Ergonovine Stress Echocardiography for the Diagnosis of Vasospastic Angina

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Coronary artery spasm has been considered one of the major mechanisms causing *dynamic* stenosis of epicardial coronary arteries, which can evoke acute myocardial ischemia. Vasospastic angina caused by coronary artery spasm has a wide clinical spectrum: one of its typical clinical manifestations is variant angina. Coronary vasospasm has also been documented to contribute to the development of unstable angina or acute myocardial infarction [1]. Classically, coronary artery spasm is diagnosed by an invasive provocative procedure during diagnostic coronary angiography. Since various noninvasive diagnostic tests for fixed atherosclerotic stenosis of epicardial coronary arteries (exercise ECG, stress echocardiography, and nuclear tests) are being used in routine daily practice, it would be useful to establish a reliable, noninvasive, and safe diagnostic method to document coronary artery spasm in the management of patients with vasospastic angina.

The rare episodic nature of coronary artery spasm makes it extremely difficult to document spontaneous coronary vasospasm in clinical practice. The noninvasive stress tests currently used are ergonovine [2], acetylcholine [3], and systemic alkalosis by hyperventilation [4]. Of these, spasm-provocation testing using ergonovine is considered the gold standard for diagnosis of coronary artery spasm because of its high sensitivity and specificity. Acetylcholine seems to have comparable diagnostic validity for intracoronary administration, but its short half-life for the abundant pseudocholinesterase in human plasma makes intravenous injection inadequate for spasm provocation.

16.1 Basic Considerations

Ergonovine maleate is an important oxytocin alkaloid and a member of the ergobasine group, an amine alcohol derivative of lysergic acid. This drug can induce coronary vasoconstriction in patients who have undergone heart transplantation, which suggests that it does not act via the central nervous system. This drug is believed to stimulate α-adrenergic

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and 5-hydroxytryptamine (serotonin) receptors [5]. After intravenous injection, the half-life of the distribution phase is between 1.8 and 3 min, and the half-life of the disappearance phase is between 32 and 116 min [6]. This rapid mode of action explains why coronary spasm most often occurs between 2 and 4 min after the injection. The use of ergonovine in incremental doses starting with an intravenous injection of 0.05–0.1 mg followed by small increments of 0.1–0.15 mg at 5-min intervals up to a maximum cumulative dosage of 0.35 or 0.4 mg is generally recommended [1]. This general guideline is based on the finding that the cumulative doses (0.1 + 0.2 + 0.3 + 0.4 mg) at 5-min intervals have the same effects as a single dose of 0.4 mg [1]. The provocative test with ergonovine performed in the cardiac catheterization laboratory has a high sensitivity (98%) and specificity (98.7%) [7].

16.2 Protocol

For a diagnosis of vasospastic angina, the possibility of significant fixed atherosclerotic stenosis of major epicardial coronary arteries is usually ruled out by means of the exercise stress test and/or pharmacological stress echocardiography. All cardioactive drugs (β-receptor blocker, calcium channel blocker, and nitrates) should be discontinued for at least five half-lives; however, nitroglycerin should be administered sublingually as necessary. Resting hypertension is usually controlled using angiotensin-converting enzyme inhibitors; uncontrolled hypertension is a contraindication of this test.

It should be remembered that some drugs, especially long-action calcium channel blockers, may have persistent effects on coronary vasomotor tone as long as 2–3 weeks after discontinuation [8, 9].

Figure 16.1 shows the classic protocol of ergonovine echocardiography. A bolus injection of ergonovine (50 μg) is administered intravenously at 5-min intervals until a positive

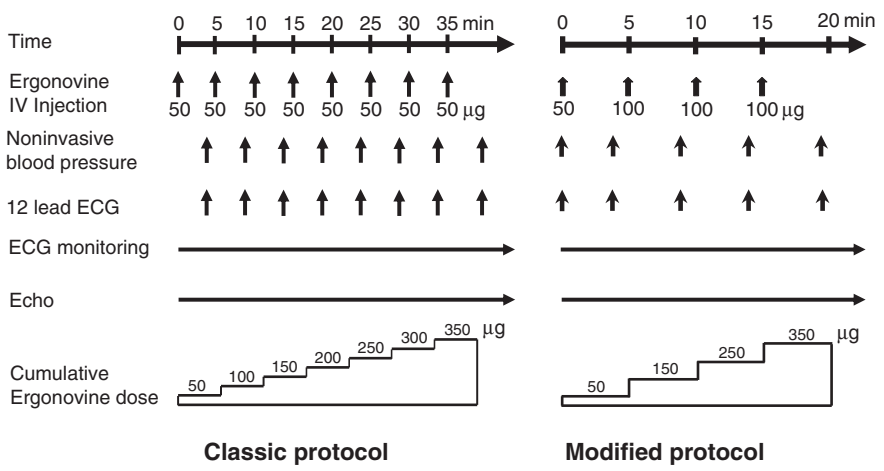

Fig. 16.1 Classic (*left*) and modified (*right*) protocols for ergonovine echocardiography

