Ergonovine test in angina with normal coronary arteries. Is it worth doing it?

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Abstract

Background: Patients with angina and normal coronary arteries are often misdiagnosed with having non-cardiac pain. Although vasospasm is a well-known entity, spasm provocation is not routinely done in the majority of hospitals at present.

Materials and methods: One hundred and sixty two consecutive patients with thoracic pain and normal coronary arteries were retrospectively studied. The characteristics of pain were analysed. One hundred and sixty one non-invasive tests (with and without imaging) were done to 126 patients before angiography. Increasing doses of ergonovine (from 1 to 30 μg) were injected into the coronary arteries to provoke coronary spasm. The correlation between ergonovine-induced spasm and non-invasive tests was studied.

Results: Oppressive thoracic pain suggestive of angina was present in 144 patients. It occurred at rest in 59 patients, only at night in 14, with effort in 40, and it was mixed in 31. Non-oppressive atypical pain was reported by 18 patients. Non-invasive tests were 94 positive, 60 negative and 7 non-diagnostic. Ergonovine test elicited coronary spasm in 85 patients (52.5%). No significant correlation was found between the positivity of a non-invasive test and ergonovine-induced spasm.

Conclusions: More than half of the patients with angina and normal coronary arteries can be diagnosed with vasospastic angina if ergonovine test is performed. Even patients with a negative non-invasive test maybe sent to coronary angiography when vasospastic angina is suspected, in order to have an accurate diagnosis.

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1. Introduction

Coronary spasm occurs mainly on stenotic plaques, but it can also occur in normal arteries. About 20% of patients submitted to coronary angiography for suspected coronary artery disease have normal coronary arteries or non-significant lesions [1]. Although vasospastic or Prinzmetal angina is a well-known clinical and angiographic entity [2–4], it is frequently non-diagnosed in clinical practice. One of the reasons may be the routine use of intracoronary nitroglycerin in many laboratories before coronary angiography, to eliminate the vascular tone of the arteries and any possible spasm [5]. As the vasodilating effect of nitroglycerin lasts for several minutes, ergonovine is not effective to detect a possible coronary spasm in patients who receive repeated intracoronary nitroglycerin [5]. In some laboratories, although nitroglycerin is not used routinely, ergonovine is neither used to look for a possible coronary spasm. These patients are frequently misdiagnosed with non-cardiac pain, which means they do not have a proper diagnosis. They suffer thoracic pain and undergo repetitive coronary angiograms during their lifetime. Other times they are treated by a psychiatrist.

In order to know the usefulness of intracoronary ergonovine test in everyday clinical practice in a South European (low risk of cardiovascular disease) country, we collected a series of consecutive patients with suspected ischemic chest pain and normal coronary arteries submitted
to ergonovine test. As many of them had a previous non-invasive test, we also analysed if these tests are useful for the prediction of coronary spasm.

2. Materials and methods

2.1. Patients

A total of 162 consecutive patients (109 men) aged 54±11 years who fulfilled the inclusion criteria were selected for the study. All but one (who was admitted with an acute coronary syndrome) were seen as outpatients in a Cardiology Surgery.

Inclusion criteria: (1) Patients with suspected ischemic chest pain who were submitted to coronary angiography and had normal coronary arteries or non-significant (<50%) lesions. In addition, all of them underwent and intracoronary ergonovine test.

The reasons for deciding coronary angiography depended firstly on the criteria of the cardiologist in charge of each patient and secondly on the patient’s choice. In some cases it was due to the high intensity or frequency of the crisis. In other cases because a non-invasive test was positive and the patient preferred to undergo coronary angiography. In other cases because the pain was very suggestive of coronary spasm. In these cases the physician explained to the patient what a coronary spasm is and the risks it has. With this information some patients chose to try medical therapy. Other patients chose to undergo coronary angiography followed by an ergonovine test in case of normal vessels, to make sure of the diagnosis.

Exclusion criteria: Patients with ST segment elevation during angina (because there was no need for ergonovine) and those with severe catheter-induced or spontaneous spasm during coronary angiography.

