and high-risk populations, all tests are more accurate in predicting low than high risk. Few noninvasive tests have the power to predict high-risk populations with annual mortality rates exceeding 20%, which means the high-risk outcome does not occur 80% of the time. In contrast, most physiological tests of ischemia have been documented to reliably define large low-risk groups of populations with coronary artery disease that have an annual risk of death of less than 1%. Because none of the physiological tests could be expected to predict exacerbation of activity of atherosclerotic plaques, it must be assumed that the documented power of these tests to predict a low-risk cardiac death must relate to assessment of the reserve of the heart to withstand ischemia caused by increasing plaque activity associated with accelerated stenosis, distal embolization of the coronaries, or total vessel occlusion.

A prior assumption has always been that the remarkable power of the exercise treadmill, perfusion imaging, and assessment of exercise left ventricular function to identify patients with coronary artery disease and low risk of cardiac death derived from information in these tests related to the resiliency of hearts of individual patients to a potential ischemic insult. All of these tests use stress to evoke increased demand for coronary blood flow, and most spontaneous coronary events are associated with a decreased supply of coronary blood flow. This fact suggests that a strong relation would be observed in the physiological response evoked by increased demand and decreased supply. Our observation that these two mechanisms of ischemia were not as closely linked in individual patients as had been assumed emphasizes new dimensions of complexity in these relations that represent fruitful areas for further investigation. We agree with Drs Danchin and Marie that our observations in these 20 patients do not undo the valid conclusions regarding the prognostic importance of physiological measurements of ischemia based on thousands of patients. We do believe the results in these 20 patients challenge simplistic explanations as to the reason these tests are prognostically important and suggest a number of important areas of future investigation.

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References

The Improper Use of the Words 'Significant' and 'Nonsignificant' for the Classification of Coronary Atherosclerotic Plaques

To the Editor:

The word "significant" is commonly used in describing coronary artery lesions and in general medical discussions. It is a powerful word that deserves careful scrutiny. What does the word mean? Does it have the same meaning each time we use it? Is the improper use of the word misleading or dangerous?

Dictionaries indicate that the word "significant" is synonymous with the word "important." Such a definition has its limitations because one then wonders about the definition of the word important.

Many regard Fowler's Modern English Usage as the wordsmith's Bible. Although experts in synonymy may disagree with Fowler, they all study his definitions. His perception of the difference in the meaning of the words "important" and "significant" is reproduced by permission of Oxford University Press.

Fowler states: signifi(y)(cant). The dictionaries give important as one of the definitions of significant, but to use it merely as a synonym for that word is to waste it. The primary sense of s. is conveying a meaning or suggesting an inference. A division in the House of Commons may be important without being significant; the failure of some members to vote in it may be significant without being important. There is no important change in the patient's condition means that he is neither markedly better nor markedly worse. There is no significant change in the patient's condition means that there is no change which either confirms or throws doubt on the previous prognosis.

The difference between the meaning of the words "important" and "significant" pointed out by Fowler is barely perceptible to me, but I am sure he perceived it as a great difference.

When a physician states, "that is a significant abnormality," he or she implies that the finding is important to the patient's current medical status or that it will influence the patient's well-being in the future. When used in this manner, one can see a little touch of Fowler.

The term "significant difference" is defined in Gould's Medical Dictionary as follows. The definition is reproduced with permission from the publisher.

A difference between two statistical constants, calculated from two separate samples, which is of such magnitude that it is unlikely to have occurred by chance alone. Usually this probability must be less than 0.05 (5%) before a difference is accepted as significant. The smaller the probability, the more significant is the difference.

The word "significance," when used in this context, is not used to indicate the clinical significance of an observation. The term "statistically significant" is a mathematical expression and nothing more; the importance to the patient requires additional knowledge. Fowler, I suspect, would not use the word "significant" to describe a mathematical phenomenon. However, the use of the word in this way is carefully defined, and its usage is well established. The problem is that everyone does not know or understand the definition.

Arteriographers have their own argot. Most coronary arteriographers use the word "significant" to describe an atherosclerotic lesion that obstructs 50% to 70% or more of the diameter of the lumen of a coronary artery. The reason for the use of the word in this way is that coronary blood flow beyond such a lesion is less than normal during rest or with exercise. Coronary arteriographers often refer to the atherosclerotic lesions that occupy less than 50% of the diameter of the lumen of the coronary artery as being nonsignificant because coronary blood flow beyond such a lesion is usually adequate at rest and with exercise.

I believe the words "significant" and "nonsignificant" are commonly used improperly when a coronary arteriogram is described to the patient, a referring physician, or for the record. Here are my reasons.