response is obtained or a total dose of 0.35 mg is reached. The 12-lead ECG is recorded after each ergonovine injection and left ventricular wall motion is monitored continuously. Positive criteria for the test include the appearance of transient ST-segment elevation or depression greater than 0.1 mV at 0.08 s after the J point (ECG criteria) or reversible wall motion abnormality by two-dimensional echocardiography (echocardiographic criteria). The criteria for terminating the test are as follows: positive response defined as ECG or echocardiographic criteria, total cumulative dose of 0.35 mg ergonovine, or development of significant arrhythmia or changes in vital signs (systolic blood pressure>200 mmHg or <90 mmHg). An intravenous bolus injection of nitroglycerin is administered as soon as an abnormal response is detected; sublingual nifedipine (10 mg) is also recommended to counter the possible delayed effects of ergonovine. These drugs can be administered as needed. The protocol can be modified just to decrease the test time (Fig. 16.1), with bolus doses of 50, 100, 100, and 100μg every 5 min up to a cumulative dose of 350 μg.

16.3 Noninvasive Diagnosis of Coronary Artery Spasm: Clinical Data

Bedside ergonovine echocardiography has been reported to be accurate and safe [8–18] (Figs. 16.2, 16.3). The sensitivity of echocardiographic criteria (detection of reversible regional wall motion abnormalities) is higher than 90%,which is far greater than that of ECG criteria (ST-segment displacement, 40–50%). Characteristic ST-segment elevation during ergonovine testing occurred in about one-third of patients with variant angina [16]; the lower sensitivity with ECG criteria can be partially explained by an earlier development of regional wall asynergy during myocardial ischemia in the so-called pre-electrocardiographic phase rather than a true false-negative finding [10–13]. The earlier detection of ischemia with higher sensitivity is very important from the safety point of view, as the vicious cycle of the ischemic cascade can be terminated earlier and the risk associated with prolonged ischemia reduced. According to the recent report of ergonovine echocardiography performed on 1,372 patients [16], the test showed very high feasibility (99.1%); transient arrhythmias – including sinus bradycardia (n = 10), ventricular premature beats (n = 10), short-run ventricular tachycardia (n = 2), and atrioventricular block (n = 4) – developed in 1.9% (26/1,372) of the patients studied. All of these arrhythmias were transient and promptly reversed with the administration of nitroglycerin and nifedipine, as described earlier. Although intracoronary nitroglycerin could not be used to reverse coronary vasospasm in this protocol, there were no serious complications such as development of myocardial infarction or fatal arrhythmia during the test [8, 9].

Unlike other stress tests for fixed atherosclerotic stenosis of coronary artery, this test shows high sensitivity even in patients with single-vessel spasm [16]; the transmural nature of supply ischemia due to coronary artery spasm may explain this difference.

As this test also showed very high specificity (>90%) for the diagnosis of coronary artery spasm before coronary angiography, invasive coronary angiography and spasm-provocation testing can be avoided for the diagnosis of vasospastic angina [16, 18].

