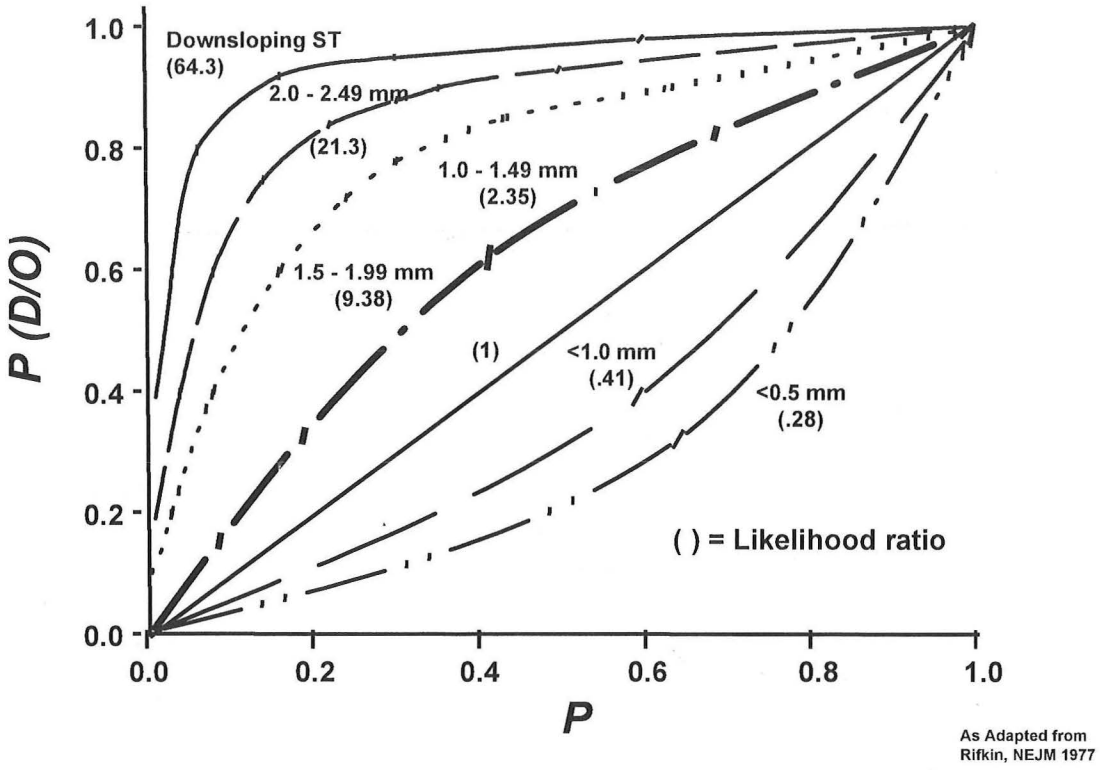
Cardiol

THE FUNDAMENTAL FALLACY OF BAYESIAN ANALYSIS OF THE EXERCISE TOLERANCE TEST: HAVE WE BEEN TAUGHT WRONG?



As Adapted from
Rifkin, NEJM 1977

Benjamin D. Levine, M.D.

This is to acknowledge that Benjamin D. Levine, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Levine will not be discussing "off-label" uses in his presentation.

Biographical Information:

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Professional Interests: My global research interest is in the adaptive capacity of the cardiovascular system. The primary models that I have used include exercise training, bed rest or spaceflight induced cardiovascular deconditioning, and high altitude. I have tried to match my clinical focus with these research interests. For example, my interest in exercise training has led to an expertise in exercise for both the diagnosis (exercise testing) and treatment (cardiac rehabilitation) of disease. Similarly, my interest in orthostatic intolerance following bed rest and spaceflight has led to a clinical expertise in syncope and disorders of the autonomic nervous system.

Case Presentations – Consider: a) is an exercise test indicated; b) what is the purpose of the test; c) what will you do with the information?

Case #1: A 45 year old sedentary male smoker, with a total cholesterol of 260 and LDL of 180 has one month of typical exertional chest pain.

Case #2: A 55 year old hypertensive female non-smoker has 2 years of atypical chest pain. She has a total cholesterol of 220, a LDL of 140, is post-menopausal, and walks every day for recreational exercise. She is being treated with quinapril for hypertension which is well controlled at rest, and also is on digoxin for paroxysmal atrial fibrillation. Her ECG shows left ventricular hypertrophy, and a repolarization effect attributed to digoxin.

Case #3: A 65 year old sedentary male had a CABG performed 3 years ago for angina and 3 vessel coronary artery disease. He is now asymptomatic with total cholesterol of 260, LDL 160, HDL 29 and wants to start an exercise program.

Case #4: A 52 year old male is one week s/p a large, anterior MI. He presented too late for thrombolytic therapy and had clear evidence of congestive heart failure during his first three days in the CCU. His lungs are now clear, but he has a persistent sinus tachycardia.

Case #5: A 55 year old male executive has no other risk factors for CAD, but has recently developed atypical chest pain.

The past decade has seen a remarkable change in the management of patients with coronary heart disease. Medical therapy, percutaneous, and surgical revascularization have all improved dramatically including aggressive lipid lowering therapy, coronary angioplasty and stenting, and new strategies for reducing the risk and prolonging the efficacy of bypass surgery. This revolution in disease management is due in part to fundamental changes in the understanding of the pathophysiology and now the biology of atherosclerosis that has driven mechanism based changes in therapy.

In contrast to patient treatment, the strategies for patient assessment have not kept up with the progress made in basic science and therapy. One of the reasons for this discrepancy is the preference by most physicians to have a test that is black and white, with outcomes that are "positive" or "negative", and therefore a disease that is either "present" or "absent." Although this strategy may be useful for clearly discrete conditions, the approach may be more complicated with disorders such as athlerosclerotic heart disease.

A consequence of the tendency towards discrete analysis of clinical problems, has been a focus on terms such as "sensitivity" and "specificity" for the interpretation of cardiovascular tests [1],[2] Sensitivity is defined as:
and represents the ability of a "positive" test to detect disease. Specificity is defined as:
and represents the ability of a "negative" test to exclude disease.

$$\textbf{Sensitivity} = \frac{\text{True "Positive"}}{\text{True "Positive" + False "Negative"}}$$

OR

The ability of a "positive" test to detect the presence of disease.

$$\textbf{Specificity} = \frac{\text{True "Negative"}}{\text{True "Negative" + False "Positive"}}$$

OR

The ability of a "negative" test to exclude disease.

Exercise testing has been used for more than 70 years for the evaluation of patients with coronary artery disease [3]. Since Robert Bruce introduced the incremental treadmill protocol as a method for standardization of the clinical exercise test [4], it has become one of the most frequently used diagnostic tests in clinical medicine, accounting for > 800,000 procedures/year. However the performance of the routine exercise test without adjunctive imaging has been vilified in the literature recently [5]. A recent meta-analysis of the ETT involving 147 studies, and >24,000 patients who had both exercise tests with ECG monitoring and coronary angiography showed that the

fig 1

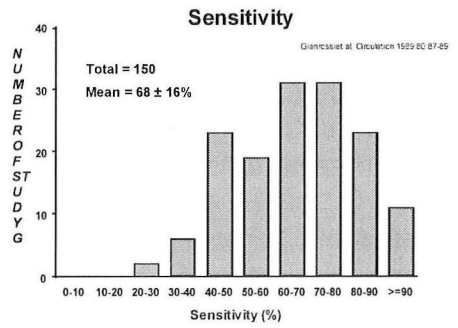
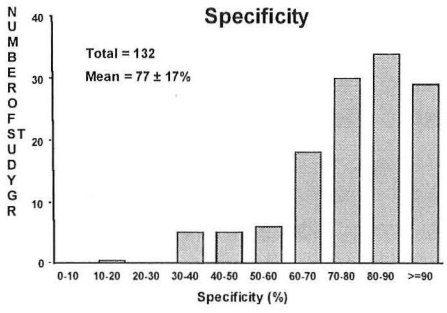


fig 2



reported sensitivity ranged from 23% to > 90%, depending on the population being studied (fig 1), with a mean sensitivity of 68% [6, 7]. The specificity was slightly better (fig 2), with a mean of 77% [6, 7]. Such relatively poor test performance has led some investigators to suggest that the routine exercise test is nearly useless for the management of patients with coronary artery disease [5].

