Hyperventilation Test

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Hyperventilation tests have been mainly used in clinical practice as a provocative test for coronary artery vasospasm in patients with suspected or documented vasospastic angina [1–4]. The rationale for the use of hyperventilation testing for this purpose is based on the demonstration that, in susceptible patients, hyperventilation may trigger a vasospasm of a major epicardial coronary artery associated with chest pain and ischemic electrocardiographic changes similar to those observed during spontaneous anginal attacks [1].

17.1 Pathophysiology

Prolonged, vigorous overbreathing decreases plasma hydrogen ion concentration, leading to metabolic alkalosis, which can trigger coronary artery spasm [1]. The increase in arterial blood pH reaches the peak at the end of hyperventilation, while ST-segment elevation usually develops during the recovery phase early after the end of the test, when arterial pH is already decreasing toward baseline but is still significantly elevated compared to basal values [4].

Another mechanism of coronary spasm in this setting can ensue, with increases in intracellular concentration of calcium ions following a decrease in the concentration of hydrogen ions, which compete with calcium for active transmembrane transport [5] (Fig. 17.1). The increase in intracellular calcium concentration can in turn elicit a vasospastic constriction of smooth muscle cells in susceptible coronary epicardial arteries [5].

17.2 Protocol

The patient hyperventilates for 5 min, with increased frequency (30 per min) and depth of breathing (Fig. 17.2). The time window of positivity usually occurs 1–5 min after the end of hyperventilation, therefore without degrading the quality of echocardiographic imaging.

E. Picano, *Stress Echocardiography*,

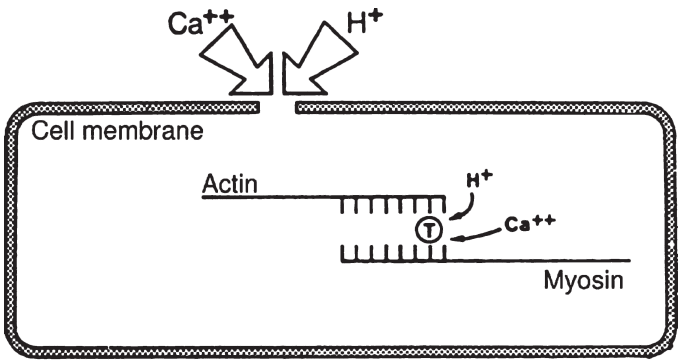

Fig. 17.1 The mechanism of contraction induced by alkalosis in smooth muscle cell. With a reduced concentration of hydrogen ions, more calcium enters the cell from the outside and more intracellular calcium reaches the regulatory troponin site, triggering contraction. (Modified from [5], with permission)

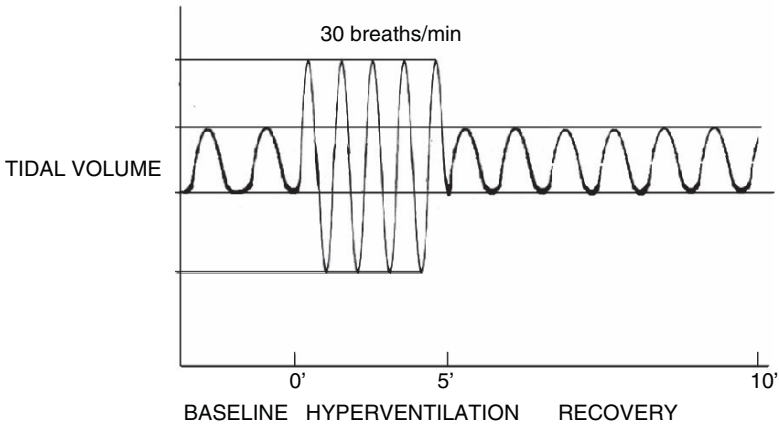

Fig. 17.2 Protocol of the hyperventilation stress echocardiography test

17.3 Diagnostic Value

The sensitivity of the test is markedly affected by the spontaneous activity of the disease; when spontaneous attacks occur frequently, a positive response to hyperventilation is observed in more than 80% of patients, while the sensitivity of the test decreases to 50% or less in patients with less active disease [1, 3, 4, 6–10]. Since hyperventilation may produce

chest pain and pseudoischemic changes in vasospasm, echocardiographic monitoring during the test can be particularly useful to demonstrate normal regional wall motion and thickening and therefore rule out the diagnosis of vasospastic myocardial ischemia. In patients with variant angina, hyperventilation can also be used to predict the ability of antianginal drugs to prevent spontaneous attacks and to select an effective medical treatment [8]; moreover, if the test yields negative results during long-term follow-up, this may indicate a spontaneous remission of the disease [8].