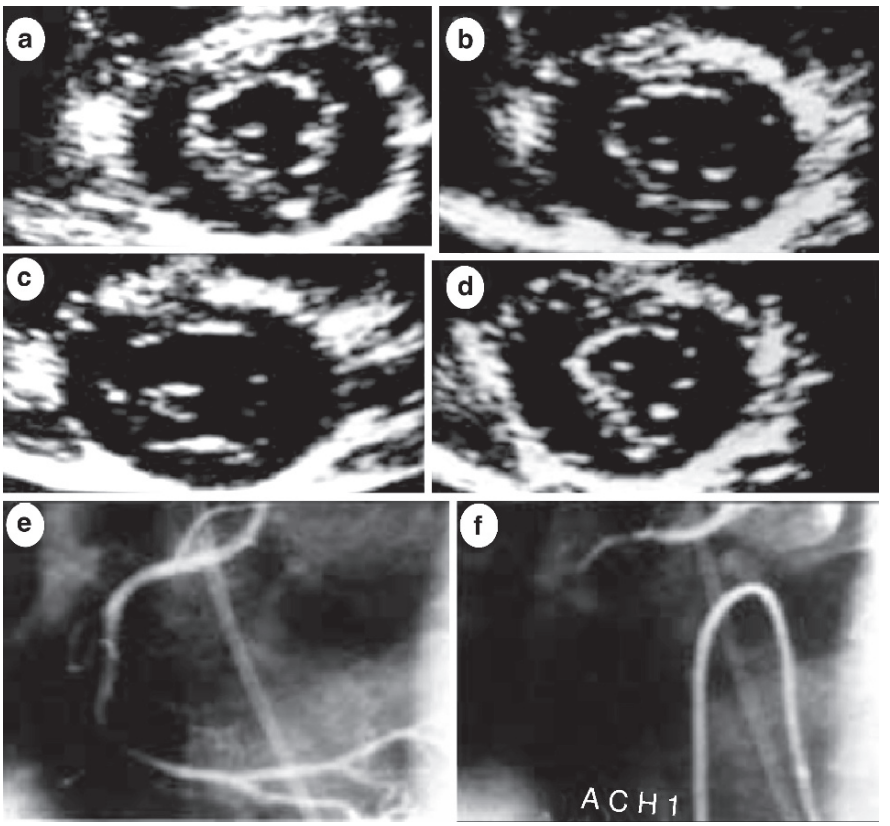

Fig. 16.2 Representative examples of **a**–**d** ergonovine stress echocardiography and **e, f** coronary angiography in a 53-year-old man with early-morning chest pain. Treadmill test results were negative up to stage 4 of the Bruce protocol, and ergonovine echocardiography was done. Left ventricular wall motion at end-systole recorded in the parasternal short-axis view was demonstrated in quad screen format. **a** Basal status. **b** Left ventricular wall motion after injection of 0.05 mg ergonovine. **c** Regional loss of systolic myocardial thickening in the mid-inferior segment with an ergonovine dose of 0.1 mg and **d** recovery of regional wall motion abnormality with nitroglycerin, a finding suggestive of myocardial ischemia in the region of the right coronary artery due to coronary vasospasm. **e** Coronary angiogram taken 2 days later revealed a normal right coronary artery. **f** Intracoronary injection of acetylcholine (ACH) provoked total occlusion of the proximal right coronary artery, which was compatible with coronary vasospasm. (From [9], with permission)

16.4 Special Safety Considerations

Issues regarding the safety of spasm-provocation testing are summarized in Table 16.1.

Ergonovine echocardiography testing, undertaken either in the catheterization laboratory or at the bedside, is a risky and challenging procedure, demanding a high degree of