Moreover, one of the most common mantras in the teaching of clinical diagnosis, is that the outcome of a test depends on the prevalence of the disease in the population being studied. This basic tenet derives from the application of Bayes Theorem, which was first presented for the interpretation of exercise tests by Rifkin and Hood in the New England Journal of Medicine in 1977 [8]. Bayes theorem relates the post-test probability of a disease, based on a clinical "gold standard", to the pre-test probability or prevalence of disease, derived from a variety of clinical and population based variables. The shape of this graphical relationship is determined by a constant L, or Likelihood ratio, and expresses the relative likelihood of observing a given test outcome among diseased and non-diseased patients. A well recognized form of this relationship is presented in fig (3). In this figure, the curve is based on the empirical value of L=7.42, which was derived as a weighted average from the 3 largest studies which considered a "positive" test to be the traditional ST depression $\geq$ 1mm, and coronary disease to be present if at least 1 major epicardial coronary artery had a lesion $\geq$ 50% cross sectional diameter stenosis by visual interpretation of a coronary angiogram. Individual points represent 17 other studies from which adequate data was available. The remarkably close agreement between the computed curve based on the likelihood ratio formulation of Bayes Theorem, and multiple other studies in the literature has led to the widespread adoption of this approach for the interpretation of exercise tests, and the general acceptance despite vigorous debate in the literature [9, 10] that the test is most useful when the pre-test probability of disease is intermediate [11].

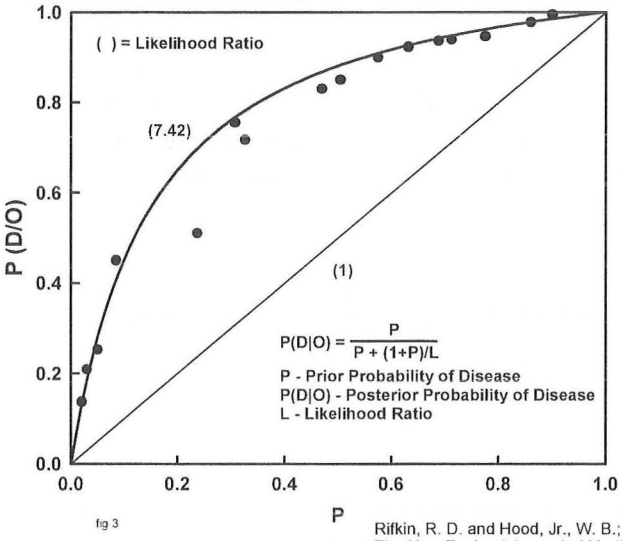


fig 3

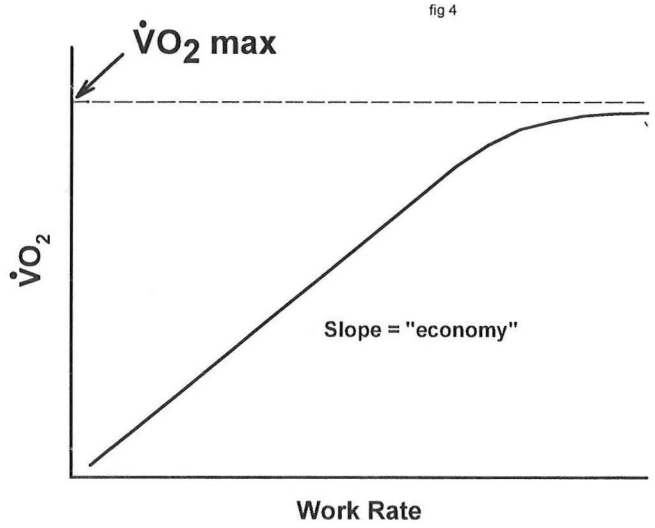
Rifkin, R. D. and Hood, Jr., W. B.;
The New England Journal of Medicine; 9/1979

However in order to follow this approach, two fundamental tenets must be accepted: 1) that an exercise test is either "positive" or "negative", and that coronary artery disease is either "present" or "absent." In the rest of this presentation, I will present evidence that neither of these conditions are viable.

The Exercise Test – A Physiologist's Perspective

Exercise physiology, and exercise testing is an essential tool for quantifying functional capacity of patients, and plays an important role in optimizing the quality of life, independent of its ability to diagnose coronary artery disease. One of the most important outcomes of an exercise test is to precisely measure work capacity and aerobic power. As the **external** work rate is increased (i.e., speed and grade on a treadmill, or Watts on a cycle ergometer) the amount of oxygen which passes along the oxygen cascade from the atmosphere to the mitochondria is increased, and the rate of ventilatory oxygen uptake, or VO2 can be measured (fig 4). The slope of the line relating VO2 to work rate is termed the "economy," and is very different for different types of exercise. For example, walking is very economical, as is cycling, and the economy of these activities varies relatively little among individuals. In contrast, running is less efficient, and activities such as swimming may convert only 10% of energy production into useful work [12, 13]. Eventually, there reaches a point where further increases in work rate do not lead to additional increases in oxygen uptake, and this value represents VO2max, or the maximal rate of ventilatory oxygen uptake [14].

fig 4



VO2max is the best objective measure of fitness, and is a widely used index of the integrity of cardiovascular function [14, 15] According to the Fick Principle, VO2 is the product of cardiac output, times the arteriovenous oxygen difference across the body. Since cardiac output is a function of heart rate times stroke volume, there are both central and peripheral factors which determine systemic oxygen transport. However except in some disease states which impair the ability of skeletal muscle to extract oxygen [16], the single most important factor

