CAD.(105)

2. End-points of the ETT

The ETT has many outcomes that are helpful in the evaluation of patients with CAD, not only from a diagnostic, but also a prognostic viewpoint.

a. The ST-segment: The degree of ST-segment depression has been combined with its configuration, time of onset and persistence after treadmill testing to increase the sensitivity and specificity of the test. Figure 12 demonstrates

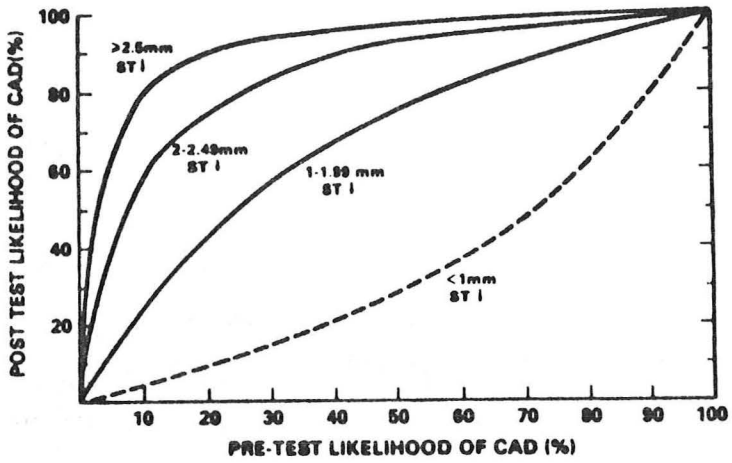


FIGURE 12: The diagnostic power of ST-segment depression depicted according to the magnitude (in mm) and the pretest likelihood of CAD.

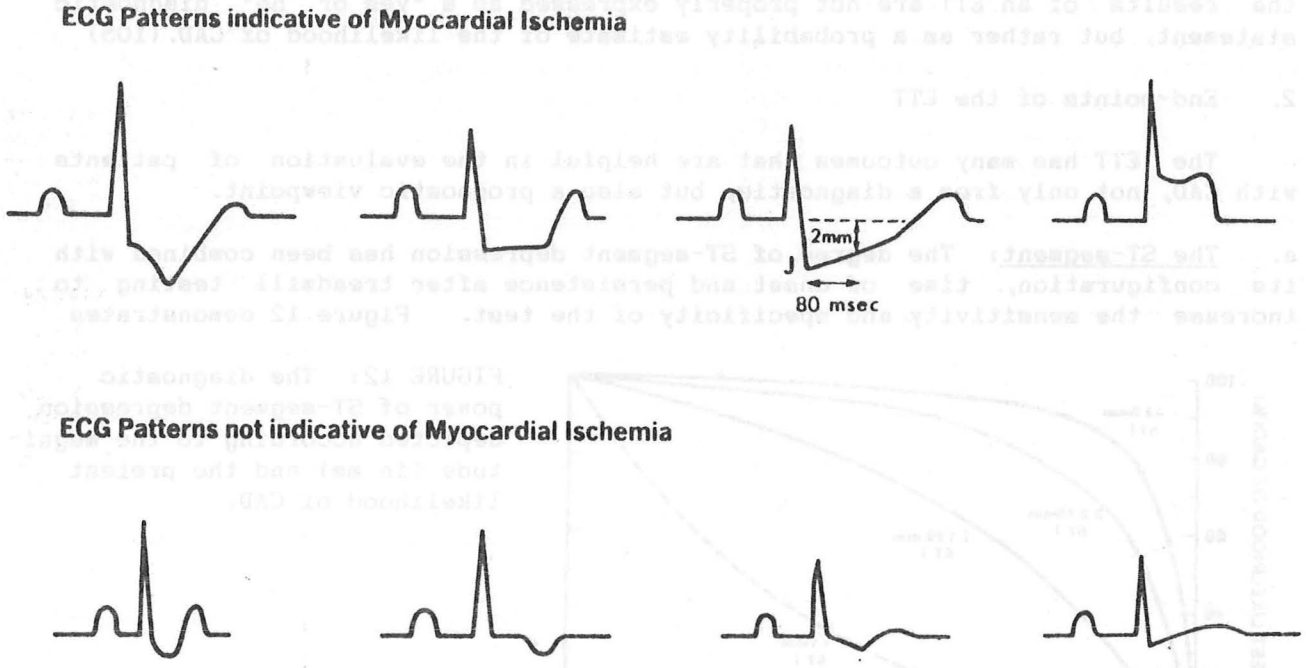
the effect of increasing degrees of ST-segment depression on the diagnostic power of the ETT. The greater the displacement of the ST-segment from its resting position, the greater the likelihood that the patient has CAD. Requiring the presence of a greater amount of ST-segment depression to consider the test "positive" results in a lower sensitivity, but higher specificity as seen below:

ST-SEGMENT DEPRESSION (MM)	SENSITIVITY	SPECIFICITY
0.5	0.80	0.60
1.0	0.60	0.90
2.0	0.20	0.98

Adapted from reference 108

The number of electrocardiographic leads monitored during the test also affects the sensitivity and specificity (116). As the number of leads used increases from 1 to 12, the sensitivity increases from 56% to 76% while the specificity decreases from 94% to 82%.

The appearance of the ST-segment also is helpful in characterizing the probability of CAD and its severity. Figure 13 depicts alterations in the ST-



Electrocardiographic criteria for myocardial ischemia consist of at least 1 mm of J point depression with downsloping or horizontal ST segments; slowly upsloping ST segment depression, defined as 2 mm of ST depression measured 80 ms from the J point; and ST segment elevation. Whereas ST segment depression indicates nontransmural ischemia, ST segment elevation often connotes more severe degrees of ischemia reflecting transmural injury. The structure of the ST segment slope is predictive for the severity of coronary disease shown angiographically (5), with downsloping ST depression indicating severe two- and three-vessel coronary artery disease more often than does either horizontal and slowly upsloping ST depression, and ST segment elevation indicating high-grade, usually proximal, arterial obstruction in patients without previous myocardial infarction.

FIGURE 13

segment that are or are not indicative of myocardial ischemia. The electrocardiographic criteria for myocardial ischemia consist of: a) at least 1mm of J point depression with a downsloping or horizontal ST-segments; b) slowly upsloping ST-segment depression, defined as 2mm of ST-segment depression measured 80ms from the J point; and c) ST-segment elevation. (117) The structure of the ST-segment slope can be related to the severity of coronary disease shown by arteriography, with downsloping ST depression indicating 2 and 3 vessel CAD more often than does either horizontal or slowly upsloping ST depression. (FIGURE 14)

FIGURE 14

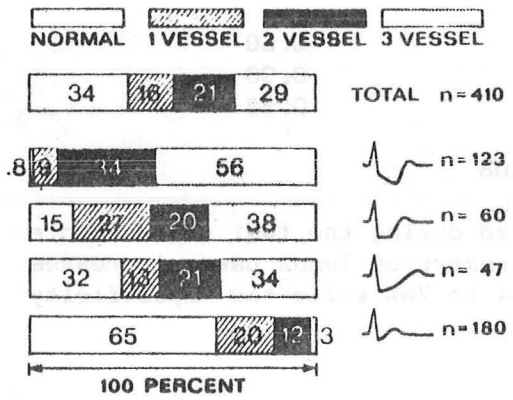
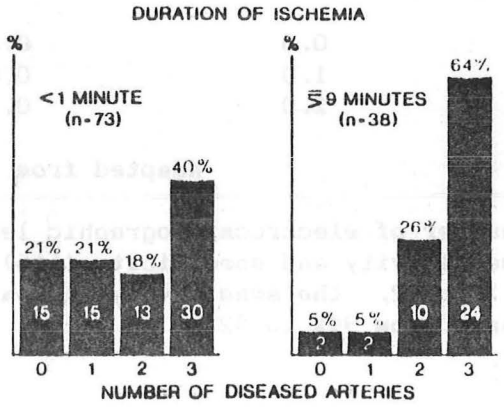


FIGURE 15



A variety of explanations have been offered for ST-segment elevation during the ETT. These include severe transmural myocardial ischemia, a worsening segmental wall motion abnormality in the area of a previous myocardial infarction and exercise induced coronary spasm in patients with variant angina (118). In the absence of a prior MI or suspected coronary artery spasm, exercise induced ST-segment elevation is usually associated with a high-grade proximal coronary lesion.

The persistence of ST-segment changes past 9 minutes into recovery is associated with double or triple-vessel disease in 90% of the patients; 64% having 3 vessel CAD. Whereas, the lengthy duration of ischemic changes in the recovery period suggests more extensive CAD, the converse is not true, in that short-lived ischemic changes are also seen in severe disease.(114) (FIGURE 15)

b. The R-wave amplitude: R-wave amplitude increases during exercise in some patients with severe ischemia.(119-120) This effect was first suggested by Brody who, using a theoretical model, determined that R-wave amplitude was related to the volume of the heart (121) That is, larger heart volumes would be associated with larger R-wave amplitudes. Ellestad emphasized that R-wave amplitude increased when severe ischemia was caused by infarction, spasm or exercise and, when it occurs, a large amount of myocardium is probably involved.(122) Bonoris et.al. found that 90% of young healthy subjects had the expected reduction in R-wave amplitude during exercise.(123) By using R-wave amplitude changes, they were able to increase the sensitivity and specificity of the exercise test. However, 14% of the healthy subjects who did not have ST-segment depression had an increase in R-wave amplitude and 25% of those with CAD and ST-segment depression had a decrease in R-wave amplitude.

c. Exercise-induced ventricular arrhythmias: Exercise-induced ventricular arrhythmias are common during ETTs and may mandate the premature termination of the test. Although serious exercise-induced ventricular arrhythmias identify patients at high risk of sudden death (124), their use as an adjunct to the diagnosis of CAD is questionable.(125,126) McHenry et.al. (127) and Froelicher et.al. (128) have both reported that the presence of exercise-induced VPBs could not accurately identify patients with heart disease from a selected population of actively employed policemen and airmen, respectively. Patients with symptoms and exercise-induced arrhythmias have a greater incidence of prior infarction, multivessel disease and abnormal ventricular contraction patterns.(126) More important however, is the prognostic importance of exercise-induced ectopy. Of 6500 patients followed for 5 years after an ETT, cardiac death occurred in 1.7% of those without VPBs or ischemic changes, 6.4% of these with VPBs alone and 11.4% of the patients with VPBs and ischemic changes.(129)

d. Exercise duration: The relationship between exercise capacity, ST-segment response and coronary disease was most clearly delineated in a study of 1472 patients who underwent ETTs and coronary arteriography.(130) Although the ST-segment was a better indicator of CAD, 71% of patients who could not exercise beyond stage I of a standard Bruce protocol had significant CAD and 39% had disease of all 3 major vessels. The prevalence of a > 50% obstruction of the left main coronary artery was 16% in those who could not complete stage I. However, treadmill stage did not correlate well with the absence of CAD since

47% of those who achieved stage IV or higher had significant CAD. These findings were confirmed by Goldschlager et.al. (114) as seen below:

# of diseased arteries	Time to Onset of Ischemia (% of patients tested) STAGE I n = 59	STAGE II - IV n = 23
0	3%	17%
1	10%	22%
2	31%	35%
3	56%	26%

Although the time to onset of ischemia rather than actual treadmill duration was assessed, the important point is the same: 87% of those with the onset of ischemia in stage I had 2 or 3 vessel CAD.

e. Exercise - induced hypotension: The normal response to upright exercise consists of a progressive increase in heart rate and systolic blood pressure (131,132). A decrease in systolic blood pressure during stress occurs most often in patients with severe CAD and acute ischemic LV dysfunction (133,134), but occasionally has been seen in: 1) patients with cardiomyopathy (135), 2) patients (especially women) without CAD (136), and 3) during prolonged strenuous exercise (137). Morris et.al. (134) determined the prevalence of exercise-induced systolic hypotension (defined as a 10mmHg decrease on 2 successive determinations) in 1020 subjects from 2 different sources: 560 clinically healthy state police officers and 460 consecutive cardiac patients who underwent both treadmill testing and cardiac catheterization. (TABLE 12) With the excep-

TABLE 12

Prevalence of Exercise - Induced Systolic Hypotension (EISH)

Subjects	n	Sex	Mean Age (Range) yrs.	with EISH no.	with EISH %
Clinically normal state police officers	560	M - 560	38(28-61)	0	0
		F - 0		-	-
Chest pain, but no significant CAD	159	M - 89	47(28-68)	1•	0.6
		F - 70	50(17-68)	0	0
Significant CAD	279	M - 242	51(18-69)	22	7.9
		F - 37	54(35-69)	0	0
Noncoronary heart disease	22	M - 17	43(30-61)	3	13.6
		F - 5	47(43-50)	0	0

• The only patient in this study receiving methyldopa and propranolol at the time of study

TABLE 13

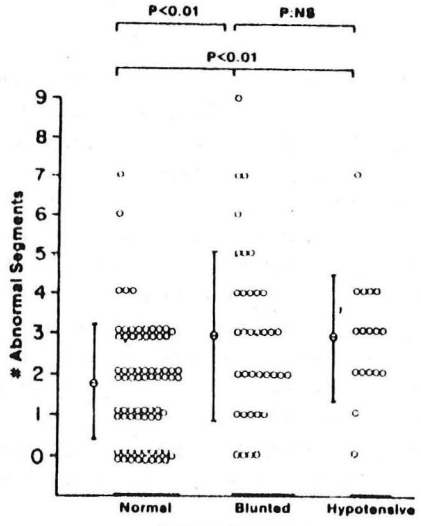
Incidence of Exertional - Hypotension In Patients With CAD

Study	n	Coronary Artery Disease 1 vessel	2-3 vessel	Left main
Morris (134)	279	0/90	22/171	3/18
Levites (136)	31	4/12	8/18	1/1
Sanmarco (139)*	313	8/68	6/216	18/29
Weiner (140)	312	12/117	27/161	7/34
Hammermeister (141)	333	12/163	20/150	2/17
Hakki (142)	127	4/61	8/57	5/9
Totals	1395	40/511 (8%)	146/774 (19%)	36/110 (33%)

* Patients with a flat blood pressure response were included

tion of one subject who was receiving medications, all those with exercise-induced hypotension had cardiac disease. When patients with obvious cardiomyopathy or valvular heart disease are excluded, exercise-induced hypotension is a fairly specific sign of significant CAD. Table 13 tabulates the incidence of exertional hypotension in those with single vessel, 2-3 vessel and left main disease pooled from 6 different studies. In addition to the relationship between exercise-induced hypotension and the anatomic severity of CAD, Hakki et.al. have shown a relationship between the presence of exercise-induced hypotension and the number of abnormal segments detected by thallium-201 imaging. (142) (FIGURE 16)

FIGURE 16



Number of abnormal segments on exercise thallium-201 images in group I (Normal), group II (Blunted) and group III (Hypotensive). BP = blood pressure; Ex = exercise; NS = not significant.

Exercise-induced hypotension is one of several predictors from the ETT that has prognostic importance. The survival of 557 medically-treated patients during 5.4 years of follow-up was determined with respect to the presence or absence of exertional hypotension (141) (FIGURE 17). Those with exertional

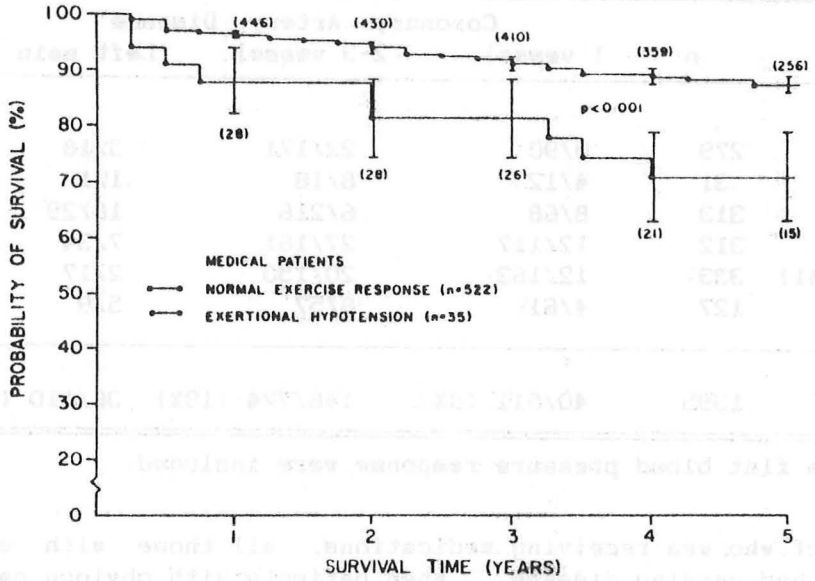
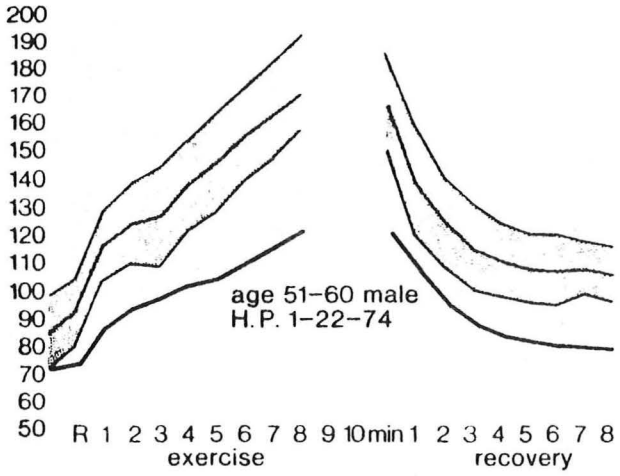


FIGURE 17

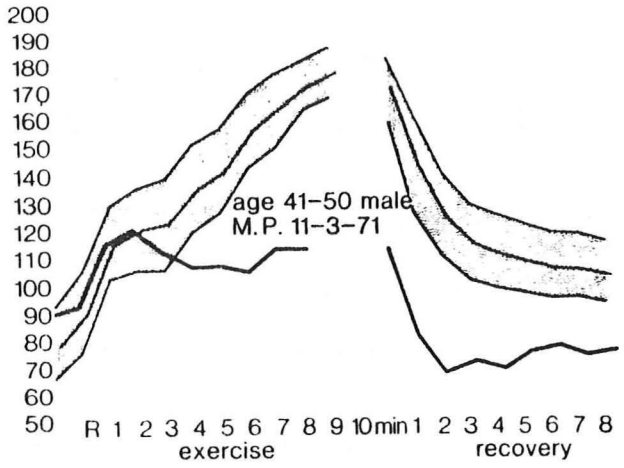
hypotension had a significantly poorer survival. This finding may be related to the more extensive CAD and LV dysfunction present in those with exertional hypotension. Weiner et.al. carried the analysis of this observation to the next step by studying 47 patients with exercise-induced hypotension who received medical treatment (n=24) or coronary bypass surgery (n=23).(140) On repeat exercise testing, a decrease in systolic blood pressure during exercise was still present in 85% of those treated medically, but entirely absent in those treated surgically. Mortality after 37 months of follow-up was 8% and 4% in the medical and surgical groups, respectively. This was not a significant difference and probably was affected by some selection bias in the choice of therapy for these patients.

f. Chronotropic incompetence: Chronotropic incompetence is defined as a pulse rate for the achieved workload that is 2 standard deviations below the 95% confidence limit of the established normal range for age and sex, in the absence of a history of endurance training or vigorous exercise program.(143) Obviously, to accurately assess this finding, the patient cannot be receiving any medication that will inhibit the heart rate response to exercise. Most coronary patients demonstrate one of three kinds of heart rate response to exercise testing. In the majority, heart rate progressively increases during exercise, just as in normals, until they are forced to stop because of angina or dyspnea. Many in this group are deconditioned due to their disease, thus the increase in heart rate occurs more rapidly than normal. In a different but smaller group, the achieved heart rate is less than predicted for age, a finding which may have significance when predicting the severity of the disease process.(144) In the final group of patients, the heart rate for achieved workload remains below

normal; these patients have true chronotropic incompetence. This is depicted graphically in figure 18. Chronotropic incompetence is a relatively rare occur-



Severe chronotropic incompetence (group 3). The heart rate response of a 52 year old man was below two standard deviations of the predicted mean.