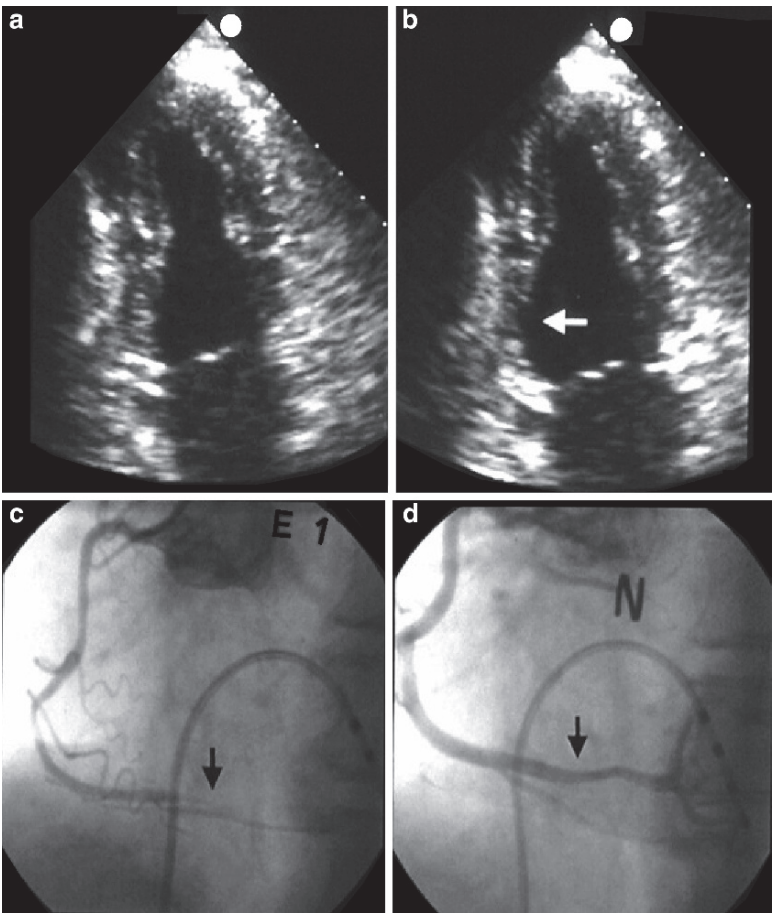

Fig. 16.3 Representative example of ergonovine echocardiography (**a**, **b**) and invasive spasm provocation testing during diagnostic coronary angiography (**c**, **d**) in a 47-year-old man. Left ventricular wall motion at end-systole recorded in the apical two-chamber view was demonstrated (**a**, **b**). Compared with the basal status (**a**), prominent loss of systolic thickening in the inferior wall developed with an ergonovine dose of 0.15 mg (**b**, *white arrow*), which was compatible with myocardial ischemia due to coronary artery spasm in the right coronary artery territory. Coronary angiogram taken 3 days later revealed no significant fixed disease. Intravenous injection of ergonovine (*E1*) provoked total occlusion of the distal right coronary artery (*C*), and the angiogram after injection of nitroglycerin (*N*) showed completely normal right coronary artery and relief of total occlusion (**d**). (Adapted from [16], with permission)

skill on the part of the operator [8]. Angiographic demonstration of reversible total occlusion of one of the major epicardial coronary arteries is in itself enough for a diagnosis of coronary vasospasm. If, however, angiography reveals only moderate vasoconstriction, as occurs more frequently in the daily clinical practice of provocation testing, other indexes of myocardial ischemia are necessary before a definite diagnosis of coronary vasospasm

Table 16.1 Potential advantages and disadvantages of spasm-provocation testing in the catheterization laboratory and at the bedside

	Advantages	Disadvantages
Provocation test during angiography	Angiographic demonstration of reversible vasoconstriction	Relatively late and insensitive ischemic markers (chest pain, electrocardiographic changes)
	Direct intracoronary injection of nitroglycerin	Invasive, perturbs vasomotor tone
	Temporary pacemaker backup	Injecting contrast agent into coronary circulation
		Continuous monitoring of whole ischemic process impossible
Bedside ergonovine echocardiography	Detection of regional wall motion abnormalities: sensitive and specific marker of myocardial ischemia, continuous monitoring, early detection and termination of ischemic cascade	Intracoronary injection of nitroglycerin impossible
	Noninvasive, does not perturb vasomotor tone	Temporary pacemaker backup impossible
	Repeat and follow-up studies	Dependent on acoustic window

can be made. In the catheterization laboratory, the development of chest pain and electrocardiographic changes, well known as relatively late events in ischemic cascade, are classic markers of myocardial ischemia. The usual 3- to 4-min wait after each injection of the drug before repeat angiography without sensitive monitoring of ischemic cascade in the catheterization laboratory may also contribute to the potential danger of the procedure. This is because the development of serious arrhythmia or myocardial infarction depends on the duration of the preceding myocardial ischemia during spasm provocation.

In addition to concerns about disturbing vasomotor tone with the catheter, injecting a contrast agent into the coronary circulation during a severe ischemic episode may increase the risk of the procedure. Myocardial imaging rather than angiography has been proposed as a more sensitive, more specific, and safer method of identifying coronary vasospasm by some physicians. The importance of intracoronary nitroglycerin for reversing an intractable vasospasm that is not responsive to sublingual and intravenous nitroglycerin has been reported [19, 20], but other published investigations indicate that intracoronary nitroglycerin is not a prerequisite for spasm-provocation testing [8–18].

The most important advantage of ergonovine echocardiography is its capacity for detecting regional wall motion abnormalities, which are sensitive and specific markers of myocardial ischemia, even before the appearance of chest pain or electrocardiographic changes. During ergonovine echocardiography, the wall of the left ventricle can be

continuously monitored, with early termination of myocardial ischemia based on the detection of regional wall motion abnormality; this is a potential and theoretical advantage of the test. In our study [8, 16], less than half of the patients with definite wall motion abnormalities showed ECG changes suggestive of myocardial ischemia, which is compatible with the premise described above. Further multicenter investigation is needed to determine whether early detection and termination of myocardial ischemia based on regional wall motion abnormalities can completely obviate the need for temporary pacemaker backup.