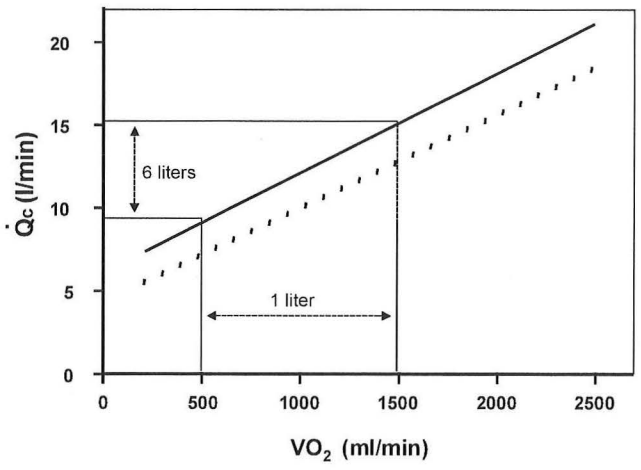


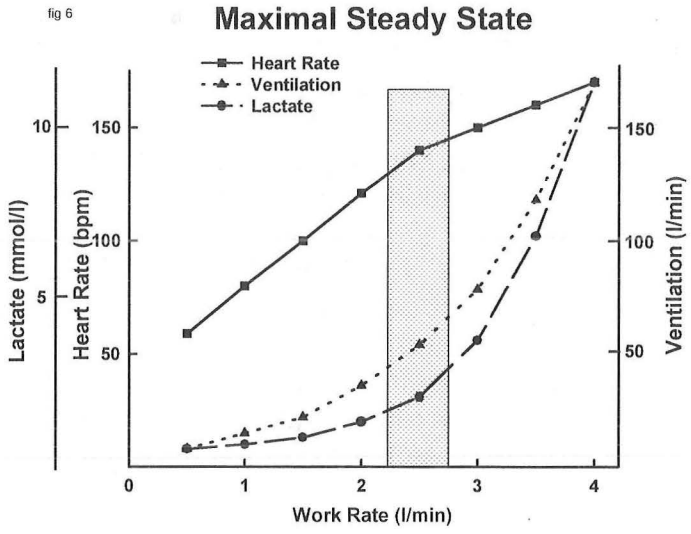
fig 5

which limits VO2max in normal individuals at sea level is the maximal cardiac output [17].

One of the most inviolate relationships in all of exercise physiology is the relationship between oxygen uptake and cardiac output. Regardless of age, gender, or the presence of various disease states, in general, it requires about 6 liters of cardiac output for every liter of oxygen uptake above rest [18](fig 5). When this relationship breaks down, it may be a sign of severe underlying disease with impending decompensation. For example, in patients with heart failure, regardless of any other clinically measured variable, the maintenance of a normal relationship between cardiac output and oxygen uptake identifies patients with relatively good short term prognosis [19]. In contrast, when the relationship breaks down, urgent transplantation may be required [19]. Thus the measure of maximal exercise capacity, or VO2max, may be viewed as a surrogate for the measure of maximal cardiac output.

Although the direct assessment of maximal cardiac output during an exercise test would be optimal, it is generally not technically practical to perform such measurements during routine exercise tests. Moreover, although the measurement of gas exchange for the calculation of oxygen uptake is much more widespread, the equipment to perform such measures remains relatively expensive and is not available in most clinical laboratories except in heart failure centers. Therefore other variables, in addition to work rate are often measured based on predictable relationships with oxygen uptake and cardiac output (fig 6).

fig 6



The most common and easy to measure variable is heart rate, which increases linearly with oxygen uptake (fig 6). The slope of this line is dependent on a number of factors, particularly fitness, and may be importantly effected by medications such as beta blockers, or calcium channel blockers. As the exercise intensity increases, there comes a point at which the rate of increase of heart rate begins to slow as maximal exercise capacity is approached, termed the heart rate break point, or "Conconi" heart rate [20, 21]. If ventilation is measured, Ve is relatively low at low levels of exercise, but as exercise intensity increases, reaches a point beyond which the rate of increase in Ve is greater than the rate of increase of VO2 [22]. This point is most precisely termed the "ventilatory threshold." Similarly, blood lactate remains low at low levels of exercise because of high rates of clearance by active and inactive skeletal muscle [23], but a certain exercise intensity is reached beyond which the rate of lactate production

exceeds the rate of lactate clearance, most precisely termed the lactate threshold, or the Onset of Blood Lactate Accumulation (OBLA). Although the term "anaerobic threshold" was popularized by Karl Wasserman in the early 70s [24, 25], and has been stubbornly persistent because of its widespread adoption by the manufacturers of software included with clinical exercise systems, it is clear that some threshold where a shift from "aerobic" to "anaerobic" metabolism occurs does not exist [23, 26]. A detailed discussion of this issue is beyond the scope of this presentation. However it is true nevertheless, that there is a level of exercise intensity for every individual, beyond which exercise cannot be sustained for prolonged periods of time. This intensity can be identified by any of the techniques mentioned above, and represents the same underlying physiological substrate [21, 26]. It usually occurs at 50-70% of maximal oxygen uptake and is an important physiological parameter to identify since most activities are performed at substantially below maximal capacity. The term "maximal steady state" is therefore preferred, to focus on this clinically relevant level of activity.

The primary unit of oxygen uptake is liters of oxygen/minute (l/min). However as a measure of work capacity, or the ability to move a human body through space, it is usually normalized to body mass, and in its most familiar form is expressed as ml/kg/min. Clinically, VO2 is normalized again to an index called a metabolic equivalent, or MET, which represents an average value of resting energy expenditure of 3.5 ml/kg/min. Thus the amount of fitness, or cardiovascular function required to

Category	Self-Care or Home	Occupational	Recreational	Physical Cond.
Very Light <3 METS <10 mL/kg*min <4 kcal	Washing, shaving, dressing Desk Work, writing Washing dishes Driving Auto	Sitting (clerical,assembly) Standing (store clerk, bartender) Driving truck Operating crane	Shuffleboard Horseshoes Bait casting Billiards Archery Golf (cart)	Walking (2 mph) Stationary bicycle (very low resistance) Very light calisthenics
Light 3-5 METS 11-18 mL/kg*min 4-6 kcal	Cleaning windows Raking leaves Weeding Power lawn mowing Waxing floors (slow) Painting Carrying objct (15-30lb)	Stocking shelves (light objects) Light welding Light carpentry Machine assembly Auto repair Paper Hanging	Dancing (social and square) Golf (walking) Sailing Horseback riding Volleyball (6-man) Tennis (doubles)	Walking (3-4 mph) Level bicycle (6-8 mph) Light calisthenics
Moderate 5-7 METS 18-25 mL/kg*min 6-8 kcal	Easy digging in garden Level hand lawn mowing Climbing stairs (slow) Carrying objects (30-60lb)	Carpentry (exterior home building) Shoveling dirt Using pneumatic tools	Badminton (comp.) Tennis (singles) Snow skiing (dwnhl) Light backpacking Basketball Football Skating (ice /roller) Horseback ridin(glp)	Walking (4.5-5 mph) Bicycle (9-10 mph) Swimming (breast stroke)
Heavy 7-9 METS 25-32 mL/kg*min 8-10 kcal	Sawing Wood Heavy shoveling Climbing stairs (mod.) Carrying objects (60-90lb)	Tending furnace Digging ditches Pick and shovel	Canoeing Mountain climbing Fencing Paddleball Touch Football	Jog (5 mph) Swim (crawl stroke) Rowing machine Heavy calisthenics Bicycling (12 mph)
Very Heavy >9 METS >32 mL/kg*min >10 kcal	Carrying loads upstairs Carrying objects (>90lb) Climbing stairs (fast) Shoveling heavy snow Shoveling 10 min (16 lb)	Lumberjack Heavy laborer	Handball Squash Ski touring over hills Vigorous basketball	Running (6 +) Bicycling (13 + or up steep hill) Rope jumping

perform various occupational, recreational, or physical conditioning activities can be represented by the number of METS, or the systemic oxygen transport above rest required for their pursuit (table 1). Thus the achievable METS is a key factor in determining a patient's functional capacity.

Maximal oxygen uptake varies with respect to a number of variables such as training status, gender and age [15]. On average, VO2max normalized to body weight decreases by approximately 5%/decade [27, 28], though this decline may be slowed by maintaining both a high level of physical activity and ideal body weight ([29, 30]). The American Heart Association has established gender, and age specific guidelines which can be used to broadly describe a patient's functional capacity (table 2).