2.2. Clinical history

Special attention was paid to the characteristics of pain and the presence of cardiovascular risk factors: hyperlipidemia (diagnosed according to the Adult Treatment Panel III criteria) [6], hypertension (blood pressure >140/90 mm Hg or normal pressure with antihypertensive therapy, tobacco (present smokers within the last 12 months) and diabetes mellitus (fasting blood glucose >126 mg/dL or antidiabetic therapy) or impaired glucose tolerance (blood glucose =140–199 mg/dL 2 h after an oral glucose tolerance test). Physical examination was performed attending specially to cardiovascular data.

2.3. Analyses

Hemogram, urine-analysis and biochemistry were performed in every patient.

2.4. Electrocardiogram (ECG)

A 12 lead ECG was recorded at rest in the supine position. None of these patients had angina during the electrocardiographic recording.

2.5. Stress tests

The patients were studied by different cardiologists and each physician chose the non-invasive stress test for his or her patients. Although the ideal stress tests are with imaging (echocardiogram or perfusion), these explorations are not always available for every patient. For this reason, the first test was an exercise stress test without imaging in 98 cases. If the test was negative or non-diagnostic and the patients came back with symptoms, another test with imaging was performed on another occasion. A total of 161 stress tests were performed in 126 patients. Ninety one patients were submitted to a single test and 35 to two different kinds of stress test. Thirty six patients were sent to coronary angiography without a previous non-invasive test, due to severe angina or high suspicion of vasospastic angina or the need to make an accurate diagnosis. The following non-invasive tests were done: 98 exercise stress tests without imaging, 46 with imaging (31 scintigraphy and 15 echocardiography) and 17 pharmacological tests with scintigraphy.

Exercise stress test was performed with an electrically braked bicycle ergometer (Siemens Elema) or with treadmill. In all cases the test was stopped after the maximal heart rate for each age was reached or in case of limiting symptoms. A 3 lead ECG was continuously monitored on a screen, and a complete (12 lead) ECG was recorded every minute during the exercise. Both visual and computer-assisted measurements of ST segment changes at 0.06 s of the J point were performed. The test was considered positive for ischemia if there was horizontal or downward ST segment shift >1 mm from baseline, measured 0.06 s after the J point, that persisted for three consecutive beats in more than one lead.

2.6. Exercise test with thallium-201 single photon emission tomography

Three millicuries of thallium-201 were given by intravenous injection during the peak exercise and the exercise was continued for one additional minute. Thallium-201 images were acquired within 10 min. Redistribution images were acquired 3–4 h after the initial stress image. Tomographic images were analysed visually by two expert nuclear physicians and the extent of thallium defects was computed, when possible, by means of the polar map. Both, visual and quantitative analysis were considered in each case. A test was positive in case of reversible perfusion defects.

Exercise test with echocardiography was performed in 15 patients with a normal rest echocardiogram. The test was
positive in case of development of asynergy (hypokinesia, akinesia or dyskinesia) in at least two of 16 segments of the left ventricle at the end of or immediately after finishing physical exercise.

Pharmacological stress test with thallium-201 was performed in patients unable to do physical exercise. The patients did not take caffeine, analogues to caffeine, dipyridamole or metilxantines in the previous 24 h. An automatic infusion pump was used to inject adenosine triphosphate (0.160 mg kg\(^{-1}\) min\(^{-1}\)) for 6 min. Three millicuries of thallium-201 were given by intravenous injection at the fourth minute of adenosine infusion, according to a previously described protocol \[7\]. Criteria of positivity were the same as for exercise gammagraphy.

2.7. Angiography

Left ventricular angiography was recorded in the right anterior oblique position, and the ejection fraction was calculated in a semi-automatic way. Selective coronary angiography was performed in the usual projections.

2.8. Ergonovine test

When possible, vasodilating drugs were withdrawn before angiography, according to their mean life. After exclusion of significant coronary disease, ergonovine was injected first in the right coronary artery and later (if well tolerated) in the left. Doses were progressively increased from 1 to 5, 10 and 30 \(\mu\)g each minute. A 3 lead ECG was continuously monitored and a 12 lead ECG was recorded at the time of anginal pain or angiographic spasm. Precordial leads were displaced downward. Coronary angiography was performed 1 min after the last ergonovine dose. In case of very symptomatic spasm the test was stopped, coronary angiography was done and intracoronary nitroglycerin (starting with 0.5 mg) was administered.