Severe chronotropic incompetence (group 3). The heart rate pulse response of a 41 year old man shows a plateau with inability to accelerate appropriately.

FIGURE 18

rence noted in approximately 9% of all ETTs (143,145) However, when present it occurs prior to or without ST-segment depression in 12% of those tested. The exact pathophysiology for this finding is somewhat obscure, but the possibility of some form of autonomic dysfunction has been postulated. (146)

g. Chest pain: In addition to all of the other variables discussed, the occurrence of angina during treadmill testing has substantial diagnostic and prognostic importance. The presence of angina increases the likelihood that an abnormal ST-segment response is due to myocardial ischemia. When patients with only an abnormal ST-segment response during exercise have coronary arteriography, approximately 64% will have significant CAD. (147) However, when those who have both angina and ST-segment changes are studied, 85% have significant disease. Of greater importance is the prognostic significance of chest pain when it occurs during an ETT. Figure 19 demonstrates that the chance of having

FIGURE 19

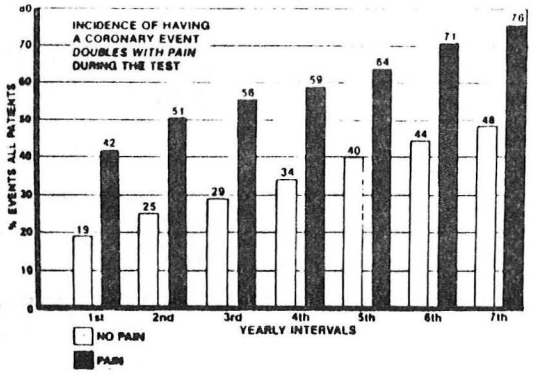
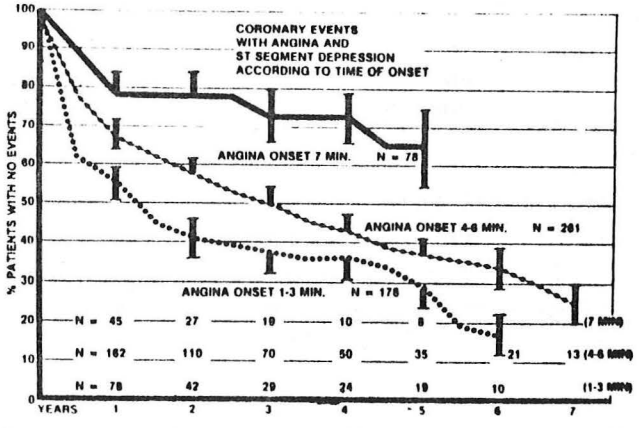


FIGURE 20



a future coronary event roughly doubles in those with angina during an ETT through 7 years of follow-up. Moreover, the time to the onset of angina is important. In general, those with the most rapid onset of angina are the most likely to have a cardiac event; this finding was less apparent in women. (FIGURE 20)

h. Exercise-induced conduction abnormalities: Exercise-induced conduction abnormalities are an uncommon event occurring about once in every 200 studies.(148) The most common abnormality is that of a left anterior hemiblock, but left posterior hemiblock, complete right bundle branch block and complete left bundle branch block have all been reported.(148-151) In many, but not all, underlying CAD is found. In these individuals the ST-segment usually becomes abnormal prior to the development of the conduction delay and subsequently, the conduction disturbance resolves when the ischemia subsides. Almost all patients with exercise-induced conduction abnormalities have the common finding of disease of the proximal left anterior descending artery with or without other lesions.

3. Problems Associated With Exercise Testing

a. The ETT in men and women: In the CASS report on exercise testing, 1465 men and 580 women underwent a graded Bruce protocol exercise test within one month of coronary arteriography.(152) Despite the type of chest pain history, the sensitivity was lower and false-positive rate higher in women. (TABLE 14) The reasons for this difference have not been defined clearly as yet, but overall exercise testing is less meaningful in women.

TABLE 14

EFFECT OF GENDER AND CHEST PAIN HISTORY
ON SENSITIVITY AND FALSE-POSITIVE RATE

Chest Pain History	SENSITIVITY	False - Positive Rate
Typical Angina		
Men	0.84	0.21
Women	0.80	0.43
Atypical Angina		
Men	0.72	0.20
Women	0.67	0.31
Nonanginal Pain		
Men	0.46	0.29
Women	0.22	0.19

From reference 152

b. False-positive results: Resting ST-segment and T-wave abnormalities increase the frequency of misleading ST-segment responses during exercise.(152) Some of the causes of a false-positive ST-segment response are listed below:

CAUSES OF A FALSE-POSITIVE ST-SEGMENT RESPONSE*

1. Resting ECG abnormalities due to digitalis or other drug therapy, left ventricular hypertrophy, Wolfe-Parkinson-White Syndrome or other preexcitation variant, electrolyte abnormality, bundle branch block or vasoregulatory asthenia.

2. Failure before exercise to exclude hyperventilation-induced ST abnormalities, recent food intake or anemia.

3. Baseline ECG instability simulating ST-segment displacement.

4. Various noncoronary cardiac disorders such as valvular or congenital heart disease, cardiomyopathy, mitral valve prolapse, hypertension and pericarditis.

*Adapted from reference 153

c. False-negative results: Without question, the most frequent cause of a false-negative ETT in a patient with CAD is an inadequate workload. When used for diagnostic purposes, the ETT should be continued until one of 4 possible end-points is achieved. These are: 1) exercise to a fixed heart rate, such as 150 beats/min (154), 2) exercise to a variable heart rate, such as 85%-90% of the age-predicted maximum (155), 3) exercise to a symptom-limited maximum tolerance (156), or 4) exercise to a physiologically documented maximal aerobic capacity (157). Although each of these end-points has some unique advantages, the two most frequently used are exercise to 85-90% of the age-predicted maximum heart rate or to a symptom-limited maximum. However, all to frequently patients terminate their ETT early because of some other factor. Claudication of the lower extremities or orthopedic problems may cause a real limitation, but in many a lack of motivation or extreme physical deconditioning cause termination before a meaningful endpoint. Hlatky et.al. examined 2269 patients who had both coronary angiography and exercise tests to determine the factors that affected the sensitivity and specificity of the ETT.(158) Of all the variables tested, maximal exercise heart rate was the most important factor affecting ETT sensitivity and the only factor that independently affected test specificity. Figure 21 demonstrates that a large number of tests were indeterminate, especially at

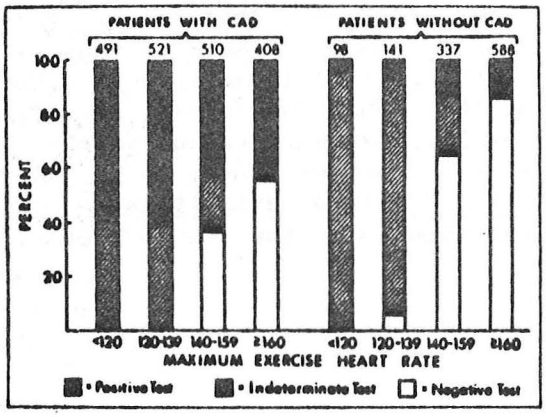


FIGURE 21: ST-segment response to exercise according to maximal exercise heart rate. The number of patients in each subgroup is indicated at the top of the column

low heart rates. All too often, physicians try to force some diagnostic value into the exercise test when none is present. An ETT that is indeterminant adds nothing to the diagnostic process. Frequently, a test that is really "nondiagnostic" is called "negative." This is incorrect. Stated in a more contemporary way: An ETT that is nondiagnostic does nothing to alter the post-test probability of disease. Although, there are circumstances where clinically useful information can be obtained from an ETT that is nondiagnostic, such an ETT cannot be used to exclude the presence of CAD.

Other factors, besides patient cooperation, may cloud the diagnostic utility of exercise testing. For example, beta-blocker therapy can obscure the interpretation of the test and impair its ability to select patients likely to have extensive CAD.(159) In the presence of beta-blockade, maximum heart rate may be blunted, exercise duration can increase or decrease and the occurrence of angina as the limiting symptom is less frequent; all these combine to limit the usefulness of the ETT as a diagnostic tool. Other studies suggest that therapy with nitrates and calcium-blockers may have a similar effect.(160)

d. The patient who cannot exercise: Many valid conditions often preclude performing an adequate treadmill or bicycle test. In these patients, dynamic arm exercise testing maybe a valuable alternative.(161-162) Although peak rate-pressure product is not significantly different, peak O_2 consumption for arm exercise is less than for leg exercise. Balady et.al. compared directly these two forms of exercise in 30 patients with CAD.(163) The results show that arm exercise is significantly less sensitive than leg exercise (FIGURE 22), with an

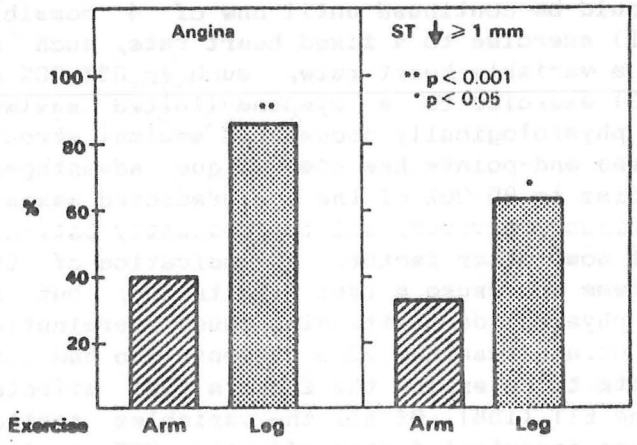


FIGURE 22: Percent of patients demonstrating an ischemic response with arm or leg exercise.

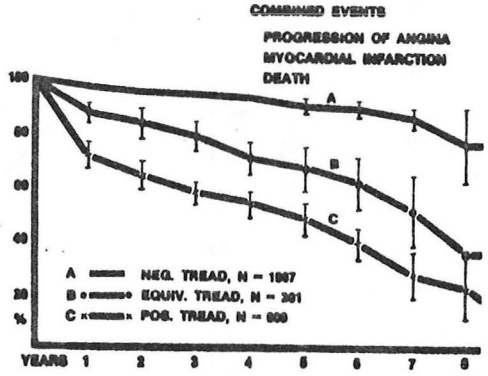
overall sensitivity of 86% for treadmill tests, but only 40% for arm-crank tests. Nevertheless, in the patient who has lower extremity impairment, arm exercise is a reasonable alternative. Unfortunately, some patients are unable to perform either type of test. In such individuals, atrial pacing has been used as an alternative form of stress.(112,164-167) This is usually accomplished by inserting a temporary transvenous pacemaker, but more recently external pacing devices have been used. As with arm-crank stress, many have felt that atrial pacing was an insensitive indicator of CAD with sensitivities as low as 20%.(112) This may be due to certain technical aspects of the methodologies

used, because when atrial pacing is continued to the end-point of either progressive chest pain, 1mm or greater ST-segment depression or 85% of the age-predicted maximal heart rate and coupled with 12 lead electrocardiographic recording, the sensitivity and specificity are comparable to that of exercise stress.(167) These results must be interpreted with some caution since most studies that compare the two techniques are performed in highly selected patients, thus extrapolation of these data to the majority of patients who present with chest pain may not be appropriate.

4. The "Early Positive" Exercise Test and Prognosis

a. Use of the ETT to determine prognosis: Until this point, our discussion has considered the utility of exercise testing to determine the presence or absence of CAD. However, not long after ETTs became used widely it was apparent that the test imparted prognostic information as well. One of the first studies to demonstrate this was that of Ellestad and Wan.(168) Follow-up data on 2700 subjects who had maximum stress tests were assembled in life tables. A positive test, defined by ST-segment depression of 1.5mm, 0.08 seconds from the J point, predicted an incidence of some new coronary event (progression of angina, myocardial infarction or death) of 9.5% per year as compared with 1.7% in those with a negative test.(FIGURE 23) The incidence of infarction or death alone also was significantly higher in those with an abnormal test. Furthermore, the importance of the magnitude of ST-segment depression and time to onset of ischemia were assessed. Although the magnitude of ST-segment depression did not affect the likelihood of future events, the time to onset of ischemia did. (FIGURE 24A and B) In those with 2mm ST depression which appeared by 3 minutes

FIGURE 23



In each figure the % of patients who remain event free is plotted vs. time

FIGURE 24A

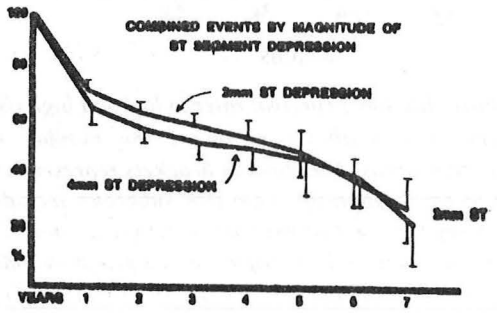
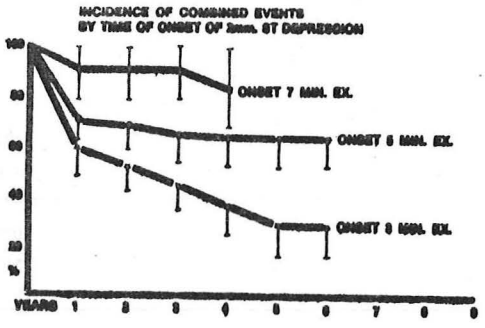


FIGURE 24B



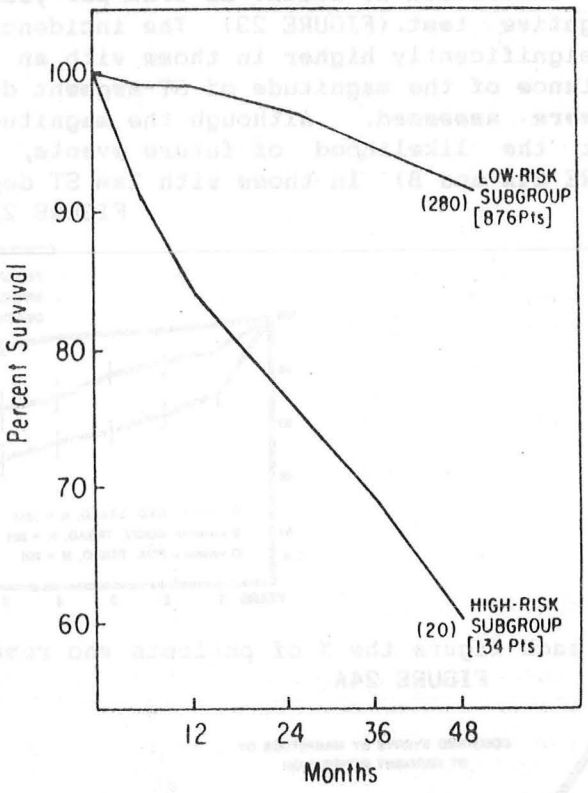
on the treadmill (a workload equivalent of 4METS), the likelihood of a future event was 15% per year, whereas it was 8% per year when the ST depression began after 5 minutes and 4% per year when it began after 7 minutes. In addition to the ST-segment response, other parameters used to characterize the patient's tolerance to exercise have been shown to be useful in predicting survival.(169-171) Although an association between treadmill performance and prognosis was established by these early studies, they did not relate these findings to coronary anatomy. This was accomplished by McNeer et.al. in a study of 1472 patients who underwent both exercise testing and coronary arteriography. (130) Almost all patients (> 97%) who had positive ETTs during Stage I or II of a standard Bruce protocol had significant CAD; many had 3 vessel disease and approximately 25% had significant (>50%) narrowing of the left main coronary artery. (TABLE 15) In contrast, patients who achieved Stage IV or greater with either negative or indeterminate ST-segment responses had a 23% prevalence of 3 vessel CAD and a 1% prevalence of left main stenosis. Utilizing a combination of exercise parameters in those patients who did not have subsequent coronary bypass surgery, the cohort could be divided into high and low risk subgroups. (FIGURE 25) Those with either a negative test, exercise duration > Stage IV

TABLE 15

Relationship of State Entered and ST-Segment Interpretation, in Combination, to Presence and Extent of Significant Coronary Artery Disease (CAD)

	CAD	3VD	>50% LMC
Stage I			
Positive (51)	98	73	27
Inadequate (34)	71	40	12
Negative (79)	52	21	10
Stage II			
Positive (159)	97	51	24
Inadequate (104)	65	27	8
Negative (186)	48	21	3
Stage III			
Positive (115)	86	41	10
Inadequate (75)	51	19	4
Negative (248)	46	11	4
≥Stage IV			
Positive (104)	77	29	5
Inadequate (37)	46	14	0
Negative (280)	36	9	1

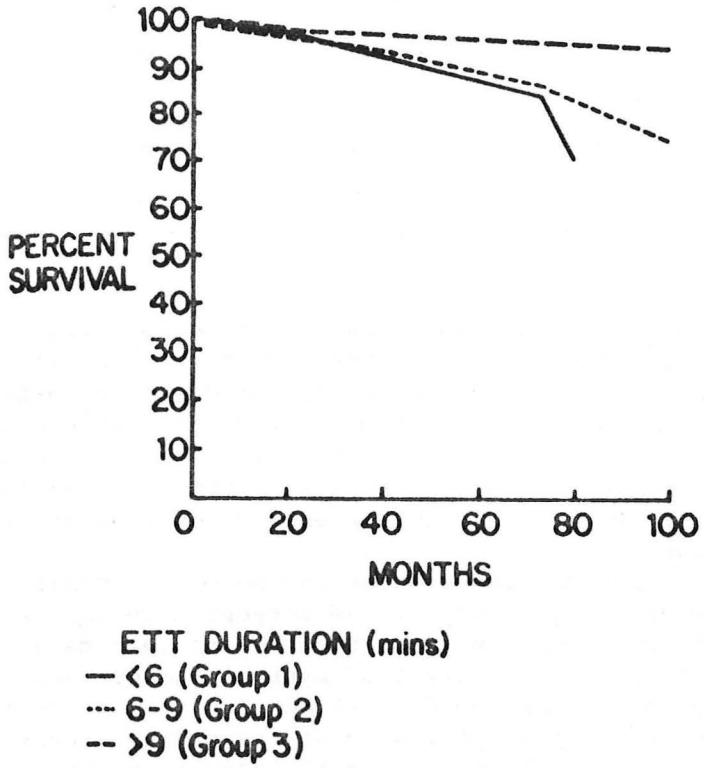
FIGURE 25



Cumulative life table survival rates in low and high risk subgroups. Numbers in parentheses represent the number of patients followed for 48 months. Numbers in brackets represent the number of patients in each subgroup. Low risk subgroup includes those patients with a negative test or exercise duration ≥ Stage IV and/or a maximum heart rate ≥ 160. High risk subgroup includes those patients with a positive test and exercise duration < Stage III.

and/or a maximum heart rate > 160 had a 94% survival after 4 years. However, in those with a positive test and exercise duration < Stage III, the survival was 85% and 63% at 12 months and 4 years, respectively. As a prognostic indicator, the most powerful of the treadmill variables in the general population is the ST-segment response, followed by exercise duration. This order is reversed in patients with known CAD. In this group, exercise duration has the highest prognostic value, after adjusting for the effects of the other variables. This finding was confirmed in a widely quoted study by Podrid et.al. which emphasized that profound (> 2mm) ST-segment depression was of lesser importance than the exercise duration in patients with CAD.(172)(FIGURE 26) This finding has been confirmed by others.(173)

FIGURE 26



Survival in Relation to Exercise Duration.