Cardiorespiratory Fitness Classification: Table 2

Age (years)	Maximum Oxygen Uptake (ml/min/kg)				
	Low	Fair	Average	Good	High
Women					
20-38	<24	24-30	31-37	38-48	49+
30-39	<20	20-27	28-33	34-44	45+
40-49	<17	17-23	24-30	31-41	42+
50-59	<15	15-20	21-27	28-37	38+
60-69	<13	13-17	18-23	24-34	35+
Men					
20-29	<25	25-33	34-42	43-52	53+
30-39	<23	23-30	31-38	39-48	49+
40-49	<20	20-26	27-35	36-44	45+
50-59	<18	18-24	25-33	34-42	43+
60-69	<16	16-22	23-30	31-40	41+

American Heart Association. *Exercise Testing and Training of Apparently Healthy Individuals: A Handbook for Physicians*. Dallas: American HeartAssociation. 1972.

Not only is the VO2max, or maximal MET level a key variable in determining functional capacity, it has inherent clinical relevance (table 3). For example, most activities of daily living require energy expenditures $\leq$ 4 METS [31, 32]. For a patient with congestive heart failure, if this level of oxygen transport exceeds VO2max, the short term prognosis is extremely poor, and heart transplant specialists use this as a critical determinant of whether a patient is in immediate need of cardiac transplantation [33]. In contrast, for a patient with coronary heart disease, the ability to exercise to 10 METS without ischemia places patients in an extremely low risk subgroup, with a 1 year mortality of < 2% [34]. A maximal exercise capacity of 13 METS, regardless of other comorbidities, or the presence/extent of ischemia predicts a similarly excellent short term prognosis.

• **1 MET**	=	**resting**
• **2 METs**	=	**level walking at 2 mph**
• **3 METs**	=	**level walking at 4 mph**
• **<4 METs**	=	**poor prognosis; usual limit immediately after MI; peak cost of basic activities of daily living**
• **10 METs**	=	**prognosis with medical therapy as good as coronary artery bypass surgery**
• **13 METs**	=	**excellent prognosis regardless of other exercise responses**
• **18 METs**	=	**elite endurance athletes**
• **20 METs**	=	**world class athletes**

As Adapted from *Fletcher, et al Circulation 95*

Table 3

Thus, the ability to measure exercise capacity precisely is an essential component of an exercise tolerance test. Unfortunately, habit and economics have conspired to reduce the precision with which most clinical exercise tests provide this information, based on the widespread use of the Bruce protocol for exercise tolerance testing. Developed by Robert Bruce at the University of Washington in the late 1960s, the speeds and grades used in the protocol were not determined by reasonable consideration and physiological principles, but by the fixed gear ratios available on the treadmill used for the initial development and validation of the concept. The biggest problem with using the Bruce protocol for testing of patients with cardiovascular disease, is the relatively large increments in VO2 required to make the transitions between the early stages. Why is this such an important issue?

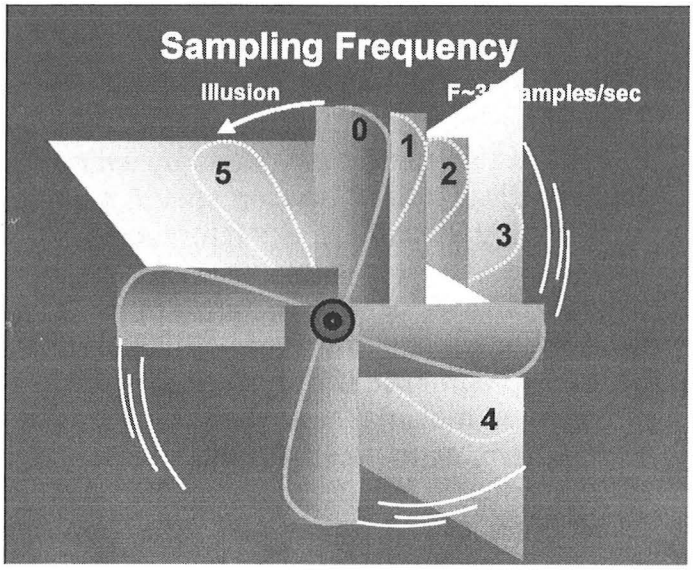
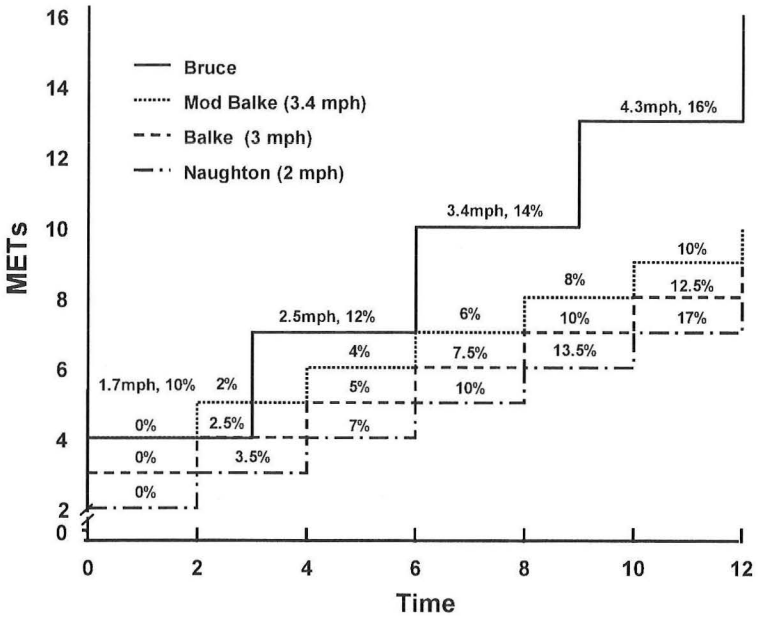


Fig 7

Fig8

It is an inherent principle in all medicine and science that the sampling frequency of any measure determines the maximal resolution of the measuring instrument (Nyqvist limit). A well known example of this phenomenon is shown in fig 7 which depicts the ability of the visual resolution of the human eye to determine the direction of motion of an airplane propeller.



For exercise testing, one of the most important pieces of clinical information comes from the ability to discriminate at least 1 MET increments in functional capacity; particularly at low levels of physical activity 1 MET may be a substantial fraction of a patient's maximal aerobic power. An example of some common clinical protocols are shown in fig 8 [32]. The Bruce protocol is unique among these by beginning at about 4 METS, and progressing with relatively large

increments in aerobic requirements of 3 METS every 3 minutes by an increase in both speed and grade. The first change in stage thus involves nearly a doubling of the work requirements (from 4-7 METS) and is virtually useless for determining true functional capacity at the level that most patients with cardiovascular disease can achieve. Alternative protocols shown in the figure begin at different intensities and walking speeds, which can be estimated by watching the patient walk in to the treadmill room. Each involves a fixed walking speed, and increments in grade which add approximately 1MET every 2 minutes. Such protocols should be the rule rather than the exception, unless the patient is young, fit, and the clinical expectation is that their exercise capacity exceeds 10 METS. Finally, since maximal work capacity provides such important, clinically relevant information, clinical exercise tests should never be stopped arbitrarily by the test administrator for fixed endpoints such as a specific workrate, or percentage of predicted maximal heart rate [35]. The latter is so variable, with a standard deviation of $\pm$ 10 bpm, as to be essentially useless for individual patients [35]. Patient specific criteria, such as fatigue, dyspnea, hemodynamics, development of signs or symptoms of ischemia, or arrhythmias are more appropriate end points, the threshold for which may be altered depending on the specific clinical situation.