16.5 Clinical Impact

Noninvasive ergonovine stress echocardiography is an effective and reasonably safe way of diagnosing coronary vasospasm in routine clinical practice for patients visiting the outpatient clinic [16] or for those admitted to the coronary care unit under the clinical impression of unstable angina pectoris [15]. Although clinical usage of spasm provocation testing has decreased significantly in Western countries and spasm provocation testing is no longer a routine diagnostic procedure, recent investigation [21] reveals significantly higher mortality and event rates with a positive result of ergonovine stress echocardiography (Fig. 16.4) in patients with near normal coronary angiogram or in those with negative stress test results for significant fixed stenosis. These results demonstrate the powerful prognostic implication of noninvasive ergonovine stress echocardiography in routine daily practice for differential diagnosis of chest pain syndrome. As this test provides an effective and powerful means of risk stratification on the basis

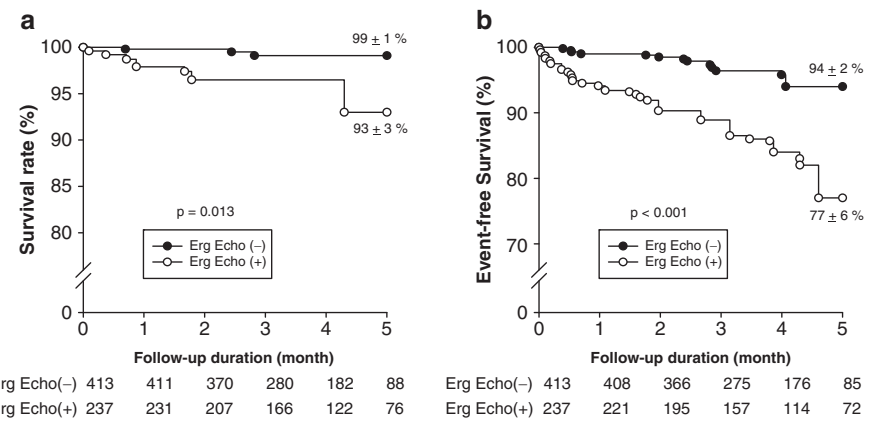

Fig. 16.4 Survival (**a**) and event-free survival rates (**b**) according to the results of ergonovine echocardiography (*Erg Echo*) in patients with near normal coronary angiogram or negative stress test results for significant fixed stenosis. (−), negative test; (+), positive test. (Adapted from [21])

of the presence of provocable ischemia in patients with no evidence of significant fixed coronary stenosis, either by direct invasive or noninvasive (by 64-slice computed tomography) coronary angiography or by noninvasive stress testing, consideration of ergonovine stress echocardiography for complete differential diagnosis of mechanisms of myocardial ischemia should be encouraged in various clinical scenarios involving patients with chest pain syndrome [22], such as patients with angiographically normal coronary arteries and a history of angina at rest, aborted sudden death [23], flash pulmonary edema [24], or suspected left ventricular apical ballooning syndrome [25]. The usefulness of the ergonovine test in monitoring the efficacy of antianginal therapy has been documented [26], but its clinical value remains uncertain. It is probably inappropriate to use the test in patients in whom the diagnosis is already established by clinical history or with concomitant ischemia in presence of angiographically documented coronary artery disease. The test can be less safe in patients with uncontrolled hypertension and previous stroke [27]. It is also important to consider vasospasm – and, if appropriate, vasospasm testing – in several clinical settings remote from the cardiology ward when ergometrine-containing or serotonin-agonist drugs are routinely given and may occasionally precipitate "out-of the-blue" cardiological catastrophes mediated by coronary vasospasm: ergometrine given in the obstetric clinic to reduce uterine blood loss in the puerperium phase [28–33] or bromocriptine given for milk suppression [34, 35], sumatriptan or ergometrine used in neurology for migraine headaches [36–39], 5-fluorouracil and capecitabine (an oral 5-fluorouracil prodrug) given as chemotherapy in (breast and colon-rectal) cancer [40–44], and, with increasing frequency, cocaine as a cause of chest pain in the ER [44–45]. In all these conditions, it is essential to think of vasospasm so as to recognize it (Table 16.2).

Table 16.2 Indications to ergometrine stress echocardiography

	Appropriate	Uncertain	Inappropriate
Patients with angina at rest and normal or near normal coronary arteries	√		
Patients with chest pain assuming cocaine, 5-FU, capecitabine, ergometrine, bromocriptine, sumatriptan	√		
Patients with suspected Tako-Tsubo syndrome	√		
Patients with unexplained flash pulmonary edema with normal coronary arteries	√		
Patients with known variant angina to test therapy efficacy		√	
Patients with known variant angina			√
Patients with uncontrolled hypertension or previous stroke			√

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