The end point was considered to be either death or surgery. There was no statistically significant difference at 80 months between survival in Groups 2 and 3; however there was a significant difference between Group 1 and Group 2 or Group 3.

b. Exercise testing to define the presence of left main and/or 3 vessel CAD: The rationale for trying to detect left main coronary disease even in those with mild angina is the improved survival such individuals have if coronary bypass surgery is performed.(174-176) As emphasized before, simple clinical descriptors can be powerful indicators of the presence of left main stenosis and should be considered prior to exercise testing. In the CASS registry, 5,347 men without unstable angina or prior myocardial infarction had an 8% incidence of signi-

ficant left main stenosis.(32) The wealth of detail made possible by the large number of patients in the CASS registry revealed some clear differences in the prevalence of left main stenosis in clinically defined subgroups. Age, sex and chest pain history all had an effect. (TABLE 16) For example, in those < 50

TABLE 16

Prevalence of Left Main Stenosis in Patient Subgroups

	LEFT MAIN > 50%		LEFT MAIN EQUIVALENT	
	< 50 yrs	> 50 yrs	< 50 yrs	> 50 yrs
MEN				
Typical Angina	0.10	0.16	0.04	0.11
Atypical Angina	0.04	0.08	0.005	0.05
Nonanginal pain	0	0.02	0.002	0.007
WOMEN				
Typical Angina	0.01	0.09	0.03	0.05
Atypical Angina	0.04	0.03	0.01	0.02
Nonanginal pain	0.007	0.005	0	0.001

Adapted from reference 32.

years, men with typical angina had a 10% prevalence of left main stenosis whereas women had a 1% prevalence. In those >50 years with typical angina, the prevalence of left main stenosis was increased, but still approximately twice as frequent in men. Other clinical predictors of left main stenosis, such as the severity of chest pain, do not appear as useful.(177) The prevalence of left main coronary artery stenosis in patients in a primary care setting is unknown, but is probably lower since all of these series are composed of patients referred for coronary angiography.

Assuming that the patient in question has some reasonable likelihood of left main stenosis, a number of studies have attempted to address the accuracy of certain exercise criteria for the identification of left main stenosis.(TABLE 17) As seen in the table, different lead systems and criteria were used to predict left main stenosis and the definition of a significant lesion also varied. Despite the difficulties of comparing these data, the yield from these studies is never high; 14% to 47% of those with these findings actually had left main disease. This can be attributed to 2 factors: 1) most of the exercise test end-points used were common and occur in many patients, and 2) the prevalence of left main coronary artery stenosis in the general population is small. Blumenthal et.al. (181) compared the predictive accuracy of several of these criteria in patients with mild symptoms.(TABLE 18) Marked ST-segment depression and global changes were the most common findings present occurring in 100% and 93%, respectively. The predictive accuracy of global changes was 57% compared to 38% for marked ST-segment depression. At the opposite extreme, exercise-induced hypotension was extremely predictive (75%) when present, but not seen frequently (21%) Therefore, despite its extreme importance, the detection of left main coronary artery stenosis cannot be accomplished accurately by stress testing alone. When coronary angiography is performed because of an "early

TABLE 17

PREDICTIVE ACCURACY OF EXERCISE CRITERIA FOR SELECTING PATIENTS WITH LEFT MAIN CAD

Study	Method	Lead System	# with L. main CAD	Criterion	Predictive Accuracy %
Bartel et al (110)	Treadmill	12 leads	31(70)*	2mm ST segment depression	24
				+ test at HR < 130	23
Cheitlin et al (178)	Treadmill	I, II, aVL, aVF V_4-V_6	11(75)	2mm ST segment depression	24
Thomson et al (133)	Treadmill	V_5	5(75)	+ test and a decrease in systolic BP with exercise	33
Goldschlager et al (114)	Treadmill	V_5	15(50)	+ test in Stage I and down sloping ST segment	33
				+ test and abnormalities persist >8 min.	21
McNeer et al (130)	Treadmill	12 leads	110(50)	+ test in Stage I or II	26
Morris et al (134)	Treadmill	V_5 with computer grading	18(75)	Systolic BP decrease of 10mmHg < peak BP	14
Blomqvist et al (179)	Bicycle	Modified Frank and computer grading	14(50)	Angina or + test at a low work capacity	41
Levites et al (180)	Treadmill	V_5	11(75)	2mm ST segment depression	24
				+ in Stage I	47

*figure in parentheses indicates % narrowing

TABLE 18

Predictive Accuracy of Several Exercise Stress Test Criteria in the Detection of Left Main Coronary Artery Disease (LMCAD) in Patients with Mild or No Angina (N = 40)

Stress Electrocardiographic Criterion	Number with Finding	Number with Finding Having LMCAD	Percent of LMCAD Group (n = 14) Identified	Predictive Accuracy for LMCAD (%)
Global changes*	23	13	93	57
Marked S-T segment depression†	37	14	100	38
Early positivity‡				
Stage 1	11	5	36	45
Stage 1 or 2	27	11	79	41
Downsloping§	26	8	57	31
Prolonged positivity‖	22	7	50	32
Hypotension¶	4	3	21	75

* The presence of simultaneous electrocardiographic changes in at least two inferior (II, III, aVF) and one anterior (I, aVL, V_1–V_4) leads.
† Two millimeters or more of flat or downsloping S-T segment depression at least 0.08 msec in duration.
‡ A positive test by electrocardiographic criteria and test duration 6 minutes or less.
§ Downsloping S-T segment depression of 1 mm or more and at least 0.08 msec in duration.
‖ A positive test by electrocardiographic criteria and changes post-test lasting 8 minutes or more.

TABLE 19

Combinations of Exercise Test Variables for the Detection of Left Main (group I) and Left Main or Three Vessel Coronary Disease (group I and II)

	Group I (n = 35)		Group I and II (n = 124)	
	Sensitivity (%)	Predictive Value (%)	Sensitivity (%)	Predictive Value (%)
Combination I	77	24	57	69
Combination II	74	32	49	74
Combination III	57	38	36	83

Combination I = 2 mm or more downsloping S-T depression with S-T depression beginning in stage 1.
Combination II = combination I plus S-T depression lasting 6 or more minutes and involving five or more leads.
Combination III = combination II plus exercise-induced angina and treadmill time 6 minutes or less.

positive" ETT, left main coronary stenosis will be found in approximately 30% of those studied. (181-183)

Besides left main CAD, certain subsets of patients with 3 vessel CAD may benefit from surgical revascularization (184-186) Therefore, a reasonable approach would be to examine the utility of exercise testing to identify patients with either left main or 3 vessel CAD. Recognizing that it was not realistic to look at only a portion of the information available in the ETT, Weiner et.al. (177) combined multiple indicators to determine the likelihood of left main or 3 vessel CAD in 436 patients. Individual clinical and exercise test variables were unable to detect left main coronary disease because of the low sensitivity and predictive values. The pattern of 2mm or greater downsloping ST-segment depression, starting in Stage I, lasting at least 6 minutes into recovery and seen in at least 5 ECG leads was highly predictive (74%) and reasonably sensitive (49%) for either left main or 3v CAD (TABLE 19) When the presence of angina and an exercise duration of < 6 minutes were added, the predictive value increased to 83%.

c. <u>Criteria for an "Early Positive" or "Markedly Abnormal" Exercise Test:</u> One problem, albeit minor, is that the criteria for an "early positive" or "markedly abnormal" exercise test are seldom defined in an identical fashion among the different studies. Nevertheless, from the many variables evaluated in these studies, it is possible to formulate a list of those findings that are indicative of important multivessel or left main CAD or an increased risk of subsequent myocardial infarction or death.

Criteria For An Early Positive Exercise Test

ST-segment response:

1. 2mm or more horizontal or downsloping ST-segment depression at a heart rate < 130.

2. Post-exercise ST-segment depression persisting > 5 minutes.

Systolic blood pressure response to progressve exercise:

1. Flat response (< 10mmHg rise for 2 stages).

2. Sustained decrease of > 10mmHg.

Exercise capacity:

1. Inability to complete stage II of a Bruce protocol or its equivalent.

2. Maximum heart rate < 70% of age predicted maximum.

3. Frequent or complex ventricular arrhythmias at a lov heart rate.

Adapted from references 4 and 187

Using these criteria, it is possible to identify a large portion of those with left main or 3v CAD, but certainly not all such individuals. Moreover, since these findings are not specific, many patients exhibiting them may manifest different anatomic findings. Nevertheless, the anatomic and prognostic implications of an "early positive" ETT are important; thus a patient with such ETT findings should be referred for coronary arteriography. Almost all of the studies upon which these recommendations are based use symptom-limited or maximal ETTs. Medical therapy, especially with the potent drugs available, can alter the usefulness of the ETT for this purpose. In a study of 57 men with stable angina pectoris, 68% had an "early positive" response before and 24% such a response after therapy with a long acting nitrate and a calcium blocker (160). The sensitivity and specificity of an early ppsitive response for predicting 3 vessel or left main CAD changed from 92% and 58% before to 42% and 75% after therapy, respectively. Therefore, antianginal therapy reduces substantially the value of the ETT as a screening tool for anatomically-important CAD.

5. Rational Indications for Exercise Testing

Recently, the Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Exercise Testing) has suggested these guidelines for exercise testing. They classified the indications for exercise testing into 3 groups.

Class I. Conditions for which there is general agreement that exercise testing is justified.

Class II. Conditions for which exercise testing is frequently used but in which there is a divergence of opinion with respect to value and appropriateness.

Class III. Conditions for which there is general agreement that exercise testing is of little or no value, inappropriate or contraindicated by risk.

The specific indications within each class were:

Class I

1. To assist in the diagnosis of coronary artery disease in male patients with symptoms that are atypical for myocardial ischemia.
2. To assess functional capacity and to aid in assessing the prognosis of patients with known CAD.
3. To evaluate patients with symptoms consistent with recurrent, exercise-induced cardiac arrhythmias.

Class II

1. To assist in the diagnosis of CAD in women with a history of typical or atypical angina pectoris.
2. To assist in the diagnosis of CAD in patients taking digitalis.
3. To assist in the diagnosis of CAD in patients with complete right bundle branch block.
4. To evaluate the functional capacity and response to therapy with cardiovascular drugs in patients with CAD or heart failure.
5. To evaluate patients with variant angina.
6. To follow serially (at 1 year or longer intervals) patients with known CAD.

Class III

1. To evaluate patients with simple premature ventricular depolarizations on the resting ECG but no other evidence of CAD.
2. To evaluate functional capacity serially in the course of an exercise cardiac rehabilitation program.
3. To assist in the diagnosis of CAD in patients who demonstrate pre-excitation (Wolfe-Parkinson-White) syndrome or complete left bundle branch block on the resting ECG.

In summary, the ETT should be viewed as a potential adjunct to the clinical assessment of the patient. Exercise stress testing does have marked limitations for the diagnosis of CAD, especially in certain subsets of patients. Furthermore, there is no need to use the test in every patient being evaluated for CAD. Nevertheless, if appropriate judgment is used, the ETT can be a highly effective and economical means to evaluate patients with chest pain.

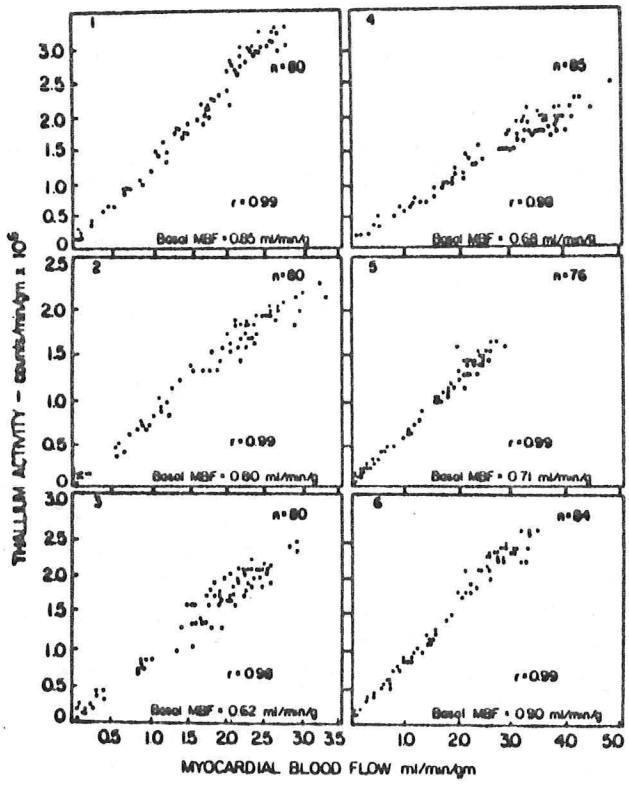
H. EXERCISE TESTING WITH THALLIUM-201 IMAGING

Myocardial perfusion imaging with thallium-201 (TL-201) has found wide application in the clinical evaluation of patients with known or suspected CAD. Knowledge of the existence of active transport mechanisms for concentrating certain monovalent cations in normal myocardial tissue has lead to the use of radioisotopes of potassium and rubidium for imaging the myocardium to assess regional blood flow.(188,189) Just about the time further work was being planned to improve image generation with Rb-81, radioactive thallium was shown to have biological properties similar to K-43 and Rb-81, but with superior physical properties for imaging with a scintillation camera.(190) Although research is being conducted with another radioisotope of rubidium, Rb-82, which has an ultra short half-life and is imaged with a positron camera, TL-201 is the most clinically utilized agent for myocardial perfusion imaging.(191)

1. TL-201 Distribution and Redistribution

a. Basic kinetics: After IV injection, the initial myocardial uptake of TL-201 is dependent on regional myocardial blood flow and extraction of thallium by the myocardium (192, 193) Approximately 85-88% of the thallium entering the coronary circulation is extracted on the first pass through the heart (194); this is diminished slightly by acidosis and hypoxemia, but drugs such as propranolol and digitalis seem to have little effect. Importantly, when coronary perfusion

FIGURE 27

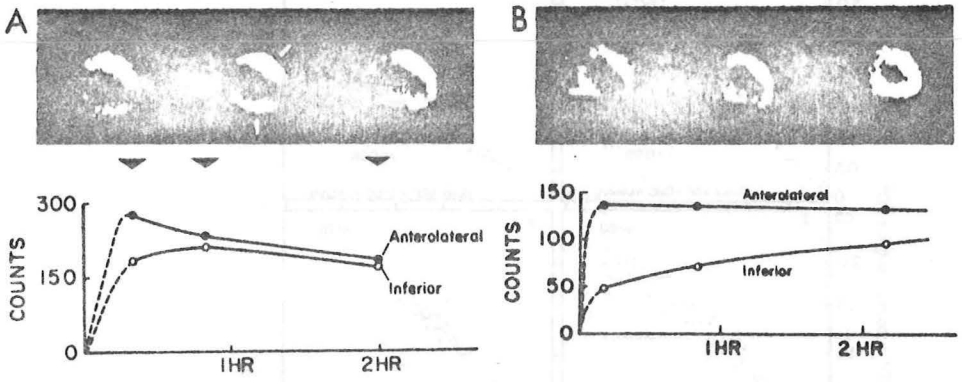


—Relationship between thallium-201 activity and regional myocardial blood flow (MBF) in six dogs during exercise.

pressure is lowered transiently, such as with a focal coronary stenosis, the amount of TL-201 extracted is not significantly altered as long as the myocardial cells are viable.(194) In contrast, with very high myocardial blood flow, the amount extracted may decrease slightly. Several studies have investigated the relationship of initial myocardial TL-201 concentration to regional blood flow as determined by the microsphere technique.(195-197) Over a wide physiological range of blood flows induced by exercise (195) or IV dipyridamole, (196,197) the uptake of TL-201 in the canine heart is proportional to regional flow. (FIGURE 26) This relationship forms the basis for the appearance of the myocardial scintigram in an individual without CAD; myocardial uptake of TL-201 is relatively homogeneous as assessed by gamma camera imaging.

b. Delayed TL-201 redistribution after exercise: After IV injection and initial extraction by the myocardium, TL-201 does not remain fixed within the myocardial cells. As soon as initial uptake occurs, there is a continuous exchange of myocardial thallium with thallium that recirculates from the systemic blood pool. Thallium is continually washing out of the myocardium and being replaced by recirculating thallium from the extracardiac pool. This process of continuous exchange explains the phenomenon of TL-201 "redistribution" which is observed after transient regional myocardial hypoperfusion or with a chronic reduction in regional flow (rest "redistribution").(194, 198-200) Redistribution is defined as the total or partial resolution of defects that are detected 5-20 minutes after IV TL-201 administration. Defect disappearance or partial improvement is assessed by obtaining delayed images 2-4 hours after the initial injection of TL-201. Figure 28 provides an example of TL-201 redistribution in

FIGURE 28



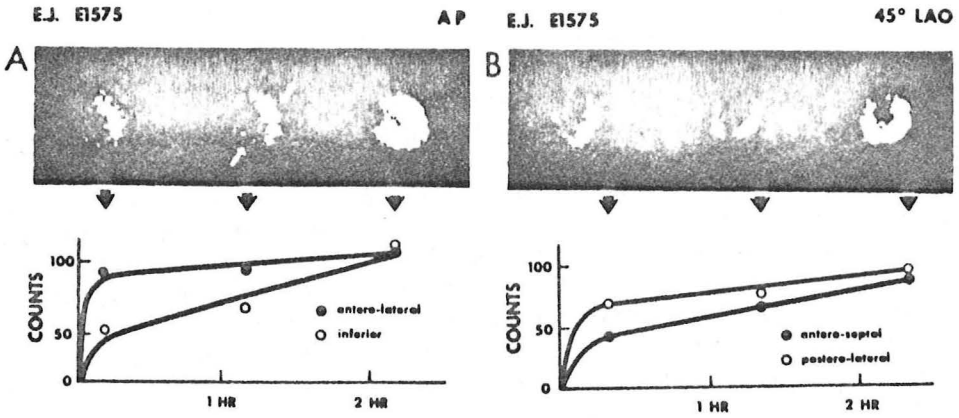
2 patients with CAD. In panel A, serial anterior projections demonstrate an exercise-induced inferior wall perfusion defect which has complete redistribution by 1 hour. The quantitative time-activity curves (below) from the anterolateral and inferior wall segments confirm the visual impression. This patient had single vessel right coronary artery disease. In panel B, the images demonstrate inferior wall redistribution and abnormal washout from the anterolateral segment (depicted by the time-activity curves below). This patient had both right coronary and left anterior descending disease. Therefore, with cessation of exercise and restoration of relatively homogenous flow to normal myocardium and to the regions perfused by stenotic arteries, filling in of the defect

occurs as TL-201 washes out of the normal region and accumulates in the stenotic region.(201) As long as cell membrane function is not impaired, myocardial cells, initially deprived of TL-201 during exercise, will continue to extract the radionuclide being circulated through the myocardium and eventually the intracellular TL-201 concentration will normalize and reach that of the other viable myocardial cells.