Myocardial Oxygen Demand and Supply

In addition to the determination of external work capacity, exercise tests provide a controlled environment for the evaluation of myocardial oxygen demand and supply. Since blood pressure is a function of cardiac output and total peripheral resistance, the blood pressure will rise during exercise depending on both the work rate (and its concomitant increase in cardiac output) and the ability of the peripheral vasculature to vasodilate appropriately. Usually, total peripheral resistance falls during dynamic exercise involving the rhythmic contraction of large muscle groups [36], though it may not decrease as much when substantial static exercise is involved (fig 9 ,[37, 38]).

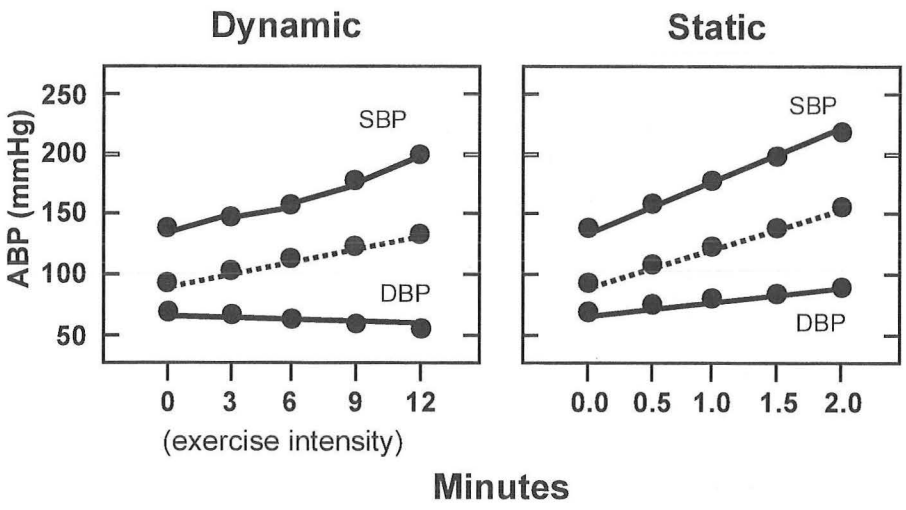


Fig 9

Myocardial oxygen uptake (MO2), or the **internal** work thus depends on the magnitude to which the well known determinants of myocardial oxygen requirements increase during exercise (fig 10). *It is important to emphasize that the MO2, rather than the VO2*

DETERMINATES OF MYOCARDIAL OXYGEN DEMANDS (MO_2)

WALL STRESS
(LV PRESSURE * LV VOLUME)
WALL THICKNESS

HEART RATE

CONTRACTILITY

fig 10

is what determines the degree to which myocardial blood flow must increase during exercise.

Although direct measures of MO2 are very difficult to make, it can be estimated using simple clinical parameters measured during routine exercise tests. Fig 11 shows the derivation of the "rate pressure product" which provides a remarkably good estimate of MO2 [39], which is weighted heavily towards the contribution of heart rate and chronotropic work, but also incorporates the significant contribution of inotropic, pressure and volume work of the heart.

$$RPP = HR_{max} * SBP_{max}$$

$$HR * (Q_C * TPR)$$

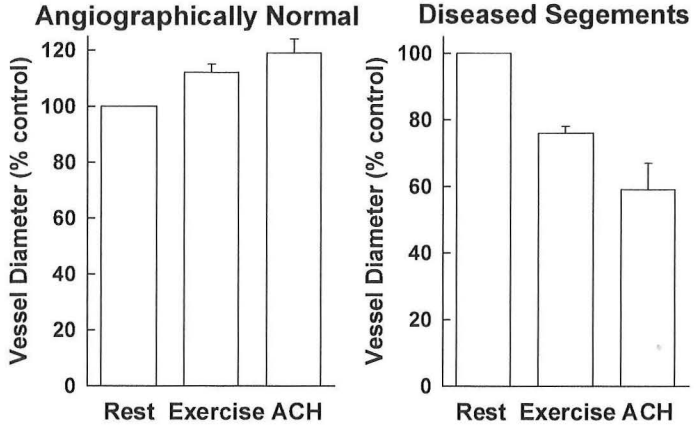
$$HR * (HR * SV) * TPR$$

$$RPP \approx HR^2 * SV * TPR$$

Fig 11

A form of the Fick equation, similar to that for *systemic* oxygen uptake emphasizes that *myocardial* oxygen uptake, MO2 is a function of myocardial blood flow time the arteriovenous oxygen difference across the heart. However the heart is unique in that it extracts the majority of oxygen that it receives even at rest. Thus the ability of the heart to augment oxygen extraction to meet increased energy demands must be met predominantly by increasing myocardial blood flow. Normally the coronary blood flow can increase by at least 5 fold both via vasodilation of small, peripheral resistance arterioles, as well as by flow-mediated vasodilation of the large conduit arteries. When atherosclerosis involves the epicardial vessels, their conduit function may be impaired. A waterfall effect begins to become physiologically significant when the total cross sectional area is approximately 75% reduced (> 50% cross sectional diameter) [40]. In addition, even modest degrees of atherosclerosis may impair the normal endothelium dependent vasodilation of the coronary arteries leading to vasoconstriction, rather than vasodilation during exercise as shown in fig 12 [41].

fig 12



Ultimately, if the ability to augment coronary blood flow is inadequate to meet myocardial oxygen demands at a given level of both systemic and myocardial work, then ischemia will develop. Probably the weak link in the interpretation of a clinical exercise test is that it uses a relatively indirect and nonspecific phenomenon to detect the presence of ischemia – shifts in the ST segment of the electrocardiogram. Examples of the type of ST segment changes that can occur during exercise are shown in fig 13 [32]. Such changes depend on a differential repolarization pattern between the endocardium and the epicardium resulting in shifts of the ST segment that may be detectable on the surface of the heart. However it is important to emphasize that these shifts occur in a graded fashion, and are proportional to the imbalance between MO2 and myocardial O2 supply [32]. More severe and intense ischemia will lead to greater shifts in the ST segment of the ECG [42]. Thus there is no magic associated with the standard clinical criteria of 1 mm ST segment depression. It is simply a convenient measure that was determined initially from the fact that the recording paper was printed with 1mm increments, and is entirely dependent on the point at which the exercise test is stopped. This critical point has direct clinical relevance as well.