According to the criteria established by Maseri \[8\], the ergonovine test was considered angiographically positive in the following cases: a) complete or subtotal occlusion of one or more segments of a coronary artery, with or without detectable stenotic plaque; b) segmental reduction of 50% or more of the diameter of an angiographically normal coronary artery segment. When the spasm produced total occlusion or severe stenosis quantification was not necessary. In case of non-severe stenosis the reduction of the diameter of the coronary artery was quantitatively assessed with the program Quantor QCA, version 3.0, Siemens. A positive test may be caused by segmental single-vessel, multivessel or diffuse epicardial coronary spasm.

Although pain and ST segment elevation were also recorded, their absence did not exclude spasm. When nitroglycerin is injected immediately after spasm, there is no time for the occurrence of pain or electrocardiographic changes.

2.9. Statistical analysis

Data were analysed in an SPSS 11 statistical package. Differences in percentages between groups were compared with the Chi-square test or with the exact test (PEPI statistical package, by JH Abramson and PM Gahlinger, 1993–2000). For stratified analysis, Mantel–Haenszel Chi-square test was used. A two-tailed \(p\) value inferior to 0.05 was considered significant.

3. Results

3.1. Clinical data

Table 1 summarises the characteristics of suspected ischemic chest pain or angina and risk factors. Although rest angina was the predominant form of presentation, effort angina ranked second and mixed angina ranked third. More than half of the patients had hypercholesterolemia and also more than half were smokers. Nearly half of them were hypertensive. Few of them had diabetes mellitus or impaired glucose tolerance. The most frequent combination was tobacco plus hypercholesterolemia.

ECG showed anterior necrosis in 1 patient and it was suggestive of posterior necrosis in two patients. Normal ECG or minor changes (mainly right bundle branch block or left anterior hemiblock) were seen in the remaining patients. None of them had ST segment elevation when the ECG was recorded.

3.2. Non-invasive stress tests

Exercise stress test without imaging was performed in 98 patients. It was positive in 48, negative in 43 and non-diagnostic in 7 patients. These 7 tests were omitted for further analysis. ST segment elevation was not found in any case.

Exercise stress test with thallium-201 was performed in 31 patients. Scintigraphy was positive in 25 and negative in 6 of them. Only 4 patients with a positive scintigraphy also...
had ST segment depression during exercise. The 6 patients with a negative thallium test also had a negative electrocardiographic test.

Exercise stress test with echocardiography was performed in 15 patients: echocardiography was positive in 7 and negative in 8 of them. Only 2 patients with a positive echocardiographic test also had ST segment depression during exercise. No patient with a negative echocardiographic test had ST segment changes on ECG.

Pharmacological stress test with adenosine and thallium-201 was performed in 17 patients. Scintigraphy was positive in 14 and negative in 3 of them. ST segment changes were not considered in these patients.

Left ventriculography showed an akinetic area in the three patients with necrosis on the ECG. The global left ventricular function was above 0.45 in all of them.

3.3. Ergonovine test

Coronary spasm was produced by ergonovine in 85 (52.5%) patients and the test was negative in 77 (47.5%). Three patients suffered ventricular fibrillation during a total coronary occlusion induced by ergonovine. Sinus rhythm was restored with an electric shock of 300 J. Table 2 shows the vessels that presented ergonovine-induced spasm. The right coronary artery was the one that presented spasm with the highest frequency. The spasm was focal in 28 cases and diffuse in 57. It produced total occlusion of a coronary artery in 8 cases and partial occlusion in 77. Catheter-induced spasm was observed in 13 patients. As the spasm was not severe and disappeared spontaneously, ergonovine test was performed in them. The test was positive in 4 and negative in 9 patients. These 9 cases were considered negative for spasm.

Table 2
Coronary arteries with ergonovine-induced spasm

<table>
<thead>
<tr>
<th>Coronary artery</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only LAD</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Only LCx</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Only RCA</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Only marginal branches</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>LAD+LCx</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>RCA+LAD</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>All the coronary arteries</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>

LAD: left anterior descending; LCx: left circumflex; RCA: right coronary artery.

3.4. Relationship between risk factors and ergonovine-induced spasm

Table 3 shows that only tobacco had a significant correlation with spasm ($p = 0.001$). The proportion of smokers was higher in men (64%) vs women (32%) ($p = 0.001$). The proportion of positive ergonovine tests was also higher in men (61%) vs. women (34%) ($p = 0.001$). A stratified analysis adjusted for sex shows that the effect of tobacco is significant ($p = 0.009$) (adjusted OR = 2.6, CI 95%: 1.3–5.0). No significant difference was seen between men and women in hypertension, diabetes or hypercholesterolemia.