Simultaneous with the accumulation of TL-201 by the previously ischemic myocardium, washout from normal segments and other ischemic segments is occurring. Thallium-201 washout in nonischemic myocardium is monoexponential and is directly related to the rate of TL-201 clearance from the blood and the ratio of myocardial to blood TL-201 concentration.(202) As noted in the example above, in the presence of a severe coronary obstruction, there can be late TL-201 clearance from the myocardium. In such segments, clearance is slower than the rate of clearance from the blood, thus giving the appearance that there is more TL-201 present in later images than in the immediate post-stress pictures. This relationship is important and has diagnostic utility in the detection of multivessel CAD.

c. Thallium-201 redistribution at rest: Thallium-201 redistribution is also observed with a severe chronic reduction in regional flow as may occur with a coronary stenosis > 90%.(203) When TL-201 is injected IV under such conditions an initial defect is observed because of the resting hypoperfusion. Subsequently, in this region, delayed accumulation occurs without any change in the chronically depressed coronary flow. The mechanism for this rest redistribution is a diminution in the intracellular efflux rate induced by chronic ischemia.(194) Figure 29 is an example of rest redistribution in a patient with

FIGURE 29



severe stable angina and multivessel CAD. Panel A depicts an anterior view and panel B a 45° left anterior oblique view. Note that delayed myocardial redistribution is present in all segments over time, indicating marked resting hypoperfusion.

d. Persistent TL-201 defects: When TL-201 is injected IV under conditions of a total and permanent occlusion of a coronary vessel or in the presence of a myocardial scar, a "persistent" defect in the vascular region of the irreversibly damaged area is observed.(198) If this region is fibrotic, then no delayed

redistribution is detected; partial redistribution is observed if there is physiologically significant flow to viable myocardium in the distribution of the occluded artery or some antigrade flow is observed. Partial redistribution suggests that a mixture of viable and nonviable tissue is present. As one would expect, this finding correlates with Q-waves on the ECG and akinetic or dyskinetic wall motion. In the animal model, persistent defects correlate with irreversibly damaged myocardium as assessed by radiolabeled antimyosin antibody uptake.(204)

e. Lung TL-201 uptake: Abnormally increased lung TL-201 uptake can be seen in certain patients on the initial post-exercise image obtained in the anterior projection with subsequent resolution over the next 30-60 minutes.(205) This abnormality represents TL-201 that is sequestered in the interstital fluid space of the lungs as a result of an elevated pulmonary capillary pressure consequent to important exercise-induced LV dysfunction.(206) Generally, patients with this finding have more myocardium at risk, multivessel CAD and lower LV ejection fractions.(205-208)

f. Right ventricular uptake of TL-201: Normally, the right ventricular myocardium is not well visualized on rest images, but may be seen in the presence of right ventricular pressure or volume overload.(209-211) Because of increased blood flow during exercise, the right ventricle will usually be seen on images obtained immediately after stress. Evalution of right ventricular TL-201 uptake during stress may have some usefulness for detecting proximal right coronary artery stenoses (212,213)

2. Detection of CAD by Thallium-201 Imaging

For individuals without significant CAD, the myocardial uptake of TL-201 is homogenous as assessed by gamma camera imaging. However, there are several situations that can result in the false impression of a defect. First, some relative diminution of TL-201 is observed at the apex of the LV since this region is thinner than the surrounding segments. Also, there is relatively less uptake in the base of the heart in the region of the outflow and inflow tracts. Second, excessive cardiac rotation may be associated with photon-deficient regions in the upper posterolateral or anteroseptal walls on left anterior oblique projections, which may be mistaken for perfusion defects. Third, in females, breast tissue interposed between the gamma camera and chest wall can also give the false appearance of a defect. Fourth, enlargement of the right ventricle can result in an attenuation artifact of the inferior wall on the anterior projection image. Finally, alterations in LV geometry can result in changes in myocardial images independent of any change in tracer distribution. In the animal model, acute cardiac dilatation during ischemia can enlarge defect size and, conversely sodium nitroprusside can decrease defect size.(214) Since most of these problems are minor and potentially correctable by careful imaging techniques, the presence of nonhomogenous myocardial uptake of TL-201 strongly suggests the presence of CAD.

a. The sensitivity and specificity of TL-201 imaging for the detection of CAD: Many clinical studies have been reported in which the sensitivity and specificity of exercise TL-201 scintigraphy were compared with the results of the

exercise ECG for the detection of CAD. Table 20 presents a collection of 22 studies, all of which utilized the visual interpretation of thallium images to detect CAD. The overall sensitivity and specificity of TL-201 exercise scintigraphy was 83% and 90%, respectively. In contrast, the combined sensitivity and specificity of the exercise ECG in these series was 58% and 82%, respectively. In most of these studies, TL-201 scintigraphy was statistically superior to the exercise ECG, but observer experience is a factor as seen below:

Effect of Reader's Experience on Accuracy of Interpretation

	READER 1 (EXPERT)	READER 2 (INTERMEDIATE)	READER 3 (NOVICE)
DIAGNOSIS OF CAD			
SENSITIVITY	85%	90%	75%
SPECIFICITY	93%	100%	87%
OVERALL ACCURACY	87%	85%	78%

From reference 237

In an attempt to avoid some of the pitfalls inherent in the subjective visual interpretation of thallium-201 scintigrams, several quantitative computer-assisted programs have been developed. (236, 238-241) Using these techniques, it has been possible to increase the sensitivity of TL-201 scintigraphy to 92% without a decrease in specificity. Furthermore, several quantitative tomographic techniques have been employed including the 7-pinhole collimator (242) and rotating slant hole collimator. (243) Each has some inherent disadvantages and are more cumbersome than standard methods. Moreover, because of the extremely high sensitivity and specificity of the conventional methods, these techniques have not as yet been shown to be superior. Single photon emission computed tomography (SPECT) offers the possiblity of true three-dimensional tomographic reconstruction. Although very promising, the full potential of this latest technique has not as yet been defined. (244)

b. Specific advantages of TL-201 scintigraphy: Thallium-201 scintigraphy has several advantages over routine stress electrocardiography. First, unlike the exercise ECG, the sensitivity of TL-201 scintigraphy remains high in patients with single vessel CAD. (TABLE 21) In 5 studies comprising 291 patients, TL-201 scintigraphy was more sensitive than the standard ETT in patients with 1- (80% vs. 39%), 2 - (83% vs. 72%) and 3 vessel CAD (96% vs. 83%). Second, TL-201 scintigraphy has been very useful for detecting and localizing individual coronary stenoses. Figure 29 depicts a schematic representation of coronary anatomy (top) and the corresponding TL-201 images (below). The left anterior descending artery (LAD) supplies the anterolateral and septal regions, the right coronary artery (RCA) supplies the inferior and inferoapical regions and the circumflex artery (LCx) the high posterolateral region. By relating the location of a perfusion defect to these anatomic patterns, stenosis of an individual vessel can be defined. Table 22 summarizes the results from 7 studies that examine the utility of the TL-201 study to define the vessel involved. The lower sensitivity for the detection of circumflex disease may be related to the lesser amount

TABLE 20

EXERCISE ECG AND TL-201 STRESS SCINTIGRAPHY FOR THE DETECTION OF CAD

STUDY	YEAR	# Of PATIENTS	ECG Sensitivity* %	ECG Specificity %	TL-201 Sensitivity %	TL-201 Specificity %
Klein (215)	1976	44	84(NA)	89	81	97
Bailey (216)	1977	83	38(65)	100	75	100
Richie (217)	1977	101	45(65)	84	76	96
Multicenter (218)	1978	190	47(73)	88	78	88
Verani (219)	1978	82	65(77)	76	79	97
Turner (220)	1978	66	71(71)	79	68	97
Botvinick (221)	1978	65	67(74)	63	85	89
Carillo (222)	1978	55	54(NA)	75	87	100
Blood (223)	1978	87	66(84)	88	93	76
Dash (224)	1979	96	52(NA)	80	81	100
McCarthy (225)	1979	128	64(79)	91	85	79
Bodenheimer (226)	1979	95	56(71)	86	75	91
Pohost (227)	1979	209	NA(64)	77	87	75
Stolzenberg (228)	1979	52	55(NA)	82	83	94
Kirshenbaum(229)	1979	61	40(64)	100	86	91
Corne (230)	1979	46	58(81)	65	96	90
Hecht (231)	1979	56	52(70)	70	100	80
Ong (232)	1980	50	NA(81)	71	70	86
Iskandrian (233)	1980	102	55(NA)	88	76	86
Schicha (234)	1980	80	48(NA)	95	92	90
Melin (235)	1981	160	74(74)	70	87	89
Berger (236)	1981	140	62(77)	82	83	90
TOTAL		2,048				
Average			58(73)	82	83	90

*Sensitivity of ECG indicated as % of patients with $\geq$ 0.1mV ST depression or (in parentheses) % of patients with either $\geq$ 0.1mV ST depression or resting Q-waves.
NA = not available or could not be extracted from data.

TABLE 21

Comprison of ETT and TL-201 Scintigraphy Related To The Extent of Coronary Disease

STUDY	# Of Patients	Sensitivity (%) 1 vessel CAD ETT:TL-201	2 vessel CAD ETT:TL-201	3 vessel CAD ETT:TL-201
Ritchie (217)	76	46:71	93:93	65:76
Bodenheimer (226)	84	47:68	79:76	83:86
Corne (230)	26	50:100	82:91	100:100
Hecht (231)	46	25:100	67:100	87:100
Iskandrian (233)	59	26:59	63:84	54:100
TOTAL	291			
AVERAGE		39:80	72:83	83:96

FIGURE 29

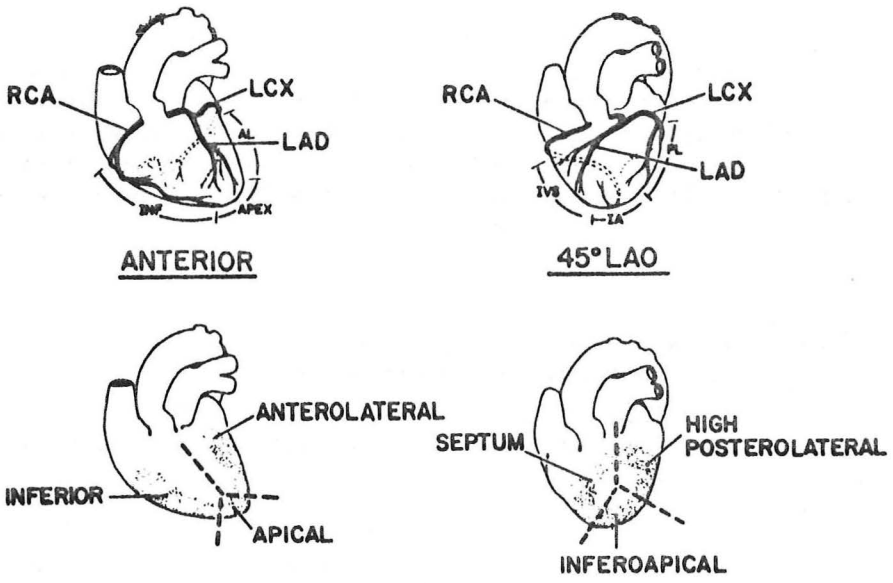


TABLE 22

TL-201 Scintigraphy And The Location Of Coronary Artery Disease

STUDY	DEFINITION OF STENOSIS (% stenosis)	OVERALL SPECIFICITY (%)	SENSITIVITY (%) RCA	LAD	LCx
Corne (230)	70	90	94	92	73
Maddahi (241)	50	82	96	83	78
Lenaers (245)	50	90	79	84	49
Wainvright (246)	70	56	74	98	83
Massie (247)	70	93	73	78	45
Rigo (248)	70	98	55	75	26
Gibson (249)	70	92	87	91	63
		AVERAGE	80	86	60

of myocardium perfused by this artery in patients with dominant right coronary arteries. Although these data suggest that the individual diseased vessel can usually be identified, the variability of coronary anatomy often makes it difficult to be absolutely certain of the exact vessel involvement. A more practical approach is to use the TL-201 scan to predict the presence of multivessel CAD. Thallium defects in 2 or 3 image segments corresponding to the perfusion regions of the 3 major coronary arteries correctly predicted 75% of the patients proven to have multivessel disease by angiography. (238,247,249,250) Third, the reliability of TL-201 scintigraphy appears preserved even in populations with a low prevalence of CAD. Evaluation of the standard stress ECG demonstrates that the false positive rate increases (specificity decreases) as the pre-test likelihood of disease decreases. Table 23 summarizes data from 3 studies where the

TABLE 23

SENSITIVITY AND SPECIFICITY OF TL-201 SCINTIGRAPHY IN PATIENTS WITH A LOW PREVALENCE OF CORONARY DISEASE

STUDY	# Of Patients	Prevalence of CAD (%)	SENSITIVITY (%)	SPECIFICITY (%)
Berman (251)	32	41	92	95
Uhl (252)	191	21	95	91
Guiney (253)	35	26	89	88
	Average	29	92	91

patients had an average 29% pre-test probability of CAD. Whether this high specificity would be preserved in a truly asymptomatic population with a very low prevalence of disease (i.e. 5%) is not known. Finally, TL-201 scintigraphy is more useful than the standard ETT in women. Friedman et.al. studied 60 women suspected of having CAD. The standard exercise ECG had a sensitivity of 32% and specificity of 41%; in contrast, the sensitivity and specificity of the exercise TL-201 scan was 79% and 88% respectively.(254) This finding has been confirmed by others (255)

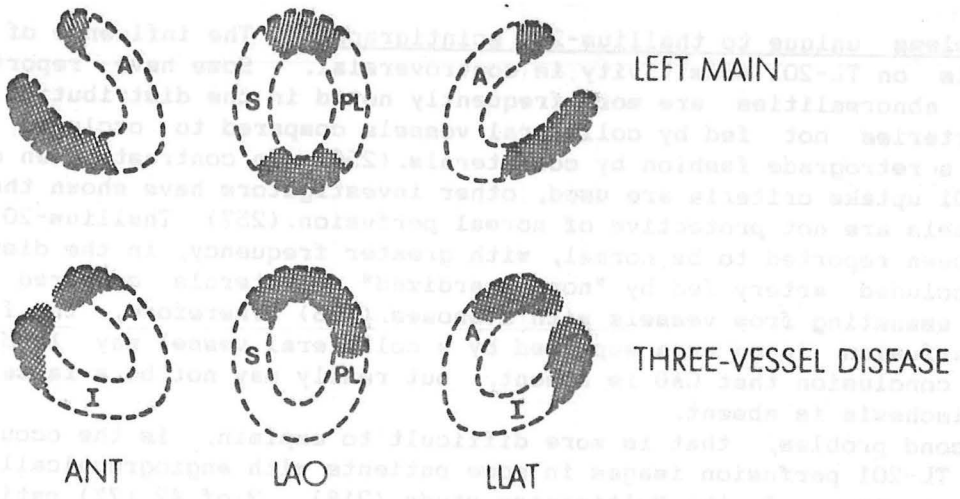
c. Problems unique to thallium-201 scintigraphy: The influence of coronary collaterals on TL-201 sensitivity is controversial. Some have reported that perfusion abnormalities are more frequently noted in the distribution of occluded arteries not fed by collateral vessels compared to occluded arteries filled in a retrograde fashion by collaterals.(256) In contrast, when quantitative TL-201 uptake criteria are used, other investigators have shown that collateral vessels are not protective of normal perfusion.(257) Thallium-201 uptake also has been reported to be normal, with greater frequency, in the distribution of an occluded artery fed by "nonjeopardized" collaterals compared to collaterals emanating from vessels with stenoses.(256) Therefore, the finding of normal perfusion in an area supplied by a collateral vessel may lead to the incorrect conclusion that CAD is absent, but really may not be a false-negative study if ischemia is absent.

A second problem, that is more difficult to explain, is the occurrence of abnormal TL-201 perfusion images in some patients with angiographically normal coronary arteries. In the Multicenter study (218), 3 of 42 (7%) patients with no or insignificant CAD had abnormal thallium studies. In other series, where TL-201 scans were performed only in those known to have normal arteriograms, the incidence of abnormal images ranges from 15% to 27%.(258,259) There are 2 potential explanations for this phenomenon. One is that patients found to have no CAD by angiography have actual abnormalities of coronary perfusion. This possibility is supported by recent evidence that such patients do exist and can manifest ST-segment abnormalities, abnormal coronary vasodilator reserve and myocardial lactate production during stress.(260,261) Therefore, in these individuals, an abnormal thallium scan may actually reflect ischemia in the absence of epicardial coronary stenoses. The second possible explanation is that many of these individuals actually have epicardial coronary stenoses whose severity was not determined correctly by angiography. Support for this derives from the fact that 35-50% of these patients were felt to have "subcritical" coronary lesions.(262) Perhaps some of these patients actually have a hemodynamically-important lesion, thus their TL-201 image is, in fact, a true positive. Other factors may be involved because 82% of those with this situation studied by Berger et.al. had one or more other cardiac abnormalities such as bundle branch block, mitral valve prolapse, atrial fibrillation or an abnormal LV diastolic pressure.(259) The third problem unique to thallium scintigraphy is the potential for infiltrating diseases of the myocardium to cause a nonhomogenous appearance of the image and, thus mimic CAD. The classical example of this is cardiac sarcoidosis.(263)

3. Detection of Left Main and 3 Vessel CAD by TL-201 Imaging

Since TL-201 scintigraphy offers an improvement in sensitivity and specificity for the detection of CAD compared to the exercise ECG, it is appropriate to question if this could be extended to the detection of "high risk" coronary disease states, specifically left main or 3 vessel CAD. Dash et.al.(224) suggested the possibility of a characteristic scintigraphic pattern for the presence of left main or 3v CAD.(FIGURE 30) In these diagrams, shaded areas repre-

FIGURE 30



sent relatively normal uptake of radioisotope and clear areas, perfusion abnormalities. Left main CAD would be characterized by anterior defects (A) on the anterior (ANT) and left lateral (LLAT) projections and septal (S) and posterolateral defects (PL) in the left anterior oblique projection (LAO). Three vessel CAD is suggested by accumulation of TL-201 in the base of the heart in all 3 views with decreased perfusion of the anterior, posterolateral, septal and inferior (I) walls. Although all of their patients with left main stenosis had an abnormal TL-201 image, only 50% displayed this characteristic pattern. In two subsequent studies, this pattern was found only in 13% and 14% of the patients with left main disease.(264,265) The low incidence of this typical left main pattern is not surprising when one considers that most patients with left main disease also have significant stenoses in one or more of the major arteries. Other stenoses in series would be expected to modify this pattern and produce a pattern more consistent with multivessel disease.