To begin with, it is not always possible to make an accurate measurement of the degree of diameter narrowing in a coronary artery. To use the word "significant" implies that the measurement is more accurate than it is.

When coronary atherosclerosis is diffuse, the reference area of a vessel may be diseased. Accordingly, in such patients, a lesion that appears to occupy less than 50% of the diameter of the lumen may cause a decrease in coronary blood flow beyond the lesion.

A markedly hypertrophied left ventricle may require a larger coronary blood flow than a normal left ventricle. Accordingly, a 50% narrowing of the diameter of a coronary artery may prevent
an adequate coronary blood flow to a hypertrophied left ventricle, whereas it may be adequate for a normal left ventricle.

Coronary arteriographers should use the terms “hemodynamically significant” or “hemodynamically nonsignificant” to indicate the hemodynamic consequences of an atherosclerotic lesion. Some arteriographers, using modern jargon, often omit the word “hemodynamic” before the words “significant” and “nonsignificant.” The omission of the word “hemodynamic” sends an incorrect message to the patient and other physicians. For example, when the word “nonsignificant” is used to describe an atherosclerotic lesion, it implies that a lesion is unimportant. This, of course, is not true.

When an arteriographer refers to an atherosclerotic plaque that occupies less than 50% of the luminal diameter of the coronary artery as being nonsignificant but omit the word “hemodynamic,” he or she should review the excellent report by Muller et al.3 It is now quite evident that a fissure may develop in an atherosclerotic plaque that occupies less than 50% of the diameter of a coronary artery. When a fissure or tear occurs in such a plaque, it sets in motion a number of factors that conspire to produce an abrupt occlusion of the coronary artery. Such an acute lesion can lead to sudden death, unstable angina, or myocardial infarction. If the patient escapes the development of a crack in the plaque or a thrombosis on the plaque and therefore escapes the acute coronary events, the plaque may become larger and eventually produce chronic high-grade obstruction that prevents adequate coronary artery blood flow beyond the lesion. When such a lesion enlarges to occupy 50% to 70% or more of the diameter of the coronary artery, it may produce chronic stable angina pectoris or occasionally may be the site of an acute clot that produces sudden death, unstable angina, or myocardial infarction. Should collateral circulation develop in parallel with the increasing obstruction, the coronary artery may become completely occluded and the patient may survive without angina or infarction.

To reemphasize, it is not possible to inspect a coronary arteriogram and identify with certainty which of the coronary lesions will cause sudden death, unstable angina, or infarction. The lesion that occupies less than 50% of the diameter of the lumen of a coronary artery may be so fragile that it is prone to rupture and produce one of the serious acute syndromes.

If the above hypothesis is true, and numerous experts believe it is, it becomes imperative that we clean up our language.2 It is misleading to state, “you have no significant coronary disease,” simply because there are no arteriographic lesions that occupy more than 50% of the diameter of the lumen of the artery. Because of this misconception, I believe we should abandon the use of the words “significant” and “nonsignificant” when describing coronary arteriograms.

A stenotic lesion is defined as a lesion that occupies 50% or more of the diameter of the lumen of the coronary artery as visualized on the coronary arteriogram. The coronary blood flow is believed to be diminished below normal beyond the lesion during rest or with exercise. If this lesion does not change, it is unlikely to cause any condition more serious than stable angina pectoris. If it is stenotic and vulnerable to disruption, it may become a nidus for thrombosis and cause sudden death, unstable angina, or myocardial infarction. Admittedly, this designation does not solve the problem of inaccurate angiographic assessment of the amount of narrowing.

In 1985, Ambrose et al1 described four types of stenotic atherosclerotic lesions. In a later communication (1989), as new information became available, Ambrose modified his 1985 description of the different types of plaques. The following classification is based on his work.

Concentric lesions produce symmetric, smooth narrowing of the coronary artery as viewed in the coronary arteriogram. Many if not most patients with stable angina pectoris have such lesions. Should a thrombus develop in a short period of time, it may cause sudden death, unstable angina pectoris, or myocardial infarction. A type I simple lesion is usually eccentric. It is asymmetrical and has smooth borders and a broad neck. It is more commonly observed in the coronary arteriograms of patients with stable angina pectoris than in patients with unstable angina pectoris. Should a thrombus develop in a short period of time, it may cause sudden death, unstable angina, or myocardial infarction. A type II complex lesion is usually eccentric. It is asymmetrical and has a narrow neck or irregular borders or both.4 Such a lesion may develop abruptly as a complication of a nonstenotic lesion because a crack may develop in an atherosclerotic plaque that occupies less than 50% of the luminal diameter of a coronary artery. The crack in the plaque stimulates a series of actions (thrombosis, spasm, or both) that may produce acute narrowing of the coronary artery so that the lesion abruptly occupies 80% to 90% or more of the luminal diameter. This may cause sudden death, unstable angina, or myocardial infarction.