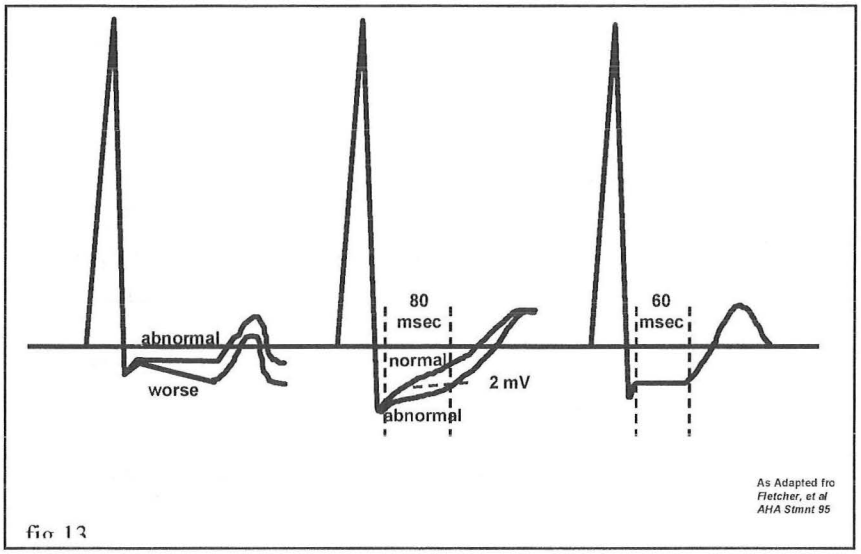
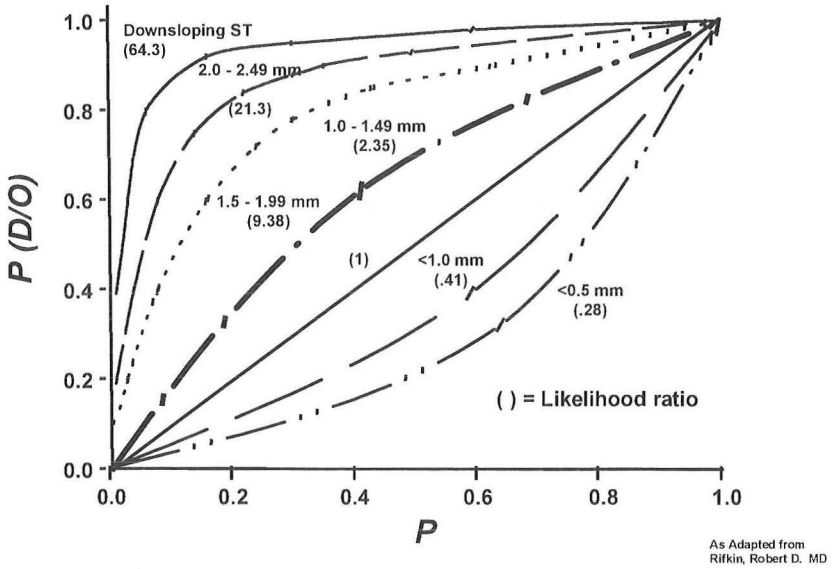


fig 13

Fig 14



The Continuous Nature of Bayesian Analysis

Often overlooked in the original paper by Rifkin and Hood cited above [8], is the fact that in additional to the grouped analysis of all tests with ST segment deviations > 1 mm, they also performed a separate analysis of ST segment deviations in 0.5 mm increments. This analysis is shown in fig 14, and demonstrates a completely

different picture of the exercise response. In this analysis, the post-test probability of angiographically significant coronary artery disease is radically different if there is 1.- 1.5 mm ST depression, compared to > 2.0 mm or downsloping ST segment depression. Even for a very low pre-test probability of disease of 20-30%, a test with >2.0 mm or downsloping ST segments would very likely demonstrate >50% coronary lesions. In fact, back in 1977, the ultimate conclusion from this presentation of Bayesian analysis was that: "the terms "positive" and "negative" are inappropriate to describe most stress-test results. Instead, it should be interpreted in terms of a continuum of risk based on the extent of ST-segment depression." [8].

A summary of what exercise testing can and cannot due is provided in tables 4 and 5.

Table 4

EXERCISE TESTING *CANNOT*:

1) Determine the structure and composition of an atherosclerotic plaque (i.e. lipid laden - rupture *prone* vs hard and calcific - rupture *resistant*.
2) Identify the presence of atherosclerotic plaques that will rupture and cause a myocardial infarction.
3) Predict the presence or absence of ischemia at workrates *greater* than that achieved on the test.

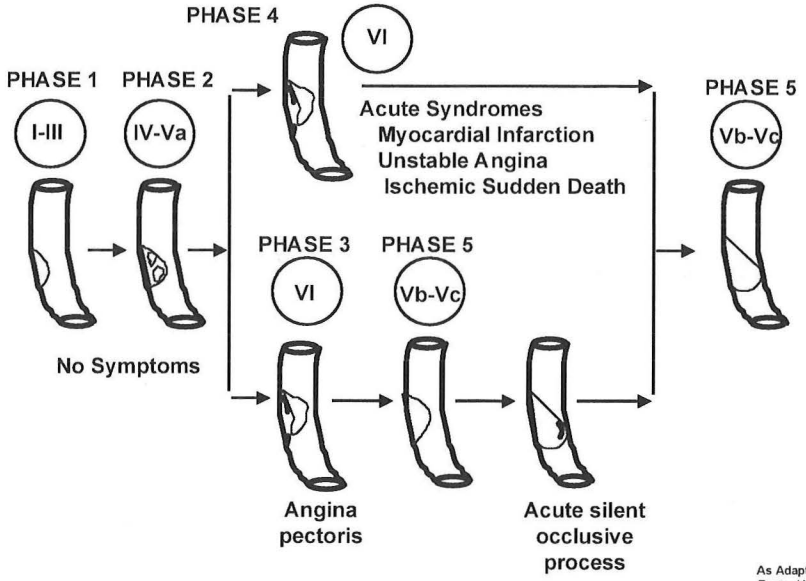
EXERCISE TESTING *CAN*:

1) Determine functional capacity.
2) Evaluate global hemodynamic and cardiovascular function during physical activity.
3) Provide a predictable, and objective setting for the evaluation of symptoms (chest pain, dyspnea, fatigue) of questionable etiology.
4) Detect the presence of myocardial ischemia during increasing $M0_2$ that is sufficient to cause a shift in the ST - segment of the electrocardiogram.
5) Identify a threshold of systemic and myocardial workrates beyond which ischemia is likely to be present.
6) Provide important clinical information that may assist in the estimation of prognosis (particularly by identifying low-risk subgroups of patients with ischemic heart disease).

Table 5

The Continuous Nature of Coronary Artery Disease

Not only are exercise test variables continuous, but modern understanding of the development and progression of coronary artery disease suggests that atherosclerosis is also a continuous variable that begins early in life. Early studies of Korean war casualties revealed that a surprisingly high number of young American men by the age of 18-20, already had the early fatty streaks, and fibrous plaques that we now know develop into



As Adapted from *Fuster V. et al*

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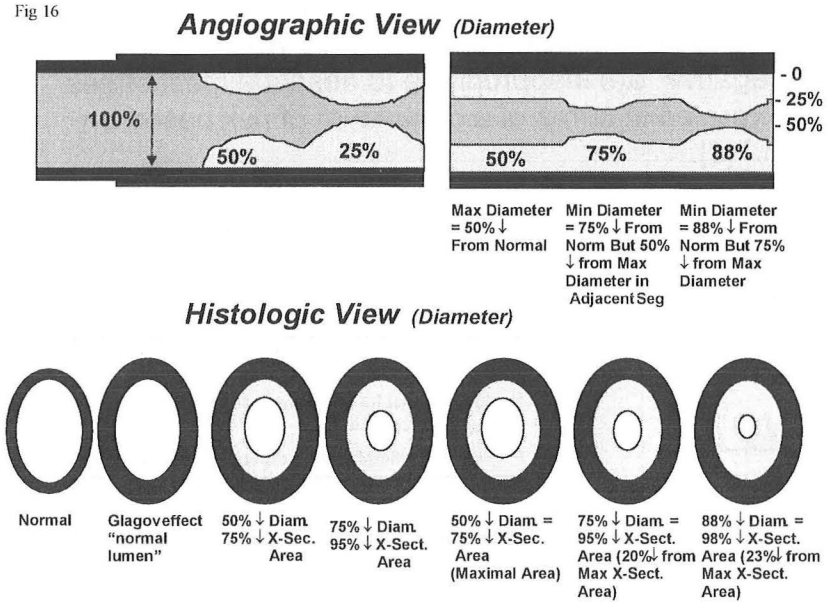
atherosclerotic lesions [43]. More recently, a comprehensive evaluation of accident victims in the US has confirmed this finding [44]. A summary of the current understanding of the nature of the progression of coronary artery disease is shown in figure 15 [45]. This figure emphasizes that not only may atherosclerosis progress slowly and continuously leading to the development of ischemia causing lesions, but it also progresses rapidly and catastrophically leading to rapid changes in vessel diameter, vascular occlusion and myocardial infarction. In fact, the majority of coronary events occur in blood vessels that are not necessarily heavily stenosed [46, 47]. Thus it should not be much of a surprise that exercise testing, which is designed to detect ischemia, would not be very good at detecting lesions that are not physiologically significant, but ultimately will experience plaque rupture and thrombosis.