3.5. Relationship between non-invasive stress tests and ergonovine test

No significant correlation was found between a positive stress test and a positive ergonovine test (Table 4). The non-invasive tests predicted the presence or absence of spasm in 85 (55.2%) cases and were non-predictive in 69 (44.8%).

Table 5
Relationship between positivity of each kind of stress test and positivity of ergonovine test

<table>
<thead>
<tr>
<th>Stress test</th>
<th>Ergonovine (−)</th>
<th>Ergonovine (+)</th>
<th>Total</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise stress test</td>
<td>Negative</td>
<td>20</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>22</td>
<td>26</td>
<td>48</td>
</tr>
<tr>
<td>Exercise thallium</td>
<td>Negative</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>12</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Exercise echocardiography</td>
<td>Negative</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Adenosine thallium</td>
<td>Negative</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>81</td>
<td>154</td>
<td></td>
</tr>
</tbody>
</table>

Among the patients with a positive test, chest pain was present with ergonovine in 30 and ST segment elevation in 15. All patients with ST elevation had pain, whereas 15 patients with pain did not have ST elevation. The quicker the administration of intracoronary nitroglycerin, the lower the probability of presenting pain or ST elevation. Eight patients had a totally occlusive spasm. Three of them had pain and only 1 had ST elevation.

ECG: electrocardiogram.
Table 5 shows the results of each non-invasive test in relation to ergonovine test. Only adenosine thallium scintigraphy did not have false negatives and exercise echocardiography showed only one false positive. However, the number of both tests was too small to rely on these results.

Among the 36 patients sent to angiography without a non-invasive test, 20 had a negative and 16 a positive ergonovine test.

4. Discussion

At the beginning of the twenty-first century cardiologists are mainly focused on prevention of atherothrombosis with better drugs, on its diagnosis with better images and on percutaneous therapy with better stents. However, new techniques are leading us to focus on anatomy and to forget physiology. Some invasive cardiologists place a stent in each coronary lesion, and give intracoronary nitroglycerin prior to angiography to eliminate any possible coronary spasm than can modify the arterial diameter [5]. However, spasm may be the cause of angina and even of myocardial infarction [9–11] and sudden death [11–14]. In fact, 3 of our patients with non-significant coronary lesions had suffered a previous myocardial infarction, probably due to coronary spasm.

4.1. Clinical suspicion of vasospastic angina

Our patients were 8 years younger than those with established coronary artery disease and the proportion of women was much higher (data not shown). Suspected ischemic pain at rest was the most frequent clinical presentation, but 40% of patients had effort pain, as those with fixed coronary stenosis. Therefore, clinical suspicion before angiography was not always possible. Few of them had diabetes or impaired glucose tolerance and the most frequent combination of risk factors was tobacco plus hypercholesterolemia. Only tobacco had significant correlation with spasm. Previous reports have found smoking as the most important risk factor for spasm [15–17], while diabetes is the most important for atherosclerotic disease [17].

No patient included in this series had ST segment elevation during stress tests. Those who presented ST elevation also had spontaneous coronary spasm during coronary angiography; therefore ergonovine was not necessary.

4.2. Spasm provocation

In patients with Prinzmetal angina, spasm can be provoked by different means. The most frequently used tests are acetylcholine and ergonovine, with similar results [18]. In general ergonovine is the test of choice [19]. The present study shows that ergonovine test induces epicardial coronary spasm in more than half of the patients with suspected ischemic chest pain and normal coronary arteries or non-significant angiographic lesions.

The ergonovine test may be negative in a patient with spasm. This may be due to insufficient dose, previous treatment with vasodilating drugs or a cool phase of the disease [19]. Sometimes the spasm is only present at the microvascular level [20], without epicardial changes. Although ergonovine is not a physiologic test, to our knowledge, no false positive tests have ever been described. It is possible for a spasm not to be followed by pain, mainly if the duration is brief or the degree of stenosis mild. In fact, if intracoronary nitroglycerin is rapidly injected when the spasm is seen on angiography, the patient may not have pain, as in many of our cases. As the expertise increases, fewer ergonovine-induced spasms are followed by angina or ST elevation.

