EDITORIAL COMMENT

A Renaissance of Provocative Testing for Coronary Spasm?*

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The term variant angina, first used by Prinzmetal et al. (1) in 1959, denotes chest discomfort with classic features of angina but occurring at rest or at night (usually the early morning hours) rather than with exertional or emotional stress. The pain is often associated with ST segment elevation and is relieved by nitroglycerin. A female predominance and frequent association with cigarette smoking, as well as migraine syndromes and Raynaud’s phenomenon, have been recognized. In 1973, spontaneous coronary spasm was documented during coronary angiography in a patient with variant angina (2), confirming the mechanism originally proposed by Prinzmetal et al. (1). Coronary spasm superimposed on minimal-to-mild atherosclerosis is the generally accepted proximate cause of variant angina, but definitive mechanisms have remained elusive. Although chest pain syndromes atypical for angina in the absence of important atherosclerotic obstructions are common, variant angina as described by Prinzmetal et al. (2) is less common but not rare. The diagnosis is challenging and requires observation of spasm associated with the patient’s typical symptoms and electrocardiographic (ECG) changes. Coronary spasm may contribute to other ischemic coronary syndromes, including variable threshold exertional angina.

Ergonovine, an ergot alkaloid used to control postpartum uterine bleeding, was found in 1949 to provoke angina, and was proposed in 1963 as a diagnostic test for coronary disease (3). In early studies, however, patients received very high doses of ergonovine. Severe angina was not uncommon and a reported death in a small series occurred in this context. The provocative report on ergonovine echocardiography was performed in 1993, but only 6 ergonovine studies were performed! Two decades ago, in our institution, we were seeing two to three new cases of variant angina per month; now we see less than two per year. The reason for this marked change in frequency is not clear. The widespread use of calcium antagonists, which are highly effective in preventing coronary spasm, is one possibility. Lack of testing is another. For example, in one of our hospitals, 1,240 non–transplant-related diagnostic coronary arteriograms were performed in 1999, but only 6 ergonovine studies were performed! Two decades ago, we were performing six ergonovine studies per week. In this context, the provocative report on ergonovine echocardiography raises a number of issues, including safety, specificity and usefulness in clinical practice.

Safety. Song and colleagues performed >1,500 ergonovine studies, most in an outpatient setting, over seven years without serious complications. This is certainly one of the largest reported series of ergonovine studies available in the literature. They used small incremental doses of ergonovine, 0.05 mg IV every 5 min, to a total maximal dose of 0.35 mg or until side effects or a positive end point (wall motion abnormality) necessitated termination. Some invasive pro-

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tocools have used ergonovine doses of 0.05 mg, 0.15 mg and 0.25 mg at 3-min intervals (3), whereas others limited the total dose to 0.2 mg (5). The authors propose that the ergonovine test with echo monitoring may be safer than the ergonovine with angiography because continuous observation of wall motion will allow earlier termination of the study, before onset of severe ischemia (manifest as chest pain and ST elevation). Continuous monitoring of the coronary angiogram is not possible. Although large, this is the experience of a single center, and safety will need to be confirmed at other centers with a wider variety of cases and in the hands of different operators before the test can be recommended in general practice. Apparently, the ergonovine echo is interpreted just as any other stress echo, implying that skill in stress echo would be adequate for interpretation of the ergonovine stress. This will need to be confirmed. The authors also mention that ST elevation occurred in 10 patients with poor echocardiographic windows. Coronary spasm, the initiating event, may be visualized early by angiography. Based on animal research, the authors suggest that the spasm-induced ischemia will produce a localized decrease in contractility (visualized by echo) before the onset of ECG changes of severe ischemia. If the continuous monitoring of wall motion contributes to the safety of this procedure, one cannot condone performing an ergonovine echo study in any patient with poor windows, as the safety is unknown and diagnostic capability is limited. Thus, the risk–benefit ratio in each patient must be also considered. We are willing to recommend procedures with significant risk to diagnose and treat critical CAD. However, we should demand a very low risk procedure to identify coronary spasm superimposed on no or only mild CAD, as these patients have been shown in both white and Japanese populations to have a relatively good outcome during follow-up.