Fig 16



This limitation is also present for virtually all routinely available diagnostic tests in cardiovascular medicine. As discussed above, the performance of an exercise test has most often been compared to coronary angiography to determine whether disease is present or absent. However coronary angiography only depicts the lumen of the coronary blood vessels and does not give a clear picture of the presence or absence of atherosclerosis as shown in figure 16).

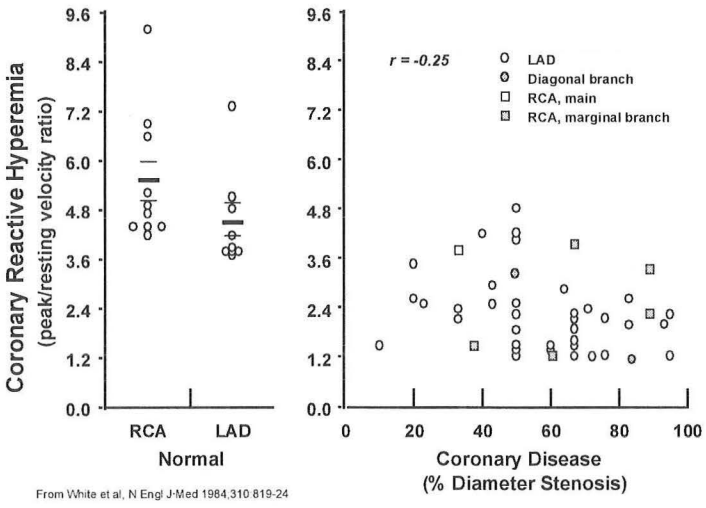
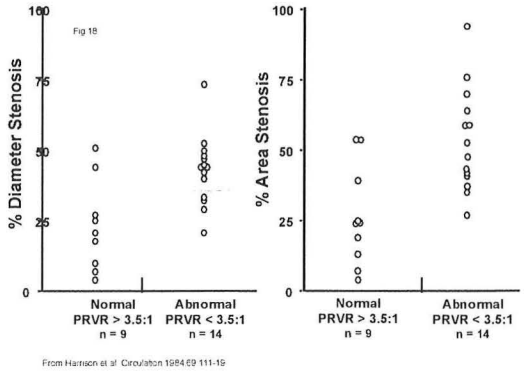


Fig 17

Moreover, most of the papers examining the performance of exercise testing have relied on visual interpretation of the coronary angiogram for the determination of lesion significance, a technique that is notoriously unreliable. First of all, there is poor inter and intra-observer variability in the assessment of coronary artery stenoses performed



by visual interpretation of coronary angiograms. For example, in a study by Zir and colleagues [48] in only 65% of cases could a group of 4 experienced observers agree that a lesion was > 50% stenosed. Furthermore, even when % diameter stenosis is determined by quantitative coronary angiography, there is poor correlation between the severity of the stenosis on the angiogram, and the magnitude of its effect on limiting coronary flow reserve (fig 17, [49]). Particularly in patients with multi vessel disease, neither % cross-sectional diameter, nor % area stenosis is particularly good at detecting patients with abnormal coronary flow reserve (fig 18,[50]), though the minimal luminal diameter may be more reliable (fig 19,[50]). Such measures appear to be more accurate when coronary disease is less extensive [51], because the % area stenosis more closely reflects the minimal luminal diameter. The presence of eccentric, long, or complex lesions may further complicate the relationship between angiographic appearance, and physiological significance of a lesion (table 6).

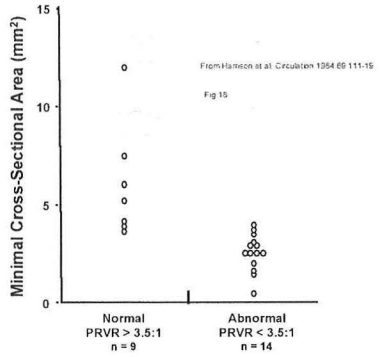
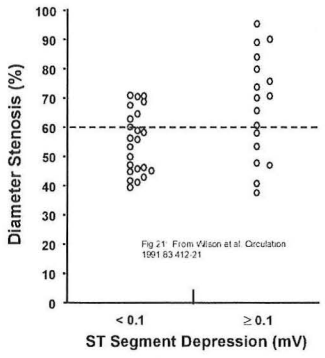


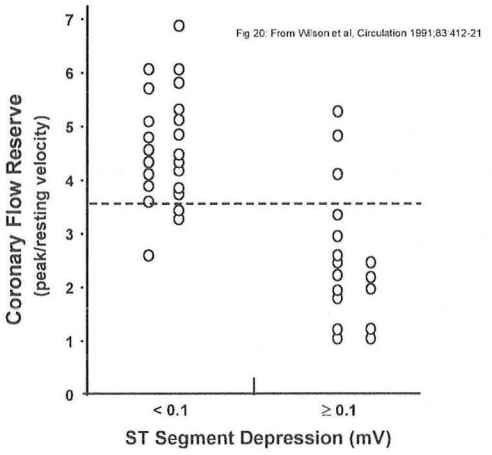
Table 6 ***PROBLEMS WITH ANGIOGRAPHY***

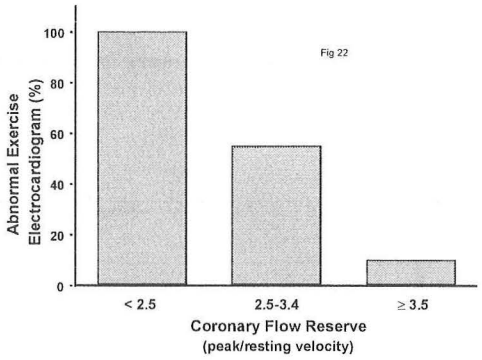
1) Poor inter - and intra - observer variability (particularly with 30 - 60% intermediate lesions)
2) Eccentric lesions
3) Diffuse disease
4) Static, resting measure

One of the most important papers which helps to explain the apparent disparity between results of exercise testing, and the "presence" of coronary artery disease by coronary angiography was published by Wilson et al, in Circulation in 1991 [52]. These investigators studied 40 patients with single vessel coronary artery disease, a normal resting electrocardiogram, and no LVH or prior MI. All patients underwent both graded treadmill exercise testing with ECG monitoring, and coronary arteriography with the measurement of lesional severity both by quantitative coronary angiography, and by the assessment of coronary flow reserve using a Doppler catheter after the injection of intracoronary papaverine. As expected from previous studies by this group, no static measure of lesion severity (% diameter or % area) predicted well patients with either ST segment deviation during exercise, or coronary flow reserve (fig 21). However the vast majority of patients with