17.4 Diagnostic Value and Clinical Guidelines

The hyperventilation test has shown excellent safety and satisfactory feasibility associated with good sensitivity (slightly lower than ergometrine) and specificity for the diagnosis of vasospastic angina (Table 17.1). It is considered slightly safer than the ergonovine test because the stimulus to vasospasm wanes as soon as the intracellular pH returns to normal; however, one should be aware that consequences of ischemia are largely independent of the form of provocation [11, 12]. Both total duration of the test and the imaging time are shorter with hyperventilation (about 10 min) than with ergonovine (approximately 20 min) (Table 17.1).

It can therefore be a useful test for the diagnosis of vasospastic angina in outpatients and in patients with contraindications to ergometrine such as arterial hypertension or previous stroke (Table 17.1). It may unmask the vasospastic origin of symptoms in patients with syncopal angina [13, 14]. However, hyperventilation is demanding for the patient who may not be able to complete it and is contraindicated in epilepsy. In patients with typical symptoms, a positive response to hyperventilation is diagnostic, thus avoiding the need to perform ergometrine testing. In patients with a negative or nondiagnostic response to hyperventilation but with symptoms suggesting vasospastic angina, ergonovine testing

Table 17.1 Tests for coronary vasospasm

	Hyperventilation	Ergometrine
Sensitivity	++	+++
Specificity	+++	+++
Safety	+++	++(+)
Imaging time	10 min	20 min
Arterial hypertension	Yes	No
Epilepsy	No	Yes
Previous stroke	Yes	No
Physically deconditioned	No	Yes

should be performed since the sensitivity of the hyperventilation test in patients with sporadic symptoms is suboptimal and a negative response cannot rule out the presence of vasospastic angina. Our policy is to perform ergometrine testing only in inpatients, whereas hyperventilation is also performed in outpatients.

Hyperventilation testing can also be used to assess the efficacy of medical therapy, such as endothelium-protective estradiol supplementation in variant angina [15] or atrial natriuretic peptide (ANP) [16] infusion. Novel, promising approaches combine mild hyperventilation followed by exercise [17] or the cold pressor test [18–21] to enhance the test sensitivity for vasospasm detection. Conceptually, this approach is similar to the combined stress approach for the diagnosis of minor forms of fixed coronary artery stenosis. In the latter case, a vasodilator stress reducing subendocardial flow supply through steal phenomenon (dipyridamole) is administered and, if the stress is negative, a second additive stressor (exercise or dobutamine), with a different mechanism of action, is administered on the shoulder of the first one to increase myocardial oxygen demand [22, 23]. In the diagnosis of coronary vasospasm, there is a hierarchy of testing for stressor potency with ergometrine being the most potent, hyperventilation the intermediate, and exercise and cold pressor the least potent stressor [9] (Fig. 17.3). Since hyperventilation acts in a different fashion than exercise and cold, the sensitivity for vasospasm critically increases with the combination of hyperventilation and either the cold pressor or exercise test (Fig. 17.3).

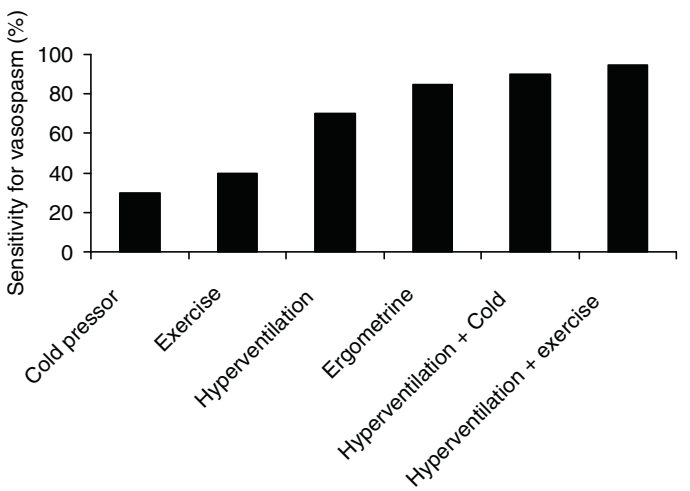

Fig. 17.3 The hierarchy of test sensitivity for the diagnosis of coronary artery disease. The continuous transverse line indicates the fixed ceiling of coronary flow reserve, which is not reduced in this ideal case of pure vasospastic angina. The *dashed lines* indicate the fluctuations of coronary tone. They occur spontaneously (*far left*, variant angina) or can be provoked by stress testing. The power of stress testing is indicated by the depth of the *dashed line*. Only tests arriving below the line of oxygen consumption at rest evoke ischemia. Cold and exercise are relatively weak stressors when used alone, but they can critically potentiate the sensitivity of hyperventilation

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