Although a very high percentage of those with 3 vessel disease will have an abnormal TL-201 scan (see TABLE 21), no characteristic pattern has been defined.(224,264-266) Accordingly, many now prefer to describe scintigraphic findings that identify "high risk" anatomy. Nygarrd et.al. defined the "high risk" pattern as one that exhibits either: a) the typical scintigraphic pattern of left main CAD, b) abnormal TL-201 uptake or washout in multiple vascular segments indicative of multivessel CAD, or c) increased lung uptake on the initial anterior image.(265) The prevalence of these findings were compared to the prevalence of "high risk" stress ECG findings similar to those described ear-

FIGURE 31

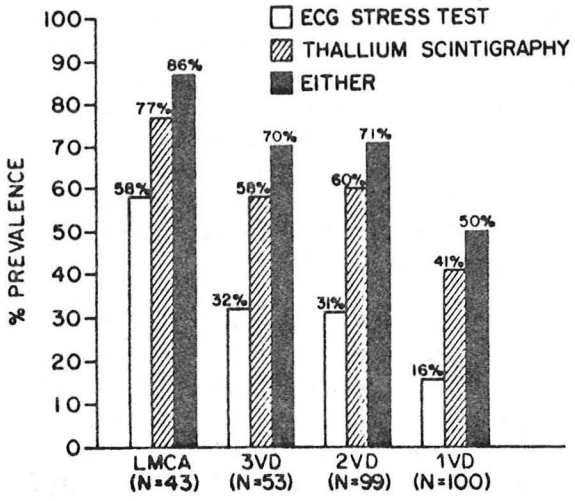
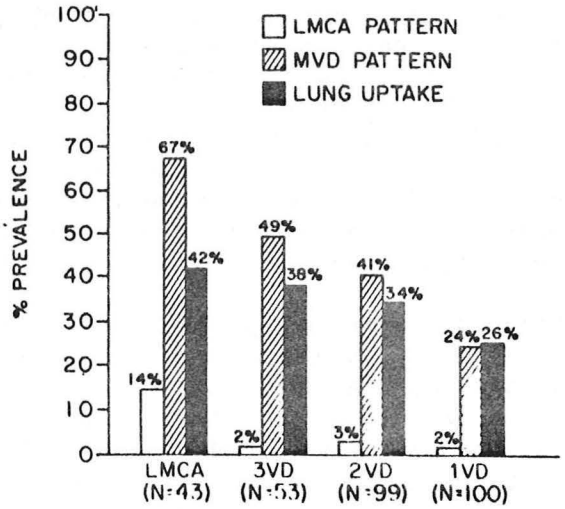


FIGURE 32



lier. The results depicted in figures 31 and 32 indicate that that prevalence (or sensitivity since the authors express these data as the % of patients with a finding/% of patients with disease) of "high risk" thallium findings was higher than that of "high risk" ECG stress test findings in patients with left main or 3 vessel disease. However, the specificity was approximately 50% since about half of the patients with one or two vessel disease had similar findings (FIGURE 20). Moreover, although the prevalence of any one of the "high risk" scintigraphic findings was 77% in those with left main disease (i.e. sensitivity = 0.77) the specificity of these findings was poor. (FIGURE 32) Similar results were obtained by Maddahi et. al. using computer-assessed quantitative analysis (267) Therefore, the combination of certain thallium scintigraphic patterns are more sensitive than the standard stress ECG but are still not specific indicators of "high risk" coronary disease states. Although these results may seem somewhat disappointing, there may be a plausible functional explanation. The belief that thallium-201 scintigraphy could identify the patient with "high risk" anatomy is based on the general concept that patients with left main or 3v CAD have more myocardium at risk. Therefore, the greater the size of a perfusion abnormality, the more likely it is that the patient has extensive CAD and is, in fact, a "high risk" patient. For example, some feel that a patient with proximal left anterior descending and circumflex disease has as much myocardium at risk as a patient with left main disease even though technically this is 2 vessel CAD and clinically may behave differently. (268) Alternatively, very proximal disease of the left anterior descending is considered "high risk" by many even though it is single vessel disease. (269) As a result of these findings, the idea has developed that the size and/or location of perfusion abnormalities could be used better to detect those with a poor prognosis, regardless of their coronary anatomy.

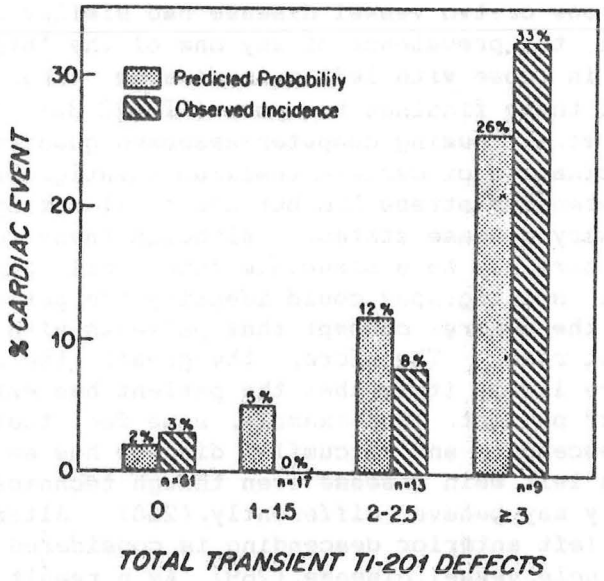
4. Prognosis As Assessed By TL-201 Scintigraphy

There are now several studies that highlight the utility of TL-201 imaging to determine prognosis in patients with CAD.

a. Prognosis when the thallium study is normal: In patients with chest pain and a normal thallium-201 exercise scintigram the overall cardiac mortality rate is approximately 0.5% per year and the nonfatal infarction rate is 0.6% per year. (270) Slightly higher rates are found in those that had a high "pretest" likelihood of CAD.(271) It is important to note that these findings were not based on the absence of CAD, since about half of those who underwent angiography in each study had CAD, including a few patients with 2 or 3 vessel disease. Therefore, the absence of a thallium-201 perfusion defect after a good quality ETT is a sign of excellent prognosis, even in the presence of CAD.

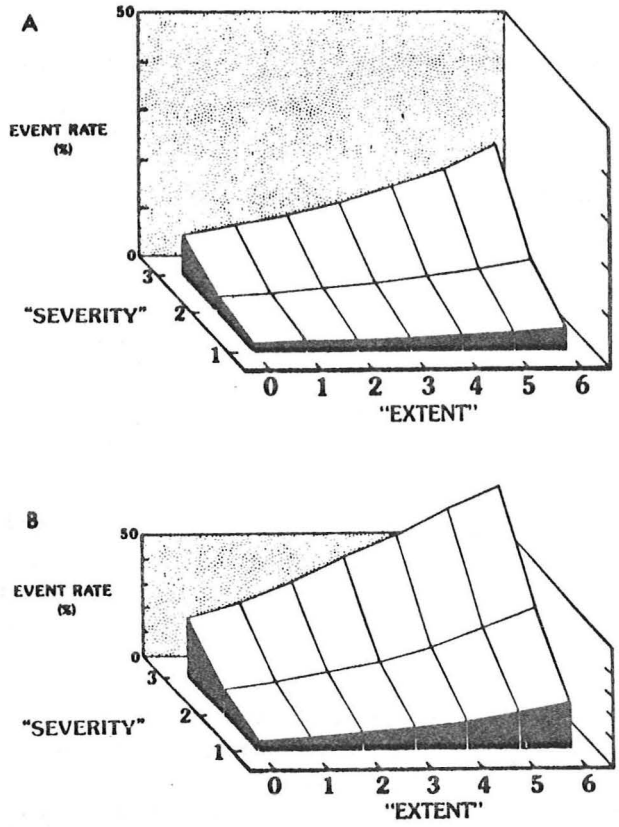
b. Prognosis when the thallium study is abnormal: Brown et.al. were the first to relate the extent of thallium abnormalities to prognosis.(272) Among 100 patients without a prior MI during a follow-up of 3.8±0.7 years, the number of transient thallium defects was the most significant predictor of subsequent cardiac events (death or MI).(FIGURE 33) Those with 3 or more transient defects had a 26% predicted probability of a cardiac event and a 33% observed incidence. A more sophisticated predictive algorithm was developed by Landenheim, et.al.(273) whereby the "severity" and "extent" of perfusion abnormalities were evaluated in patients who could (panel A) or could not (panel B) achieve 85% of

FIGURE 33



Probability of a future cardiac event (cardiovascular death or myocardial infarction) versus observed incidence of event as a function of the number of transient thallium-201 defects in 100 patients without previous myocardial infarction.

FIGURE 34



Combined effect of extent and severity of hypoperfusion on coronary event rate in the 1,414 patients who were able to exercise to at least 85% (average 99%) of maximal heart rate (A), and the 275 patients who were not able to achieve 85% (average 76%) of maximal heart rate (B). The graph was generated using multiple linear regression of the logistically transformed event rates (weighted for different sample size by their standard deviations) shown in Table 5. In each case, event rate rises as a curvilinear function of extent and severity. There is at least a threefold increase in event rate for the latter group (B) in comparison with the former group (A) (note that the event rate axis for B is half that of A).

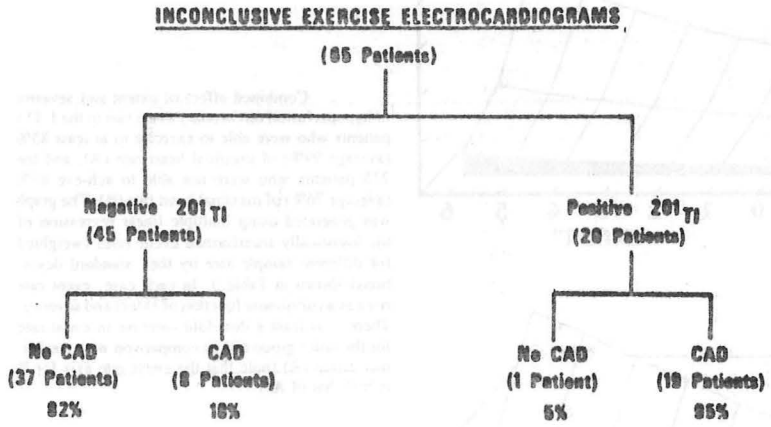
their predicted heart rate. (FIGURE 34) Using this model, the coronary event rate could be estimated over a wide range; it was 0.4% per year in those who could exercise well and had no perfusion abnormalities compared to 78% per year in those with poor exercise capacity who had extensive perfusion alterations. Therefore, the magnitude of perfusion abnormalities on the TL-201 scan have a clear prognostic implication. Similar findings have been noted when TL-201 scintigraphy is used to predict future cardiac events in patients after uncomplicated infarction. (274)

5. The Patient Who Cannot Exercise Adequately

a. <u>The nondiagnostic ETT: Is TL-201 any better?</u> In many patients, the routine stress ECG is deemed "nondiagnostic" because > 85% of the age-predicted maximum heart rate is not achieved before the test is terminated, usually for a non-cardiac symptomatic endpoint such as fatigue, leg cramps, weakness, etc... Perfusion scintigraphy may still be helpful in such individuals because an abnormality of coronary perfusion may occur soon after increasing myocardial O_2 demand even before the cellular metabolic changes associated with ST-segment depression. Although there is probably a minimal level of exercise that must be achieved before the test can be considered negative (275), the level of exercise achieved influences the stress ECG more than the TL-201 scintigram. In patients achieving < 85% of their maximum heart rate, the TL-201 scan will have a greater

frequency of being abnormal than will the exercise ECG.(276) Iskandrian et.al. studied 65 patients who had inconclusive exercise ECGs; 54% were judged inconclusive because submaximal exercise had been performed, the remainder were inconclusive because resting ST segment abnormalities obscured the interpretation of the ECG.(277) The outcome of TL-201 testing in these patients is seen in figure 35. In this series the sensitivity and specificity of TL-201 imaging

FIGURE 35



for the detection of those with CAD was 70% and 95%, respectively. These values were significantly better than the stress ECG alone. Another potential concern is the effect of beta-blocker therapy on the accuracy of thallium scintigraphy. Although sensitivity was unchanged in those receiving beta-blockers, specificity was significantly decreased (87% without beta-blockers, 42% with beta-blockers).(278) In other words, beta-blocker therapy may cause a false-positive thallium scintigram. Therefore, to increase the diagnostic yield of TL-201 scintigraphy, it is advisable to discontinue beta-blocker therapy if at all possible. The potential for other medications (i.e. calcium-channel blockers) to influence the TL-201 scan have not been investigated.

b. <u>TL-201 scintigraphy with dipyridamole:</u> In patients who cannot exercise properly, thallium scintigraphy coupled with the administration of dipyridamole has been suggested as an alternative. The powerful coronary vasodilating effect of dipyridamole increases regional blood flow in areas perfused by normal coronary vessels, but not in zones supplied by stenotic arteries. This produces a heterogeneous flow pattern that can be detected by TL-201 scintigraphy when the radioisotope is administered at the peak of the vasodilatory effect.(279,280) Delayed redistribution is observed 2 to 4 hours later if underlying CAD is present without irreversible damage (279,281) Certain patients receiving dipyridamole during TL-201 scintigraphy will manifest clinical ischemia reflected by the development of angina and ST-segment depression.(282) These latter findings are probably related to the experimentally demonstrated decrease in subendocardial blood flow ("coronary steal") that is evident during maximal vasodilation in the presence of a critical stenosis.(279) The sensitivity and specifi-

city of dipyridamole TL-201 imaging for CAD detection is in the range of 90%, which is comparable to that of exercise scintigraphy with quantitative methods.(281,283,284) TL-201 scintigraphy with dipyridamole has been shown to be useful in evaluating patients prior to major vascular surgery (285) and has prognostic value in patients with a recent myocardial infarction.(286) Since intravenous dipyridamole is not approved for routine clinical use in the United States, the utility of large oral doses (200-400mg) in tablet form (287) or as an oral suspension (288) has been evaluated. The sensitivity and specificity were excellent and compared favorably with the intravenous form.(TABLE 24)

TABLE 24

Sensitivity and Specificity of Thallium-201 Scintigraphy With Intravenous and Oral Dipyridamole Administration for Detection of Significant Coronary Artery Disease

	Group I		Group II	
	Oral Dose (200 mg)	Intravenous Dose*	Oral Dose (400 mg)	Intravenous Dose*
Sensitivity (%)	65	85	84	79
Specificity (%)	100	100	100	86

*0.142 mg/kg per min for 4 minutes.

However, approximately 50% of the patients experience transient side effects including nausea, headache, dizziness, flushing, or vomiting. Angina and arrhythmias may occur in 25-30%, but would probably also have occurred during exercise testing. Myocardial infarction is a possibility if severe ischemia is prolonged, but this can usually be prevented by the prompt administration of I.V. aminophylline.

6. Rational Uses Of Thallium-201 Scintigraphy In CAD

Since thallium-201 scintigraphy is more time-consuming and considerably more expensive (range $600 to $900) than routine stress testing it is logical to limit its use to patients who would derive the greatest benefit from the results. If the study can eliminate the need for coronary arteriography, then the expense is justified. Unfortunately, in many circumstances a thallium study is obtained in patients with an obvious need of arteriography or in situations where it is unlikely to be of great benefit. Although it is difficult to make general statements that will depict every situation, thallium scintigraphy may be very helpful in the following:

a) The "uninterpretable" ETT: Nonspecific resting ST-segment depression, left ventricular hypertrophy, pre-excitation patterns, digitalis therapy or metabolic abnormalities all may cause the results of the stress ECG to be inconclusive. Patients with such "uninterpretable" ETTs are well suited for TL-201 scintigraphy, especially if they can exercise to a high workload (219,225,236,275) Patients with LBBB also may benefit, but septal perfusion defects may occur even in the absence of CAD.(289) All of the contributing factors should be con-

sidered and one would like to know that the patient has a reasonable exercise capacity before investing in a TL-201 study. For example, it is unlikely that an elderly patient with a sedentary life style will be able to generate enough cardiac work to make the TL-201 study worthwhile. Because of this it may be reasonable to assess exercise capacity with a standard stress ECG first, even though it will be uninterpretable.

b. The "inadequate" ETT: As discussed earlier, TL-201 scintigraphy may be of some benefit in patients who cannot exercise to at least 85% of their age-predicted maximum heart rate, but frequent mistakes are made because the whole clinical situation is not considered. The patient must be able to perform some reasonable level of exercise, such at least a heart rate maximum of 120 beats/-minutes. If less than 6 minutes of exercise is performed in a patient with a reasonable likelihood of CAD, this finding alone suggests a poor prognosis. In many instances a TL-201 scan is ordered when the clinical data and ETT suggest that arteriography is indicated. The high cost of TL-201 imaging precludes it being ordered to clarify every inadequate ETT. Although it is difficult to make generalizations that apply to each situation, frequent mistakes are made because physicians fail to consider all the clinical information.

c. The patients in the middle: Similar to routine stress testing, those patients who will derive the greatest benefit from thallium scintigraphy are those with an intermediate likelihood of CAD. This would include:

- Asymptomatic patients with an abnormal stress ECG.
- Nonanginal chest pain in patients with an abnormal or nondiagnostic stress ECG.
- Atypical chest pain in men regardless of the stress ECG.
- Typical angina in women with an equivocal stress ECG.
- Typical angina in men with a negative stress ECG.

Since the sensitivity and specificity of thallium scintigraphy are generally superior to those of the stress ECG alone, the likelihood of disease can be determined with greater confidence. Despite this, a recent report has shown that clinicians more frequently use thallium scintigraphy to confirm results in patients at the extremes of pretest likelihood of disease.(290)

d. Screening the asymptomatic patient: In general, the use of exercise testing with TL-201 scintigraphy for screening purposes in asymptomatic patients cannot be endorsed because a substantial number of positive test results will be "false-positive" according to Bayes theorem. Furthermore, the detection and treatment of presymptomatic CAD has not been shown to be of clear benefit. However, certain crucial occupations (i.e. airline pilots) may require periodic screening and for this purpose TL-201 scintigraphy is superior to routine treadmill testing.

I. EVALUATION OF CAD WITH RADIONUCLIDE VENTRICULOGRAPHY

Simultaneous with the initial clinical use of TL-201 for the detection of CAD, a radionuclide method for the evaluation of ventricular function was being developed. Two different techniques for functional imaging have emerged: the first-pass method and the equilibrium-gated blood ppol method. Although the type of imaging equipment and acquisition methods are different, both can provide an assessment of ventricular function and wall motion at rest and exercise. Since the gated equilibrium method seems to be the most popular and is used exclusively at Parkland and the VA, our discussion will be limited to this method.