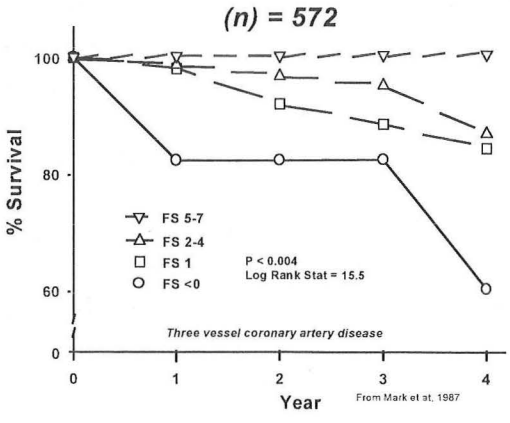
no or minimal ST segment deviation during exercise had normal coronary flow reserve (fig 20) regardless of lesion severity, confirming the ability of the coronary circulation to augment coronary blood flow to match increases in MO2 during exercise. In contrast, the majority of patients with abnormal ST segment deviation during exercise had abnormal flow reserve (fig 20). Furthermore, 100% of patients with severely reduced flow reserve (peak/resting velocity < 2.5) had significant ST segment during exercise (fig 22). Thus although this study involved a relatively select patient population, it confirms the fact that ST segment depression during exercise is directly related to impaired coronary flow reserve, and normal coronary flow reserve, regardless of lesion severity is usually associated with the absence of ischemia significant enough to be detected by the surface ECG.





Exercise Responses as an Additional Risk Factor for Cardiovascular Mortality

Because of the continuous, rather than discrete nature of both exercise testing and coronary artery disease, a number of investigators have attempted to use treadmill scoring systems to emphasize the results of an exercise test as an additional risk factor for cardiovascular disease morbidity and mortality [53]. The two most common ones are the Duke scoring system [54, 55] and the VA score developed by Froelicher and colleagues which has recently been combined into a consensus score [56]. The Duke sccre subtracts the magnitude of ST depression multiplied x 5, and the presence of angina that is either limiting or non-limiting multiplied x 4, from the METs achieved during exercise. A simple nomogram has been developed that can be used clinically (fig 23 – see separate page). This score was initially developed and validated in two in-patient populations referred for coronary angiography. Even for patients with 3 vessel CAD, this score was able to distinguish high risk from low risk patients (fig



24). The same score also has been validated in an outpatient population with equal or even better performance [55]. A similar score has been developed by VA investigators, with similarly good ability to identify high and low risk patients [57]. Although the approaches differ somewhat, the key point is that a continuous measure of performance on an exercise test can be used as an additional risk factor in determining overall morbidity and mortality in patients with coronary heart disease.

In summary then:

TAKE HOME MESSAGES

1). Exercise testing is not "*positive*" or "*negative*"

2). Coronary disease is not "*present*" or "*absent*"

3). Exercise testing is a powerful tool to:

- **determine functional capacity**
- **identify the myocardial and systemic workrates that may provoke myocardial ischemia *within the limits of the ECG to detect it***
- **assist in the management of patients with cardiovascular disease**

DUKE NOMOGRAM

Connect the ST-segment deviation line with the Angina during exercise line to mark the crossing ppoing on the ischemia rreading line. Connect the ischemia reading line with the Exercise capacity in METS to determine the aaverage annual mortaility, and estimated 5-year
survival

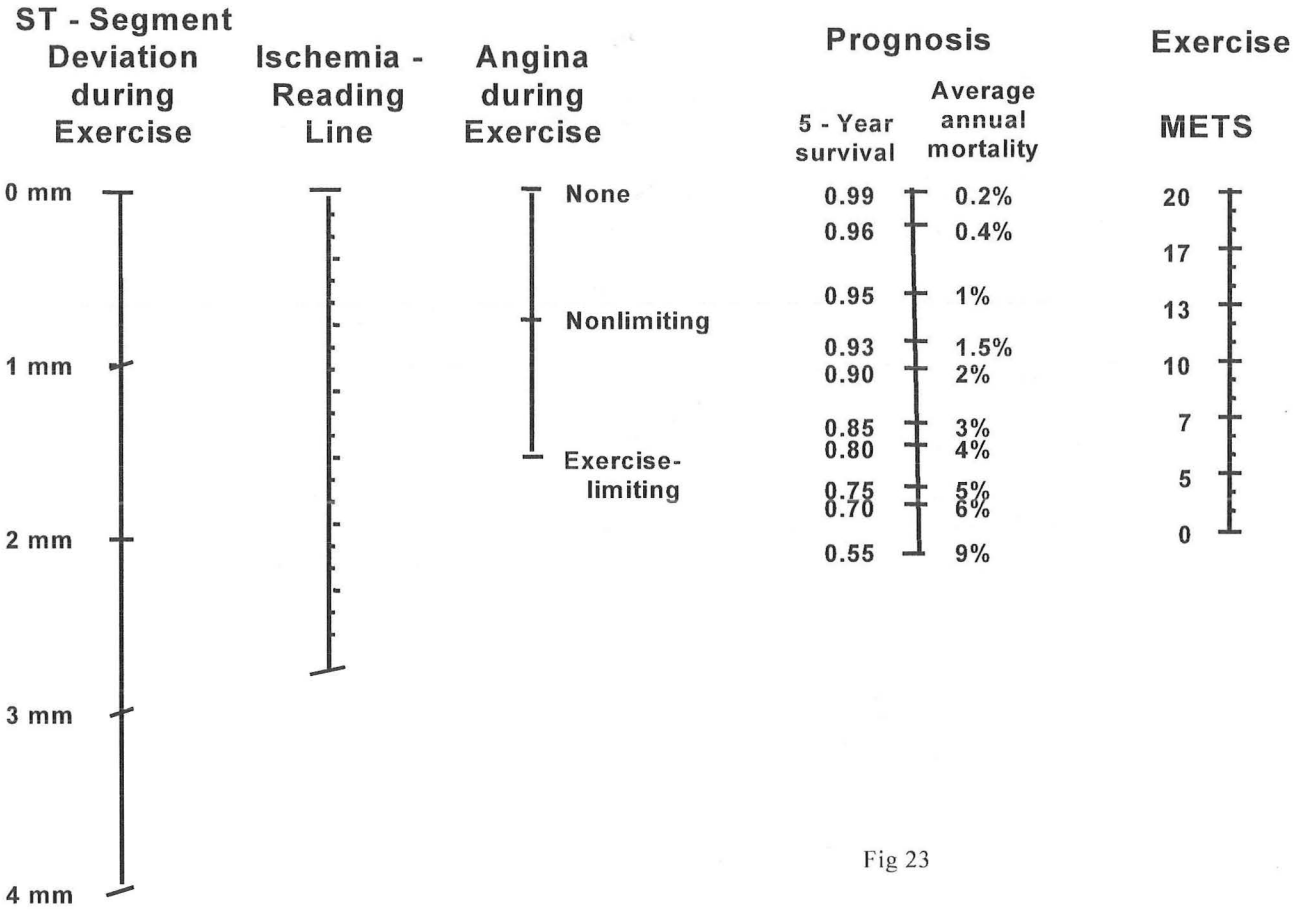


Fig 23

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