As pointed out by Ambrose, type II lesions are occasionally concentric, exhibiting ulcerations, irregular borders, overhanging edges, or associated thrombi. Such a lesion may develop abruptly as a complication of a nonstenotic lesion because a crack may develop in lipid-laden atherosclerotic plaque. The crack in the plaque may stimulate the development of thrombosis, spasm, or both. They may cause acute ischemia syndromes including unstable angina, sudden death, or myocardial infarction.

The point being made here is that Ambrose originally described type II lesions as being eccentric rather than concentric. He later pointed out that a few type II lesions occur when the plaque is concentric.5 This led him to characterize all type II lesions as being complex. The word “complex” was also used by Williams et al in their classic descriptive article in which the morphology of the plaque causing unstable angina was described.

Ambrose et al defined these atherosclerotic lesions as “three or more serial and severe (20-70%) closely spaced obstructions in a coronary artery.” The segment between the severe lesions might or might not show diffuse irregularity.4 There was only one patient in the study by Ambrose et al who had multiple irregularities. This patient had stable angina pectoris. One would suspect that the shape of the lesion, as described for type I and II eccentric lesions, would predict the clinical syndrome.

A nonstenotic lesion occupies less than 50% of the diameter of the lumen of the coronary artery. The coronary blood flow is believed to be normal beyond the lesion during rest and with exercise. The patient may have no symptoms or any other signs of myocardial ischemia.

There are three subsets of nonstenotic lesions. Regrettably, the coronary arteriographer cannot distinguish between them, and because of this they cannot be accurately classified. This highlights the need for a practical method that can identify vulnerable lesions that are subject to an abrupt tear and disruption. The word “practical” deserves emphasis because an expensive method that is used by only a few coronary arteriographers will not meet the goal.

In subset 1, the atherosclerotic plaque may remain stable and may not increase in size or thrombogenicity. In subset 2, the plaque may increase in size but may not become thrombogenic. The plaques may eventually occupy more than 50% of the lumen of the coronary artery (see discussion of concentric lesions). In subset 3, the plaque is vulnerable in that it is subject to a tear or crack perhaps because it is lipid laden. Should a tear develop, the plaque may enlarge abruptly and obstruct coronary blood flow as described in the discussion of type II stenotic lesions. This may lead to sudden death, unstable angina, or infarction.

The recognition that some lesions are harmless while others are potentially lethal highlights the need for a method to identify the lesions that are vulnerable to disruption.

To reemphasize, the point being made is that it is not correct to state that all lesions that occupy less than 50% of the diameter of the lumen or a coronary artery are nonsignificant.
When lesions are divided into stenotic and nonstenotic but vulnerable lesions, it is possible to envisage that appropriate medication (determined by the clinical syndrome that is present), coronary angioplasty or coronary bypass surgery, and subsequent risk factor control are needed for stenotic lesions and that appropriate medication and strict risk factor control (including careful attention to the management of lipid abnormalities) may be needed for nonstenotic vulnerable lesions. Coronary bypass surgery is not indicated for nonstenotic lesions, and angioplasty may be harmful, especially when it is used to compress a vulnerable plaque.

In the future, when the biochemical features of vulnerable, nonstenotic plaques are identified, they may represent a target for a new treatment, including the possible use of localized gene therapy.

The word “significant” has been overworked and is commonly misused. The use of the word in statistical analysis is carefully defined, and its use should obviously be continued. On the other hand, the term “nonsignificant,” when applied to atherosclerotic lesions in the coronary arteries, is often misleading. To avoid misleading others, I recommend we accept Ambrose’s recommendation that coronary arteriographers divide the lesions into stenotic lesions and nonstenotic lesions. It is important to recognize that some nonstenotic lesions, which by definition do not appear to impede normal coronary artery blood flow, should not be labeled as nonsignificant because some of the vulnerable lesions may rupture and produce acute conditions such as sudden death, unstable angina pectoris, or myocardial infarction.

The classification of atherosclerotic coronary lesions offered here is based on the current thinking of many investigators. It is based on a hypothesis that is likely to change as new data are accrued.

I am not a coronary arteriographer, but I am profoundly interested in the subject because words such as “significant” and “nonsignificant” do not communicate the true situation as it is viewed today.

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