1. The Technique of Gated Equilibrium Cardiac Blood Pool Imaging

This technique provides a means of imaging throughout the cardiac cycle by synchronizing the collection of scintillation data with electrocardiographic events. Repetitive sampling of many beats is performed until an adequate count density is obtained.(291,292) Several requirements must be met to insure valid data of high quality: (1) cardiac performance must be stable during acquisition of the data; (2) movement of the patient relative to the detector must be minimized; (3) radioactivity must remain intravascular at a constant concentration during the acquisition of data; (4) the framing intervals chosen must be sufficiently short to allow for temporal resolution adequate for the given heart rate; and (5) the duration of data acquisition must be sufficiently long for adequate count density and spatial resolution. Using the equipment that is available currently, all of these factors are easily addressed and satisfactory images can be obtained in most patients.

a. Variables assessed by radionuclide ventriculography: Using radionuclide ventriculography (RVG) a vide spectrum of functional variables can be assessed. Most can be evaluated both at rest and during exercise. A partial list of these variables is seen below:

Left Ventricle

- Ejection fraction (291, 292)
- End-diastolic, end-systolic and stroke volumes (293, 294)
- Cardiac Output (295)
- Wall motion
  - Visual (296)
  - Quantitative (297)
- Ejection rates (298)
- Filling rates (299)
- Ejection fraction or stroke volume functional images (300)
- Fourier phase and amplitude images with histograms (301)

Right Ventricle

- Ejection fraction (302)
- End-diastolic and end-systolic volume (303)

Other Variables

Left atrial function (304)
Pulmonary blood volume (305)
Hepatic blood volume (306)
Systolic pressure/volume ratio (307)

Although many of these variables have been shown to have some utility for the detection of CAD. (291-294, 296-302, 305-307), the majority of studies have concentrated on the use of the LV ejection fraction and wall motion response to exercise.

b. Normal and abnormal responses to exercise: On the basis of studies performed in subjects without evidence of cardiac or pulmonary disease, the normal ventricular response to exercise has been defined as an absolute increment of at least 5% in the left ventricular ejection fraction (LVEF) without the development of a new wall motion abnormality (308,309) This normal physiological response to exercise is usually associated with a small increase in LV end-diastolic volume and decrease in LV end-systolic volume (307), but the position in which exercise is performed (upright vs. supine) may modify this response (310) An increase of more than 5% in the LV end-systolic volume during exercise is considered abnormal. Others have defined the normal response by the absolute level of LVEF achieved during exercise.(311,312) It is important to note that in some apparently normal subjects > 60 years, LVEF does not increase normally with exercise and actually decreases in some patients.(313) This has been ascribed to the normal aging process. For patients in whom the resting LVEF is 75% or greater, the normal response has been defined as no diminution in EF with exercise (314) In such patients, it cannot be expected that a further decrease in end-systolic volume and associated increase in LVEF will occur with exercise. Inadequate stress due to physical limitations may be associated with a normal response despite underlying cardiac disease (309), whereas normal patients receiving beta-blocking agents may not demonstrate the appropriate increase in LVEF.(315)

2. Sensitivity And Specificity For The Detection Of CAD

Table 25 summarizes the experience with exercise RVGs for detecting CAD in 771 patients from 12 early studies. A new regional wall motion abnormality induced by exercise had a sensitivity of 76% and specificity of 95%. Failure to increase the LVEF with exercise had a sensitivity of 88%, but lower specificity, at 76%. When both variables were used together, exercise RVGs had an overall sensitivity of 89% and specificity of 91%. This was higher than that for stress ECG changes, even when studies that did not report ECG data were excluded. The fact that the sensitivity of the RVG is higher than that of the stress ECG is most likely due to the fact that abnormalities of LV contraction occur at a lower ischemic threshold than exercise-induced ST depression.(327)

a. Factors affecting the accuracy of the RVG: There are many factors that can affect the diagnostic accuracy of the rest and stress RVG. First, patients with single vessel disease especially of the right or circumflex vessels are less likely to have abnormal function during exercise.(316,328) Similar findings are

TABLE 25

COMPARISON OF EXERCISE ECG AND THE EXERCISE RVG FOR CAD DETECTION

STUDY	METHOD	# of Patients	ECG SEN. (%)	ECG SPEC. (%)	RWM SEN. (%)	RWM SPEC. (%)	EF SEN. (%)	EF SPEC. (%)	RWM and +EF SEN. (%)	RWM and +EF SPEC. (%)
Rerych (316)	FP	60	77	-	80	-	97	-	97	90
Borer (309)	E	84	68	95	94	100	89	100	95	100
Berger (317)	FP	73	55	100	47	100	73	100	87	100
Caldwell (318)	E	39	-	-	-	-	93	67	-	-
Borer (319)	E	53	-	-	-	-	-	-	93	100
Verani (320)	E	38	-	-	-	-	-	-	53	94
Kirshenbaum (321)	E	61	64	100	-	-	-	-	76	55
Caldwell (322)	E	52	44	91	-	-	93	54	-	-
Jengo (323)	FP	58	81	94	95	100	86	100	98	100
Pfisterer (324)	E	45	66	71	-	-	97	43	-	-
McEvan (325)	FP	144	-	-	52	100	76	52	-	-
Elkayam (326)	E	64	-	-	89	75	-	-	-	-
	TOTAL	771								
	AVERAGE		65	92	76	95	88	76	89	91

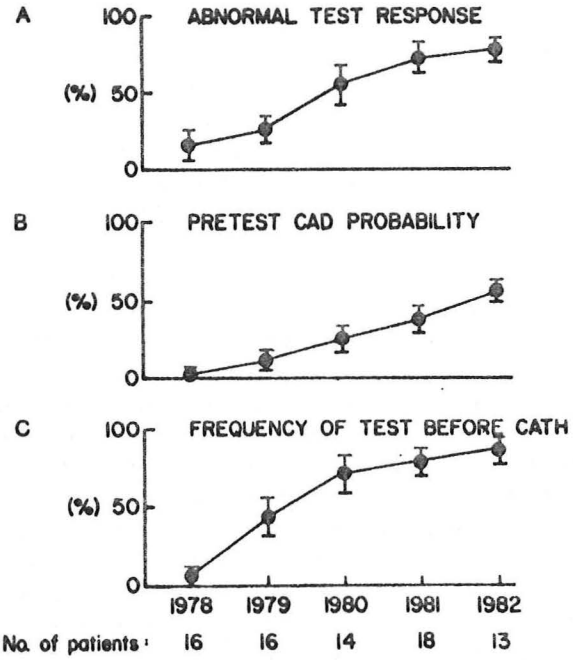
RWM=regional wall motion; EF=ejection fraction; FP=first pass; E=equilibrium; SEN=sensitivity; SPEC=specificity

seen with TL-201 in that the sensitivity for the detection of RCA or CX disease is somewhat lower.(TABLE 22) Although the change in LVEF during exercise is usually more marked in those with multivessel CAD, there is considerable overlap. Gibbons et.al. studied 281 patients with CAD and a normal resting LVEF and found that 81% had an abnormal response of LVEF to exercise.(329) The extent of CAD was only one of the variables that influenced the change in LVEF with exercise. Obviously, the factor of greatest importance is the amount of myocardium at risk, since among patients with single vessel disease there can be a wide variation in LVEF response.(330) Also, collateral vessels can affect the EF response. Second, the level of exercise and exercise end-points can affect the test results. An abnormal LVEF response to exercise is more common in patients with CAD who have chest pain or ST-segment depression during stress than in patients who have inadequate exercise.(317,331) Upton et.al.(327) exercised patients with CAD at 2 levels: submaximal, in which no patient developed ST-depression or angina and maximal during which all patients had either angina or ST-segment depression. Abnormal EF responses were encountered in 72% during submaximal exercise and in <u>all</u> patients at the higher level. Although some have found the presence of angina not to affect the EF response (309), most would agree that like TL-201 scintigraphy, the diagnostic power of the RVG can be affected by the level of stress performed. Third, left ventricular function at rest can affect the LVEF, during stress. Port et.al.(332) correlated the response of the LVEF during exercise to the resting LVEF in 150 patients with CAD. Patients with a normal resting LVEF developed the most profound decreases in exercise LVEF whereas those with resting LVEFs < 25% rarely had a further decline in LVEF during stress. This remained true even after the influence of exercise duration, extent of coronary disease and exercise end-point were considered. The most plausible explanation for this finding is that the frequency and magnitude of LV dysfunction during exercise depends on the amount of potentially ischemic myocardium present. Those with marked LV dysfunction at rest have more fibrosis and consequently less muscle mass in jeopardy. This view is supported by the observation that ECG evidence of ischemia is frequently not observed during exercise in patients with LV dysfunction at rest.(333) Fourth, certain drugs can modify the ventricular response to exercise and, thus alter the test accuracy. Nitroglycerin improves LV function, both at rest and during exercise in patients with CAD when given sublingually immediately prior to the test (334) or more chronically in the form of topical paste.(335) Several investigators have reported a decreased sensitivity of exercise RVGs among patients receiving propranolol (315,336), although others have not observed this difference.(337) Propranolol can improve regional and global LV performance in patients with CAD who manifest ischemic dysfunction during exercise without propranolol, but no significant effect is seen when ischemic changes are initially absent.(315,336,338) The effect of calcium channel blockers also has been investigated.(339-341) Similar to propranolol, no substantial alteration in resting function is observed. However, an abnormal functional response to stress was prevented especially if ischemia was present during exercise before treatment. Therefore, because drugs clearly can modify the response of the LV to stress, RVGs for diagnostic purposes should be performed in the absence of drug therapy if at all possible. Finally, approximately 30% of women with chest pain and normal epicardial coronary arteries will demonstrate either a decrease or failure to increase their LVEF during exercise. (311) While it is possible that this represents myocardial ischemia associated

with "small vessel disease" there also may be fundamental differences in the mechanism whereby women develop a normal response of stroke volume to exercise.(342) Other factors, such as severe hypertension, volume depletion and the level of previous physical conditioning can also affect the LVEF response to stress and must be considered before concluding that the results of the stress RVG indicate the presence of CAD.

b. What is the real specificity of the RVG? In 1983, Rozanski et.al. published an article entitled "The declining specificity of exercise radionuclide ventriculography."(343) They, and others had noted that although exercise RVGs were initially reported to be a very specific test for coronary artery disease (308,309,316,333), later studies demonstrated a substantial false-positive rate (312,313,320,344) In this study, the results of the exercise RVG in 77 patients with normal coronary arteriograms were related to the year in which the testing was performed. Figure 36 shows the results of this analysis. The frequency of

FIGURE 36



Abnormal Responses, the Probability of Disease, and the Sequence of Testing in the 77 Angiographically Normal Patients Studied between 1978 and 1982.

The frequency of abnormal ejection-fraction or wall-motion responses (Panel A) increased from 19 per cent in 1978 to 79 per cent in 1982; the mean probability of coronary-artery disease (CAD), exclusive of the result of radionuclide ventriculography (Panel B), increased from 3 to 56 per cent; and the frequency of radionuclide ventriculography before coronary angiography (CATH, Panel C) increased from 6 to 85 per cent.

an abnormal test result (LVEF or wall motion response) increased from 19% in 1978 to 79% in 1982. Since all these individuals had normal coronary arteries by angiography, these are false-positive responses. The pretest probability of CAD (exclusive of the RVG result) increased from 3% to 56% over this time period and the frequency of the RVG preceding the catheterization increased from 6% to 85%. Since all these tests were performed and interpreted in the same laboratory, under the same conditions, the only plausible explanation for this finding is that the patient population tested had changed. The cause of this change is probably related to the manner in which the RVG was introduced into clinical practice. Most of the early studies with RVGs compared the "sickest of the sick" to the "wellest of the well." That is, sensitivity and specificity were determined by evaluating patients after coronary arteriography; most with CAD had multivessel involvement, prior myocardial infarctions or both and many of the "normals" included young healthy volunteers or patients already known to have normal coronaries. This was true for their patients as well since the pretest likelihood of CAD in 1978 was only 3%. Based on these initial studies in somewhat biased populations, clinicians came to the opinion that stress RVGs were sensitive and specific for the diagnosis of CAD and, as a result, the test was used as a tool to determine the need for coronary angiography. As a result, in 1982, 82% of their patients had the RVG prior to angiography as compared to only 6% in 1978. If this analysis were carried to an extreme and only positive responders referred for angiography, the sensitivity would be 100% since all patients with disease would have a positive test. Conversely, the specificity would be 0% since all those without disease also would have a positive test. Therefore, a paradox develops: the better the test appears, the more likely it becomes that it will be used to determine the need for angiography; then, the more it is used for this purpose, the worse it appears. This phenomenon has been noted with other tests (345), is predictable (346) and is consistent with Bayes theorem. Therefore, when discussing specificity it is important to remember that exercise RVGs are not specific for CAD. Abnormal LV performance during exercise has been reported in many noncoronary conditions, in particular valvular heart disease (347,348), hypertension, and congestive or hypertrophic cardiomyopathies (349)

A second and perhaps more vexing problem is the definition of the normal response because different "normal" populations have different functional responses to exercise. Rozanski et.al.(350) evaluated the response of the LVEF to exercise in 3 different groups of "normals": a) 62 patients who had normal coronary arteriograms during the clinical evaluation of chest pain; b) 9 healthy, young volunteers; and c) 737 patients with unknown coronary anatomy, but a pretest likelihood of CAD that averaged only 34% based on age, sex, symptoms and the results of cardiac fluoroscopy, stress ECGs or thallium-201 scintigraphy. A wide range of EF responses was noted. In those with normal coronary arteriograms, 34% had an abnormal LVEF response and 35% developed abnormal wall motion during exercise. In contrast, all normal volunteers had a normal EF and wall motion during exercise. Therefore, volunteers and patients with a low disease probability provide too strict a standard and their use will cause specificity to be overestimated. On the other hand, catheterized normal patients provide to lenient a standard and their use will underestimate specificity. The problem of choosing the appropriate referent population for diagnostic testing does not have an easy solution. For this reason, to apply the data from a given study to your own patients you should ask the question: Were the

patients in whom the test performance was evaluated similar to the patients that I would refer for testing?

3. Rational Uses of the Exercise RVG and Comparison to TL-201 Scintigraphy

One obvious question is whether the exercise thallium study or exercise RVG is better for detecting and assessing CAD. Table 26 summarizes the results of

TABLE 26

COMPARISON OF EXERCISE TL-201 AND RVGs FOR CAD DETECTION

STUDY	# of Patients	TL - 201 SENSITIVITY (%)	TL - 201 SPECIFICITY (%)	RVG SENSITIVITY (%)	RVG SPECIFICITY (%)
Caldwell (318)	39	91	100	94	67
Borer (319)	53	81	90	93	100
Verani (320)	38	81	100	53	94
Kirshenbaum (321)	61	86	91	76	55
Jengo (323)	58	93	94	98	100
Pfisterer (324)	45	74	86	97	43
Elkayam (326)	64	96	75	89	75
Johnstone (351)	33	69	100	77	100
Total	391 Average	84	92	85	79

several studies that have directly compared the 2 techniques in the same patients. The sensitivity of both techniques is similar at 84% and 85%, but the specificity of the thallium study was higher (92% vs 79%). As discussed above, this is most likely due to the large number of noncoronary conditions that may cause an abnormal EF response to exercise.

In deciding which of these 2 approaches to use, it is worth emphasizing that both tests are time-consuming to perform and require a high level of technical sophistication. In that regard, the experience of a given laboratory with one or the other technique may be a crucial factor. In my opinion, there is no clear "better" test; under certain circumstances each has advantages and disadvantages. Below are listed some factors that may help determine which test is preferred:

<u>Tl-201 PREFERABLE</u>

1) In the presence of certain arrhythmias (i.e. atrial fibrillation, frequent ventricular premature beats) which may interfere with the ability to properly "gate" the blood pool scan.

2) Usually performed with upright exercise (i.e. treadmill or upright bicycle) which is sometimes easier for patients and is more like the normal physiological situation.

3) More easily coupled to standard exercise protocols (i.e. Bruce etc...) and requires only a standard treadmill, not a supine table.

4) When the presence of CAD needs to be evaluated in a patient who may have exercise-induced LV dysfunction for some other reason (i.e. valvular disease or HBP) For example, screening an airline pilot with hypertension.

5) When the LVEF is severely depressed at rest.

EXERCISE RVG PREFERABLE

1) When a measurement of LVEF is also necessary

2) When extraneous factors could cause the impression of decreased or heterogeneous myocardial uptake (i.e. large breasts, mastectomy, left pleural fluid, pacemaker hardware etc...)

3) When RV function must also be assessed.

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4. EXERCISE RVGs AND PROGNOSIS IN CAD.

Like TL-201 scintigraphy, exercise RVGs have been employed for determining prognosis in patients with known CAD. As noted before, patients with left main stenosis and, in some situations, 3 vessel CAD have a poor prognosis. Therefore, Phillips et.al.(352) assessed the ability of the exercise LVEF response to identify those with and without this anatomy. In their series of 250 patients with CAD, 10% had left main stenosis and 18% severe 3 vessel CAD. Of those patients who manifested a decrease of > 10% in LVEF during stress, 53% had either left main or 3 vessel disease (22% had left main, 31% had 3vessel CAD). In contrast, of those who had an increase or less than a 5% decrease in LVEF during stress only 6% had 3vessel CAD and none had left main stenosis. Thus, a large (> 10%) decrease in EF during stress suggests a 50% chance that severe "high risk" CAD is present. Subsequently, they extended these observations to show that mortality and the requirement for subsequent revascularization were directly proportional to the magnitude of LVEF decrease during stress (353) In those with only a small decline in exercise EF (0-4%) there was no mortality and a 16% incidence of the need for coronary bypass surgery during 30 months of follow-up. In contrast, when the exercise LVEF decreased by > 10%, mortality was 7% and 37% of the patients required surgery during followup. In both of these studies, many of the patients had moderately depressed LV function at rest and important symptoms, both of which are known to be prognostically important. Since the authors did not consider these effects independently, it is difficult to assess the additional contribution of the exercise data. However, Bonow et.al.(354) examined a population of patients that was more uniform and known to be at low risk. They evaluated 117 patients with well-preserved LV function

(LVEF > 40%) who had only mild (Class I or II) symptoms or were asymptomatic. They found that the EF response during exercise was useful in identifying those with a greater chance of death or increasing angina (FIGURE 37) Moreover, in

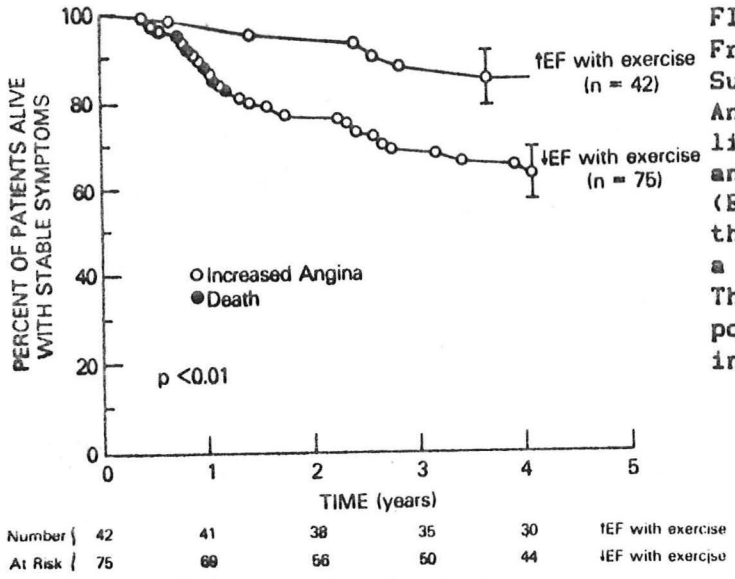
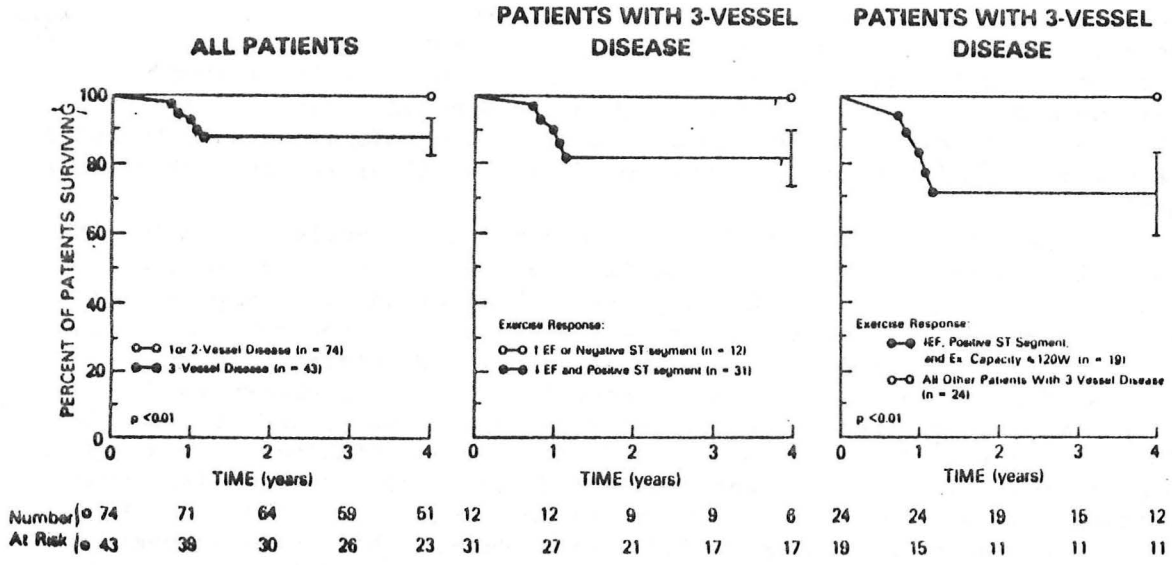


FIGURE 37: Influence of Ejection Fraction Response to Exercise on Subsequent Mortality and Increased Angina Requiring Operation. The life table curve for patients with an increase in ejection fraction (EF) with exercise is compared with the curve derived for patients with a decrease in ejection fraction. The number of patients with potential follow-up at each year is indicated for each group.