Specificity. To determine the specificity of a test, one must have some reasonable reference standard. Song et al. (9) compare the results of noninvasive ergonovine echo with the results of invasive ergonovine testing. The specificity of ergonovine in conjunction with coronary angiography was addressed by Bertrand et al. (6) in 1982. When ergonovine was given in >1,000 consecutive patients undergoing catheterization, the frequency of positive ergonovine provocation was as follows: 1.2% in patients with chest pain atypical for angina pectoris and normal/near normal arteries; 4.3% in patients with effort angina only; 13.8% in patients with effort plus rest angina; 38% in patients with rest angina (203 patients); and 0% in patients with cardiomyopathy. Overall, 59% of spasm episodes occurred on fixed lesions in this study (6). These data allow us to conclude that patients with rest angina only are much more likely to have a positive ergonovine study than patients with either chest pain atypical for angina or effort angina only. Also, the data on the sensitivity of ergonovine testing with angiography are limited as there is no reference standard except observation of spontaneous spasm. We cannot conclude that a negative ergonovine study excludes spasm with 100% certainty as a mechanism of chest pain. In the institution where Song and colleagues practice, 200 to >300 evaluations for possible coronary spasm were ordered each year. Overall, 32% of the ergonovine echos in their center were positive, with 44% positive tests in patients suspected of having variant angina. For most of their patients, the only screening for significant fixed atherosclerotic obstructive disease was an exercise stress test with only ECG monitoring, which has a sensitivity of only 75% to 80% for detecting significant CAD. Perhaps fewer ergonovine studies would have been necessary if a more sensitive screening test for fixed CAD had been used. One must be concerned that ergonovine testing would be associated with higher risk for complications in patients with more severe CAD. In the selected subset of patients who underwent angiography, the authors found agreement (both studies positive or both negative for provoked ischemia) in 202 of 218 patients (93%), suggesting equivalent diagnostic accuracy. Of note also, 152 of 218 patients had a positive ergonovine angiographic test (70%). This is a much higher positive rate than the overall population, confirming that this is a highly selected group, perhaps a group selected for angiography due to the positive ergonovine echo. One cannot extrapolate the accuracy of the test in this highly selected group to the overall population in which it was ordered or to some other population in which it may be utilized in the future. It would be interesting to know the severity of fixed coronary disease found in these patients who were selected for angiography, and whether the ischemic territory identified by the two tests was the same. We and others have described cases with spasm occurring in multiple coronary arteries. This may be more difficult to recognize by echo monitoring. In the initial description by Song et al. (10) in 1996, in which the sites of spasm identified by echo and angiography were compared, the echo failed to identify cases of multivessel spasm. This may occur if the ergonovine-echo study is terminated as soon as any wall motion abnormality is identified and may not be an important clinical limitation.

In summary, it would seem prudent to perform a more sensitive screen for significant fixed coronary disease prior to any noninvasive ergonovine-echo study, to avoid subjecting a patient with a severe coronary lesion to provoked spasm in an outpatient setting without the ability to promptly reverse spasm with intracoronary nitroglycerin. Patients with positive ergonovine tests will still be a mixed group, with most having minimal-to-moderate fixed disease and some patients having severe disease missed by initial screening test. We must also ask ourselves whether a positive ergonovine-echo suggesting spasm would be enough for patient management, or would we still need a better characterization of the severity of fixed disease with angiography?

Usefulness. Finally, we must ask ourselves how we will use this noninvasive ergonovine-echo test in clinical practice in
an era when we rarely bother to use ergonovine in the catheterization laboratory. In the most recent American College of Cardiology/American Heart Association Coronary Angiography Guidelines, expert consensus supported the usefulness of provocative testing for coronary spasm in patients with “recurrent episodes of apparently ischemic cardiac pain at rest” and “normal or mildly abnormal coronary angiogram” but no clinical observations to substantiate the diagnosis of variant angina (11). Song and colleagues report a steady decline in the use of ergonovine during angiography at their institution in Korea, accompanied by an increase in the use of ergonovine-echo. There has been a similar marked decline in the use of ergonovine in the catheterization laboratories in U.S. institutions, even without the availability of a noninvasive test to take its place. We must ask ourselves why we have abandoned the use of ergonovine and what has happened to the patients with coronary spasm who we worked so hard to identify in the late 1970s and early 1980s. Perhaps cardiologists are now only interested in patients in need of angioplasty or stenting and do not want to be bothered with milder forms of ischemic heart disease. Some may consider the test too time-consuming to be performed in the busy invasive-interventional laboratory. Perhaps some are still concerned about the safety of ergonovine, even in the catheterization laboratory, where a serious complication, although rare, is not acceptable in a disease with a relatively good prognosis. Perhaps we see variant angina less often because of the widespread use of calcium antagonists for chest pain and/or hypertension. Maybe cardiologists have found that an empirical trial of calcium antagonists, perhaps combined with nitrates, is as helpful as an ergonovine test used to be in the evaluation of possible spasm. We suspect that many cardiologists became disillusioned with the indiscriminate use of ergonovine in patients with chest pain syndromes atypical for transient ischemia. What should they do with the positive results that sometimes occurred in these patients? Did they lose confidence in a test that was perhaps overused and maybe even inappropriately used? In this setting, did they stop considering the diagnosis of variant angina and abandon any attempt to confirm the diagnosis and perhaps manage symptoms more appropriately? The report of Song and colleagues challenges all of us to look more carefully for patients with variant angina and consider whether a renaissance in provocative testing for coronary spasm is needed.

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