Although spasm can also be studied with ergonovine-electrocardiography in a coronary care unit [19] or with ergonovine-echocardiography [21,22], only patients with normal coronary arteries or mild to moderate lesions should be submitted to this test [19]. If the coronary angiogram is performed in our centre, we inject ergonovine into the coronary arteries immediately after angiography. Considering that intracoronary nitroglycerin is sometimes the only effective means to reverse a spasm [23], ergonovine test in a catheterization laboratory is probably safer than in any other place.

When ergonovine test is performed in an echocardiographic laboratory or a coronary unit the spasm cannot be seen, and the test is only stopped when contractility or electrocardiographic changes are present. The difference with angiography is that these spasms have to be present for a longer time to be detected.

4.3. Correlation between non-invasive and invasive tests

In our study there was no significant correlation between stress-induced ischemia and ergonovine-induced spasm: many tests were false positives and many were false negatives (Tables 4 and 5). The false positives may correspond to real ischemia due to microvascular spasm [20] or disease [24]. In fact, a number of patients had thoracic pain during ergonovine injection but the test was considered negative if spasm was not seen on angiography. Due to the small size of our ECG register and displacement of precordial leads, only outstanding ECG changes could be noticed during angiography. False negative non-invasive tests may be due to the fact that spasm is not always induced by exercise or adenosine.

4.4. Previous studies

In a previous study [25] we reported on 8 patients with coronary spasm on normal arteries. They had a negative electrocardiographic exercise stress test and a positive
thallium scintigraphy. These patients are included among the 162 of the present study. In this study some patients with a positive thallium stress test did not have ergonovine-induced spasm. Thallium defects were generally milder than in patients with spasm. Some mild positive gammagrapic tests may actually be false positives.

Although many papers on this topic have already been published, our main goal is not to provide another paper on Prinzmetal angina, but to encourage cardiologists to reach a proper diagnosis for patients with suspected ischemic pain and normal coronary arteries. Compared with a previous paper by Bertrand et al. [26], we found a much higher proportion of ergonovine-induced spasm in patients with effort angina. The proportion of ventricular fibrillation in patients with spasm is similar: 2.98% in Bertrand’s series vs 3.70% in ours.

4.5. Clinical implications

In many patients with suspected ischemic pain and normal coronary arteries ergonovine test may induce coronary spasm. When vasospastic angina is clinically suspected, angiography is advisable to reach an accurate diagnosis in spite of negative results of previous non-invasive tests. Diagnosis of coronary spasm is important because spasm is a well-known cause of myocardial infarction [9–11] and sudden death [11–14]. These complications can be prevented with proper treatment. In all cases nitroglycerin must be avoided before angiography.

4.6. Limitations of the study

1. Selection bias. As our study is retrospective, it reflects real life instead of a group of selected patients with a lot of exclusion criteria. Patients with suspected coronary disease and a negative stress test are told they probably have normal arteries or non-severe coronary lesions, which generally implies good prognosis. For this reason some of them refuse angiography. If every patient had been sent to angiography, more ergonovine tests could have been positive. On the other hand, our group is highly conscious of the probability of coronary spasm when a patient has repetitive crisis of oppressive pain at rest, mainly at night. Many of these patients are submitted to angiography with the suspicion of coronary spasm. Probably the principal reason for the high frequency of spasm in our patients is clinical suspicion by the cardiologist. This leads to ask for coronary angiography without previous intracoronary nitroglycerin and ergonovine test whenever the coronary arteries do not have significant lesions.

2. Non-invasive tests were not performed to every patient and some of them were submitted to two different tests. It would be better for the study to have a single test for each patient.

3. Ergonovine test. The right coronary artery had spasm more frequently than the others (Table 3). This can be biased because the test usually begun in the right coronary artery and sometimes another injection was not performed in the left artery after induction of a very symptomatic spasm in the right.

In conclusion, in the absence of ST segment elevation during angina, coronary spasm can only be diagnosed if suspected and provoked. In a South European country spasm is frequent (52%) in middle aged men and women with suspected ischemic chest pain (even of exercise), risk factors and angiographically normal coronary arteries. Therefore, we think that ergonovine or any other test to induce coronary spasm is advisable. An important precaution is to avoid nitroglycerin administration prior to coronary angiography, because in this case the test would become negative.

References