FIGURE 38



Influence of Anatomic Severity of Coronary-Artery Disease, Reversible Ischemia, and Exercise Capacity on Survival.
Survival curves are shown for patients with three-vessel disease as compared with those with one- or two-vessel disease (A), patients with three-vessel disease and an increase in ejection fraction (EF) or a negative ST-segment response to exercise as compared with those with three-vessel disease and both a decreased ejection fraction and a positive ST-segment response with exercise (B), and patients with three-vessel disease and a decrease in ejection fraction during exercise, a positive ST-segment response, and exercise capacity of 120 W or less as compared with all other patients with three-vessel disease (C). The number of patients with potential follow-up at each year is shown for each group. ($P<0.01$ by Mantel–Haenszel test.)

the subgroup of patients with 3 vessel CAD, their data suggested that patients with an increased risk of dying could be identified by their exercise capacity and objective signs of reversible ischemia. (FIGURE 38 right panel) The prognostic power of the RVG was confirmed by Pryor et.al. (355) who followed 386

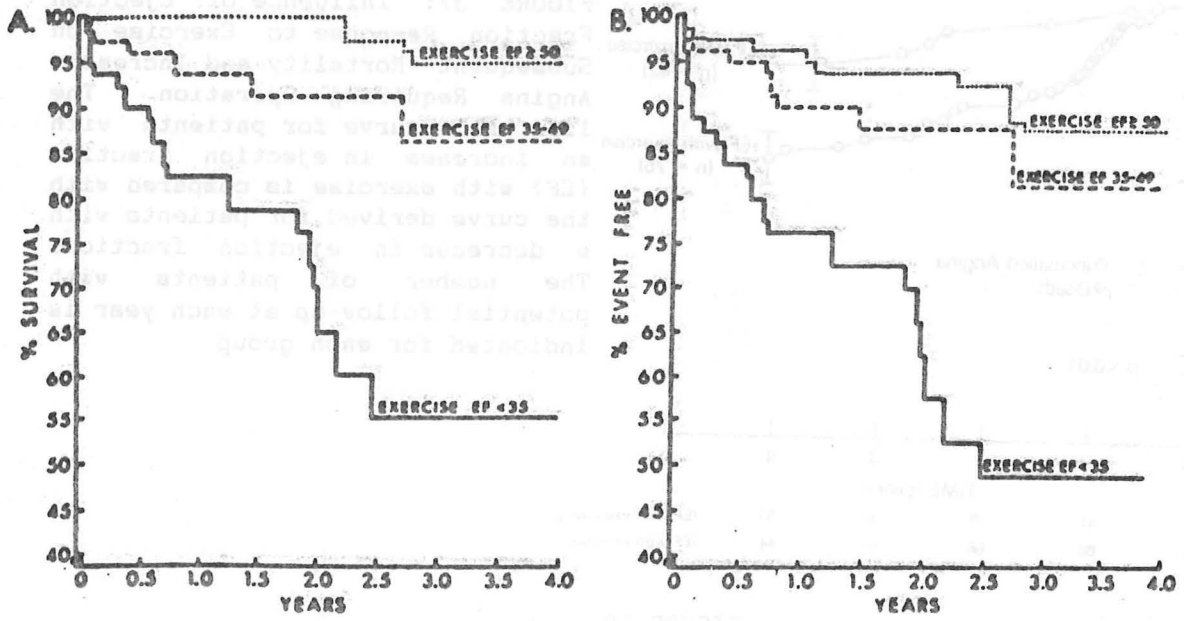


FIGURE 39

consecutive medically treated patients for 4 years. Figure 39 demonstrates the percent survival (left panel) and percent that were cardiac event free (right panel) as stratified by the peak exercise ejection fraction. As the peak exercise ejection fraction diminished, so did survival and the likelihood of an event-free course. However, common to this and many of these studies is the criticism that no attempt was made to determine if the information contributed by the RVG was helpful beyond that obtained from the clinical characteristics alone. (345)

The results of the exercise RVG studies cited above would indicate that high-risk patients with CAD can be identified by the extent of reversible myocardial ischemia reflected by the EF response. Whether patients who exhibit an abnormal response have an enhanced survival with surgical compared to medical therapy is not known based on the results of randomized trials. In one nonrandomized study, patients who demonstrated the greatest decrease in EF preoperatively had the most favorable outcome with surgery as judged by survival statistics and relief of pain. (356) (FIGURE 40) Similar findings were noted by Kronenberg et.al. who reported that patients showing the greatest improvement postoperatively were those demonstrating the most significant fall in EF in response to exercise preoperatively. (357) In summary, these data suggest that the functional response of the LV to exercise can be helpful in predicting anatomy, prognosis and the response to revascularization in patients with CAD.

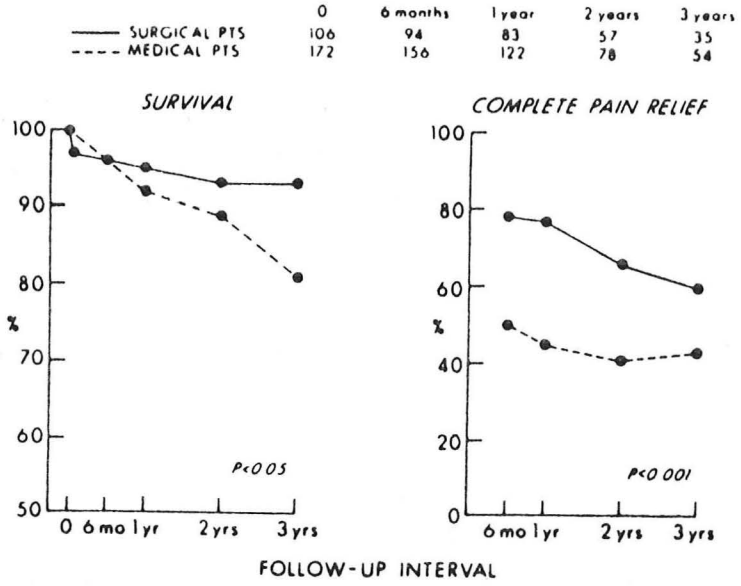


FIGURE 40: Life-table curves comparing the survival and incidence of complete pain relief in patients treated surgically and medically in 278 patients undergoing exercise radionuclide angiography. The solid line represents patients with a positive radionuclide angiogram, whereas the dotted line represents patients with a negative radionuclide angiogram.

J. CARDIAC CATHETERIZATION AND CORONARY ARTERIOGRAPHY

Although the clinical examination and noninvasive techniques described above are extremely valuable, they are far from perfect. For that reason, the definitive diagnosis of CAD and a precise assessment of its anatomical severity and effects on LV performance require cardiac catheterization and coronary angiography.(4) As with any diagnostic procedure, the decision to perform catheterization and angiography must be based upon a careful balance between the risks of the procedure and the anticipated value of the information obtained.

1. Cardiac Catheterization: What Is The Risk?

a. Major complication rates for cardiac catheterization: Table 27 summarizes the reported major complication rates for cardiac catheterization. Generally in these studies, catheterization-related mortality was defined as death that occurred: a) during the procedure, b) within 24 hours after the procedure and was not attributable to any non-catheterization related cause, or c) several days after the procedure, but clearly precipitated by an event occurring during the procedure. As these studies demonstrate, the occurrence of these major complications varies substantially, but, in general, have decreased in the more recent surveys. This probably reflects continuing improvements in catheter design, radiographic equipment and contrast agents, all aimed at improved patient safety. Because of this, complication rates from the earliest studies may no longer be relevant.

TABLE 27

COMPLICATIONS OF CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY

STUDY	YEAR	# Of Patients	Complications (%) Within 24 Hours DEATH	MI	CVA	COMMENTS
Adams (358)	1973	46,904	0.45	0.61	0.23	No Heparin
Takaro (359)	1973	3,044	1.6•	-	-	VA Study •Complications up 10 days
Sones (360)	1976	52,953	0.07	0.03	0.008	All brachial method
Adams (361)	1979	89,079	0.14	0.17	0.09	
Society for Cardiac Angiography (362)	1982	53,581	0.14	0.07	0.07	
CASS (363)	1983					
age < 65		17,165	0.06	0.29	0.05	
age > 65		2,144	0.19	0.79	0.19	

The recent report from The Society for Cardiac Angiography defines more clearly the patients who are at greatest risk.(362) Seventy-seven percent of the 53,581 patients in this survey were evaluated for CAD; the remainder comprised those with valvular disease, congenital disease or other cardiac conditions. The important findings relevant to the patient with suspected CAD are summarized in Tables 28-30. From these data, several points should be empha-

TABLES 28-29

MORTALITY RATE BY AGE GROUP

AGE	MORTALITY RATE
< 1	1.75%
1 to 60 years	0.07%
> 60 years	0.25

MORTALITY BY FUNCTIONAL CLASS

Functional Class	Mortality Rate (%)
I	0.02
II	0.02
III	0.12
IV	0.67
Unknown	0.12

TABLE 30

MORTALITY RATE IN PATIENTS WITH CAD

Anatomic Class	# Of Patients	Mortality Rate (%)
Normal or minimal disease	11,418	0
1 vessel	6,601	0.03
2 vessel	7,706	0.05
3 vessel	11,884	0.16
Left main $\geq$50%	2,452	0.86
Unknown	1,143	0

sized. First, mortality rate is related to age with the very young and older adult at greatest risk. This finding was confirmed by the CASS survey(363). Second, as the functional class deteriorates mortality increases. Finally, mortality increases in those with the most serious anatomic findings. It is important to note that in those who were studied and found to have no significant disease (11,418 patients) there was no mortality. These findings suggest that the "sickest" patients (i.e. those with left main and 3 vessel CAD or severe symptoms) have the greatest likelihood of mortality. Of course, these are the patients in whom the procedure is most indicated. In contrast, for those in whom the procedure is being done to "rule-out CAD" (i.e. those who have minimal functional impairment or are found to have normal coronaries), the mortality rate is similar to that of standard exercise testing (0.01%)(364) Obviously, there are other important complications that may occur as a result of cardiac catheterization and substantial cost factors. These must be balanced against the potential benefits of performing the most definitive diagnostic procedure available. Some contend that the procedure is used too frequently while others feel it is not used enough.(365,366) Although this issue does not have a crisp answer, consider the following statistics assembled from the American Heart Association and National Center for Health Statistics:

- Approximately 4,670,000 people in the USA have coronary heart disease.
- Of these, approximately 1.5 million will suffer a MI this year.
- Of those who have a MI, 520,000 will die; 200,000 will die before they every reach a hospital.
- It is estimated that approximately 500,000 cardiac catheterizations will be performed this year. Of these, about 25% will be performed for non-coronary problems or will be in patients who are found not to have CAD. Thus, 375,000 procedures will be performed on those with CAD.

THIS MEANS THAT:

- Only 11% of the patients with CAD will have catheterization yearly.

- Assuming an overall procedure mortality rate of 0.11%, there will be 413 deaths as a result of cardiac catheterization.

- For each person with CAD who dies as a result of cardiac catheterization, 1259 will die as a result of their disease.

Clearly, I have made some assumptions in the presentation of this information including the implication that cardiac catheterization would somehow save the lives of many who will die. Nevertheless, these data do not appear to suggest that too many catheterizations are being done. I am not suggesting that every patient with the slightest hint of CAD be subjected to catheterization, but I do believe that more patients have suffered complications or died because their CAD was either not diagnosed or improperly evaluated than have ever suffered because a truly "unnecessary" catheterization was performed.

Because of the every-increasing emphasis on cost-containment and the overall safety of cardiac catheterization, many centers have now developed outpatient cardiac catheterization facilities. With proper patient selection, the safety of this approach is excellent and the cost averages 24%-40% less than that of hospital-based services.(367,368) In light of these potential benefits, The American College of Physicians recently has endorsed hospital-based outpatient procedures.(369)

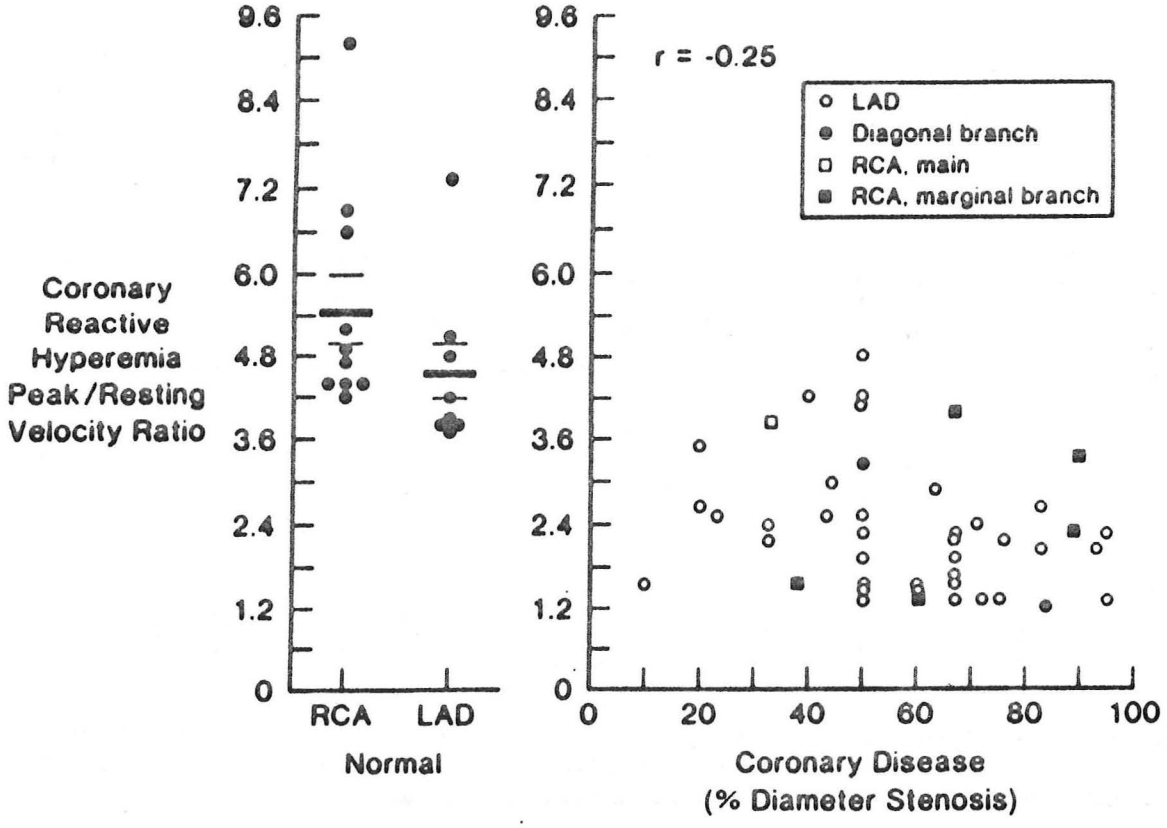
2. Coronary Angiography: Is it the "gold standard"?

a. <u>The problems:</u> Despite dramatic improvements in coronary angiographic techniques, interpretation of the exact location and severity of obstructive lesions in the coronary arteries remains imperfect. Once an atherosclerotic narrowing is localized, its severity is usually expressed as "percent stenosis", the reduction in diameter relative to the nearby "normal" lumen. Although this approach is used by the majority of cardiologists, cardiac surgeons and radiologists, there are several shortcomings. First, numerous studies have documented substantial interobserver and intraobserver variability in the interpretation of the coronary arteriogram.(370-373) For example, DeRouen et.al.(372) found that 11 experienced cardiac angiographers had an average standard deviation of 19% in the estimation of the worst lesion in defined arterial segments from clinical studies. Even under the best of circumstances, when the lesions are well-seen and potential errors in locating them are eliminated, expert angiographers, as a group, estimate the severity of specified lesions with a variability averaging 7% to 012%. Second, the primary method for validating the arteriographic interpretation of a coronary stenosis has been to compare angiograms with postmortem pathological studies.(374) Such comparisons may not be appropriate, because the coronary arteriogram reflects the luminal geometry of the distended vessel, whereas in most pathological studies, undistended vessels have been examined.(375) Hence, it is not surprising that most of these studies have concluded that coronary angiography usually underestimates the severity of the actual lesion.(376) In contrast, other studies suggest that lesions in the 60% to 90%

range may be overestimated. (372, 377) Angiographic overestimation of lesion severity also may occur because of inadequate filling of the vessel with contrast, abnormalities of coronary runoff or concomitant coronary artery spasm. Moreover, technical problems at the time of the study or differences in radiographic magnification and distortion may cloud the interpretation. (378, 379) Finally, the most important factor may be the usual diffuse nature of coronary atherosclerosis. (376) Although lesions often appear as focal obstructions separated by uninvolved areas angiographically, pathological evaluation usually reveals diffuse involvement (380) This diffuse involvement commonly results in an underestimation of the demoninator for the equation expressing the percent diameter stenosis.

The value of the visual interpretation of coronary arteriograms has been challenged recently by White et. al. (381) Caliper measurements of the degree of coronary stenosis were related to the reactive hyperemic response of coronary flow velocity studied with a Doppler technique at the time of coronary bypass surgery. The coronary reactive hyperemic response previously has been used extensively to measure coronary vasodilator reserve. (382, 383) Increasing degrees of vessel obstruction cause a gradual diminuation of the reactive hyperemic response, thus it was expected that the measured coronary vasodilator reserve would be inversely proportional to the percent stenosis severity. However, this was not found. Figure 41 presents the results of this study. In

FIGURE 41



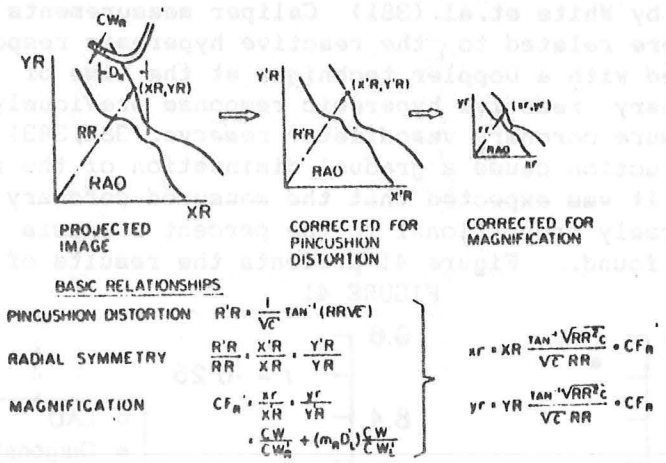
Relation between the Measured Percentage of Vessel-Diameter Stenosis for the Most Severe Lesion Assessed from the Coronary Angiogram and the Coronary Reactive Hyperemic Response (Ratio of Peak to Resting Velocity) Obtained from Doppler Velocity Recordings at the Time of Open-Heart Surgery, for All Vessels Studied.

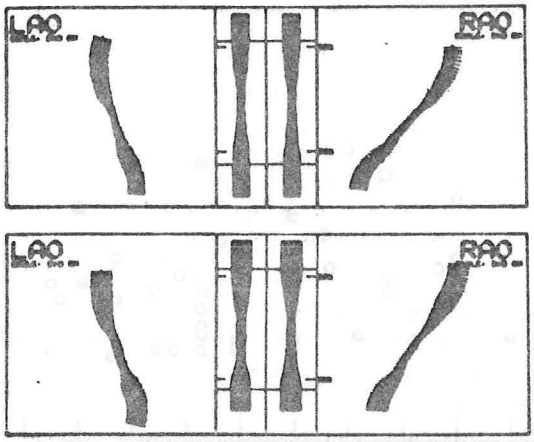
The left panel shows reactive hyperemic responses in normal coronary vessels, and the right panel shows responses in abnormal vessels. RCA denotes right coronary artery, and LAD left anterior descending artery; "diagonal branch" refers to the branch of the left anterior descending artery.

normal vessels (left panel) coronary vasodilator reserve was 5.5±0.5 in the RCA and 4.6±0.4 in the LAD. In contrast, those with CAD had depressed vasodilator reserve, but there was no correlation with the angiographic assessment of severity. These findings suggested that the conventional angiographic assessment of coronary obstructions may be subject to considerable error.

b. Potential solutions to the problem: Solutions to the problems associated with the visual assessment of coronary stenoses have developed in two different areas. Several investigators have developed quantitative, computer-based methods to evaluate coronary angiograms.(385-388) These methods usually require 2 orthogonal views and correct for out-of-plane magnification and pincushion distortion.(FIGURE 42) From this analysis absolute vessel dimensions, cross-

FIGURE 42





CONTROL

	NORMAL AREA [mm²]	MINIMUM DIAMETER [mm]	MINIMUM AREA [mm²]	FLOW RESISTANCE [mm Hg/cm³/sec]
ABSOLUTE	5.2	1.03	0.87	10.3
% STENOSIS		60%	83%	

NITROGLYCERIN

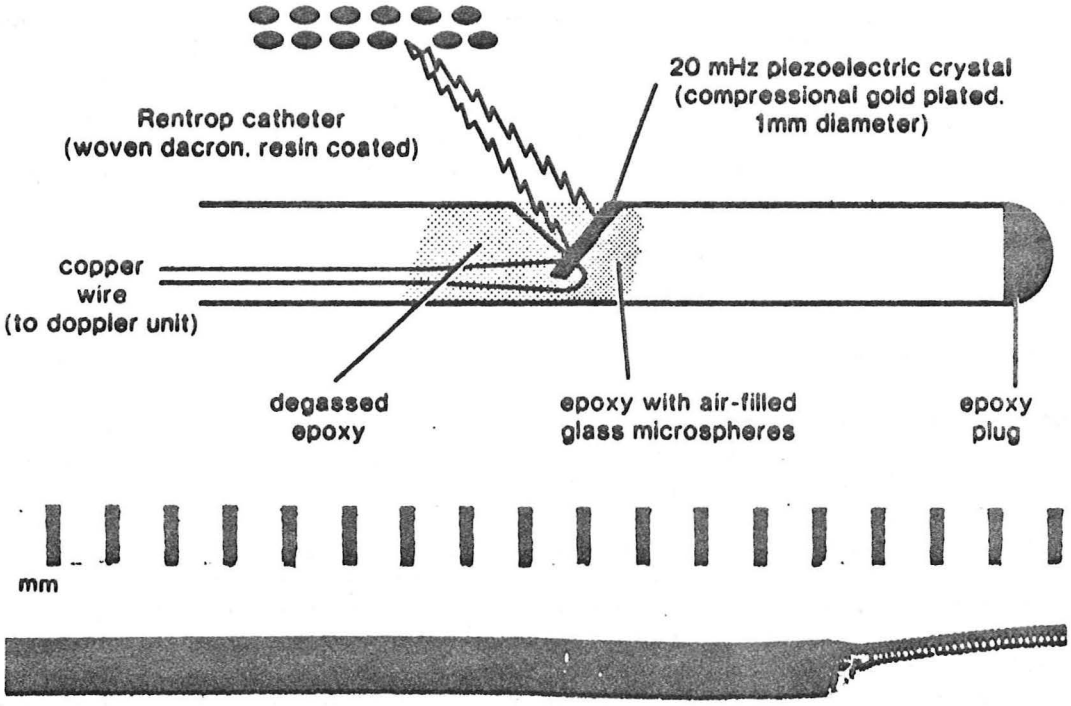
ABSOLUTE	7.6	1.18	1.12	6.5
% STENOSIS		59%	83%	
CHANGE with NITROGLYCERIN	2.4 (46%)	0.15 (15%)	0.25 (29%)	-3.8 (37%)

FIGURE 43: Representative computer printout of segmental stenosis images and dimensional data for pre- and post-nitroglycerin (0.4 mg, sublingual) angiograms of this 60 per cent mid-right coronary artery stenosis.

sectional area and length can be calculated to derive a very precise 3 dimensional evaluation of stenosis severity.(FIGURE 43) When such quantitative measurements are compared to the intraoperative assessment of the coronary hyperemic response, a good relationship between vessel minimal cross-sectional area and coronary flow reserve is found.(389) Moreover, Kirkeeide et.al. have developed and validated the concept that coronary flow reserve can be predicted by quantitative coronary arteriography when all dimensions of a coronary artery stenosis are considered.(390) Therefore, it appears that quantitative analysis techniques offer substantial improvement to the interpretation of the arteriogram. Presently, these methods have only been available in selected research centers, but soon several commercial companies will market systems for this purpose.

The second method to improve the assessment of stenosis severity and determine its functional importance has been to actually measure coronary flow reserve during the catheterization procedure. This can be accomplished in one of two ways. Coronary blood flow velocity can be measured directly using an intracoronary doppler catheter.(391,392)(FIGURE 44) Coronary blood flow velocity is

FIGURE 44



Top, Schematic diagram of the distal portion of the coronary Doppler catheter. The copper wires attached to the piezoelectric crystal exit from the proximal end of the catheter and are connected to a pulsed Doppler meter. *Bottom*, Photograph of the distal 3 cm of the catheter. A very flexible coiled wire has been attached to the tip to enhance safety in human studies.

measured at rest and again after the intracoronary administration of papaverine, a potent, short-acting vasodilator.(393) The ratio of flow-velocity during vasodilation to flow velocity at rest is the coronary vasodilator reserve of the vessel. Presently, there are several limitations to this technique including: a) a small risk of coronary dissection due to catheter manipulation, b) inability to study some vessels because of anatomic factors, and c) poor signals with interference from the vessel wall. Coronary flow reserve also can be estimated using digital radiographic methods.(394-397) These measurements are based on the fact that under hyperemic conditions, contrast agents reach the myocardium earlier and with greater density (intensity). Four to 7 ECG-gated diastolic pictures are made as a radiographic contrast agent is precisely administered into the coronary circulation by a power injector. Then, by subtracting a "mask" image of the heart obtained prior to the administration of contrast, a contrast medium appearance picture (CMAP) can be formed. In this format, color modulation is used to depict the contrast medium appearance time and intensity modulation is used to depict peak contrast medium density. A pair of CMAPs are obtained reflecting flow at rest and after the administration of a potent coronary vasodilator. By analyzing the rate and intensity of contrast appearance in regions subserved by the various vessels, coronary flow reserve can be estimated. This technique has been validated in the dogs (395) and used to assess coronary flow reserve in patients with normal arteriograms (398), saphenous vein grafts (399) and before and after coronary angioplasty.(400) This technique also has limitations including artifacts caused by: a) motion or irregular cardiac rhythms, b) superimposition of vessels and other dye-containing structures (i.e. coronary sinus), c) poor flow at rest distal to a very severe lesion and d) collateral flow from the contralateral coronary vessel. Despite the limitations occurring with these 2 techniques, they both offer the possibility of a more physiological assessment of the significance of a coronary stenosis in the catheterization laboratory.

RECOMMENDATIONS FOR THE EVALUATION OF THE PATIENT WITH CHEST PAIN

A. CURRENT THERAPY OF CAD

We began this review by emphasizing that the diagnosis, prognosis and management of the patient with CAD are all interrelated. Proper evaluation must be directed not only to establishing the correct diagnosis, but also to determining the prognostic and therapeutic implications of the diagnosis. For this reason, we should consider briefly the major therapeutic modalities and their indications. Presently, the therapy of CAD is accomplished by medications, coronary artery angioplasty (PTCA) or coronary artery bypass surgery. Although years passed before 3 randomized trials were completed, we now have a reasonably clear understanding of those who acquire an improved life expectancy from surgery. These results are summarized in Table 28. Ironically, almost simultaneously with the publication of these studies, the technique of coronary angioplasty was being developed. Now that these studies tell us which patients do and do not benefit from surgery, we are forced to ask the question: Would angioplasty be better? The rapid proliferation of coronary angioplasty as a treatment modality is drastically altering the therapy of CAD and, not unexpectedly, the manner in which patients are evaluated. Randomized studies of angio-

TABLE 28

RANDOMIZED TRIALS OF
MEDICAL VS. SURGICAL THERAPY IN CORONARY DISEASE

	Improved Survival with Surgery				
				3-vessel disease	
	LEFT MAIN	1-vessel disease	2-vessel disease	LV dysfunction	Normal LV function
VA Study (401)	Yes	No	No	Yes+	No
European Study (174)	Yes	No Data	No	No Data	Yes
CASS (402)	Yes*	No	No	Yes+	No

* = derived from nonrandomized patient studies (176)
\+ = derived from long-term follow-up experience (185,186)

plasty are now beginning and hopefully will determine the proper role for this technique before the same question is necessary regarding laser therapy of the atherosclerotic lesion.

Nevertheless for the here-and-now, the evaluation of angina should be focused toward determining if the patient has a situation for which surgery or angioplasty are potentially beneficial. In 1986, general indications for surgery are:

1. Severe, disabling angina pectoris poorly responsive to medical therapy.

2. Unacceptable limitations in lifestyle imposed by angina pectoris or by drug side effects.

3. Left main coronary artery stenosis (> 60%)

4. 3 vessel CAD with:
   a) LV dysfunction at rest, or
   b) normal LV function at rest, but poor exercise tolerance and evidence of important inducible ischemia.

(Adapted from reference 403)

These indications are intended as general guidelines only and are not absolute. The individual clinical circumstances of each patient must be considered.

Since there are no randomized studies, the indications for coronary angioplasty are more variable. In 1986, reasonable indications for coronary angioplasty are:

1. Severe angina pectoris poorly responsive to reasonable medical therapy in a patient with acceptable coronary anatomy.

2. Objective evidence of marked ischemia regardless of symptoms in a patient with acceptable anatomy.

3. Asymptomatic or mildly symptomatic patients with "compelling" anatomy such as proximal LAD or dominant RCA stenoses.

(adapted from references 404,405)

Again, these indications are only guidelines and must be considered along with the success and complication rate of the physicians pereforming the procedure.

B. CONCLUSIONS AND RECOMMENDATIONS

Considering the influences of prognosis and treatment, I have developed a general algorithm for the evaluation of the patient with chest pain suspected to be angina.(FIGURE 45) Based upon the history alone, it is possible to develop a reasonable estimate of the likelihood of CAD in an individual patient. In those with a high or very high likelihood of CAD, subsequent testing should be directed toward risk stratification, not confirmation of the diagnosis. In those with a low or intermediate likelihood of CAD, the diagnosis must first be confirmed and then risk stratification performed. Often, this can be accomplished with the same test. Much has been written about noninvasive methods to identifiy those at "high risk." When such patients are identified, the further evaluation is not in question, invasive testing is indicated. Conversly, frequently the physician can prove that a patient is "low" risk. Although these patients may have CAD and angina, their exercise performance is good and they can be proven to have only a small amount of myocardium at risk. In these patients, invasive testing is not mandatory. However, what about those in the middle; those who are neither "high" nor "low" risk. These are the patients we see every day. They are the ones who:

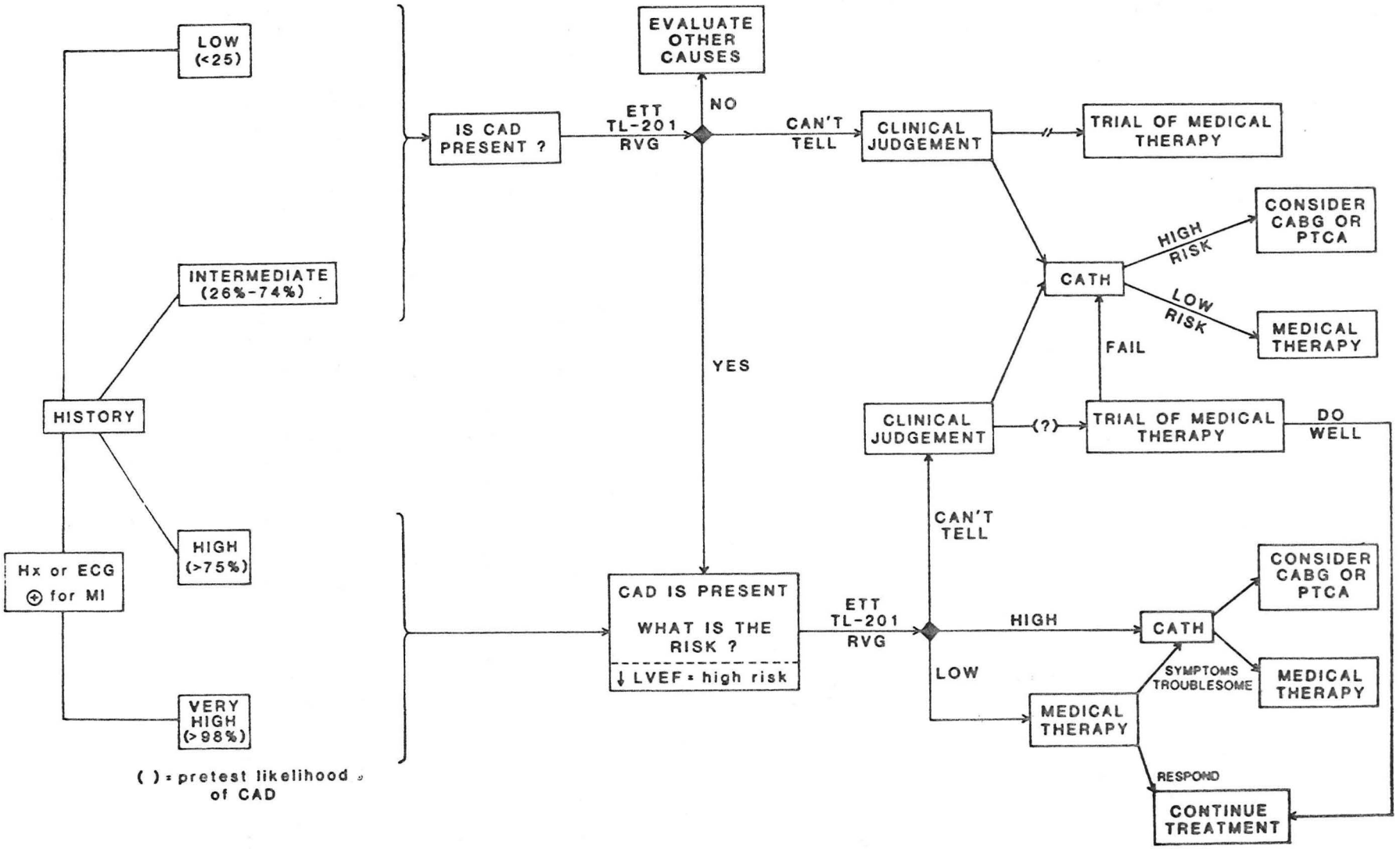
- have chest pain that usually sounds like angina, but not always,

- had a severe, prolonged episode of chest pain 2 weeks ago, but none since,

- have neither 4mm of ST-segment depression after 3 minutes nor 1mm of ST depression after 12 minutes on the treadmill.

What is the appropriate evaluation for these individuals? Of course, there is no single correct answer to this question; each case must be considered individually. However, the fact remains that the disease being evaluated is still the leading cause of death in the United States today. Because of this, it seems inappropriate to remain uncertain of the diagnosis or only guess at the risk to the patient. If noninvasive testing can accurately establish the diagnosis and risk, angiography is not necessary. However, when the diagnosis is in doubt or the risk is not clear, invasive testing should be strongly considered.

TABLE 45


LOW (<25)
INTERMEDIATE (26%-74%)
HIGH (>75%)
VERY HIGH (>98%)
HISTORY
Hx or ECG ⊕ for MI
( ) = pretest likelihood of CAD
IS CAD PRESENT ?
ETT TL-201 RVG
EVALUATE OTHER CAUSES
NO
YES
CAN'T TELL
CLINICAL JUDGEMENT
TRIAL OF MEDICAL THERAPY
CATH
HIGH RISK
CONSIDER CABG OR PTCA
LOW RISK
MEDICAL THERAPY
FAIL
CLINICAL JUDGEMENT
(?)
TRIAL OF MEDICAL THERAPY
DO WELL
CAN'T TELL
CAD IS PRESENT
WHAT IS THE RISK ?
↓ LVEF = high risk
ETT TL-201 RVG
HIGH
CATH
CONSIDER CABG OR PTCA
LOW
SYMPTOMS TROUBLESOME
MEDICAL THERAPY
MEDICAL THERAPY
RESPOND
CONTINUE TREATMENT

APPENDIX

PROBABILITY. - An expression of opinion, on a scale of 0 to 1.0, about the likelihood that an event will occur.

PRETEST PROBABILITY. - The probability of disease before doing a test. (Synonyms: prior probability, pretest risk.)

POSTTEST PROBABILITY. - The probability of disease after the results of a test have been learned. (Synonyms: posterior probability, posttest risk.)

ODDS. - The odds of an event is another way to express its probability.

$$\text{Odds} = \frac{\text{Probability of event}}{1 - \text{Probability of event}}$$

PREVALENCE. - The likelihood of a positive test result in a diseased person. (Synonym: true-postive rate, abbreviated TPR.)

TEST SENSITIVITY. - The likelihood of a positive test result in a diseased person. (Synonym: true-positive rate, abbreviated TPR).

$$\text{Sensitivity} = \frac{\text{Number of diseased patients with positive test result}}{\text{Number of diseased patients}}$$

TEST SPECIFICITY. - The likelihood of a negative test result in a patient without disease. (Synonym : true negative rate; abbreviated TNR.)

$$\text{Specificity} = \frac{\text{Number of nondiseased patients with negative test result}}{\text{Number of nondiseased patients}}$$

FALSE-POSITIVE RATE (FPR). - The likelihood of a positive test result in a nondiseased patient.

FALSE-NEGATIVE RATE (FNR). - The likelihood of a negative test result in a diseased patient.

LIKELIHOOD RATIO. - A measure of discrimination by a test result. A test result with a likelihood ratio greater than 1.0 raises the probability of disease and is often referred to as a "positive" test result. A test result with a likelihood ration of less than 1.0 lowers the probability of disease and is often called a "negative" test result.

$$\text{Likelihood ratio} = \frac{\text{Sensitivity}}{\text{False-positive rate}}$$

BAYES' THEOREM. - A simple algebraic expression for calculating the posttest probability of disease if the pretest probability of disease [P(D)] and the performance characteristics of a test are both known.

Probability of disease if test result is positive:

$$\frac{P(D) \times TPR}{P(D) \times TPR + [1 - P(D)] \times RPR}$$

Probability of disease if test result is negative:

$$\frac{P(D) \times FNR}{P(D) \times FNR \quad [1 - P(D)] \times TNR}$$

Probability of positive test result:

$$P(D) \times TPR + [1 - P(D)] \times FPR$$

Odds ratio form of Bayes' theorem:

Posttest odds = pretest odds x likelihood ratio

EXAMPLE: A clinician is planning to use a test with a sensitivity (TPR) of 0.9 and a false-positive rate (FPR) of 0.05. Suppose the pretest probability of disease, P(D), is 0.25. The probability of disease if the test result is positive is expressed by the following formula:

$$\frac{P(D) \times TPR}{P(D) \times TPR + [1 - P(D)] \times FPR},$$

or

$$= \frac{0.25 \times 0.9}{0.25 \times 0.9 + 0.75 \times 0.05} = \frac{0.225}{0.225 + 0.0375} = 0.857$$

The pretest odds are 0.25/0.75 = 0.33 to 1.0. The likelihood ratio for the test is 0.9/0.05 = 18.0.

Posttest odds = pretest odds x likelihood ratio = 0.33 x 18.0 x 6 to 1.

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