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Review

Is there a role for provocation testing to diagnose coronary artery spasm?

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Abstract

Spontaneous coronary artery spasm is an important cause of morbidity both in patients with coronary artery disease and in those with variant angina. A number of pharmacological agents have been identified which can provoke coronary artery spasm in susceptible patients. The role of provocation testing in the clinical diagnosis of coronary spasm is controversial. This is reflected by variations in the clinical use of provocation testing between specialist cardiac centres. Provocation testing appears to be a sensitive method of identifying patients with variant angina and active disease but such patients can often be diagnosed clinically. The specificity is less clear. There is little evidence that altering patient therapy on the basis of a positive test modifies prognosis. There may be a role for provocation testing in rare patients with refractory disease to identify a target site for coronary stenting. A more widespread use of these tests in patients with undiagnosed chest pain syndromes would not currently be recommended.

Keywords: Coronary spasm; Diagnosis; Provocation testing; Coronary stenting

1. Introduction

Coronary artery spasm can be defined as the reversible focal constriction of a segment or segments of coronary artery such as to cause restriction of coronary blood flow and myocardial ischaemia. The discontinuous nature of the spastic response distinguishes coronary vasospasm from more generalised vasoconstriction [1]. Spasm may occur spontaneously or be induced, either physically by catheter trauma [2], by physiological manoeuvres such as hyperventilation [3–6], or by the administration of a number of pharmacological agents [7–18]. Both the large epicardial coronary arteries and smaller intramyocardial branches may be affected [19]. Following the demonstration of reversible coronary spasm at angiography [20], research focussed on the development of a safe, sensitive and specific test to identify patients prone to episodes of symptomatic coronary spasm. Once identified, the aim was to effectively treat such patients in order to improve symptoms and, if possible, prognosis. Clinical interest in diagnostic testing for coronary artery spasm has varied since its introduction in the 1970s. In European and North American practice the focus on the identification and management of fixed coronary stenotic disease has led to a decline in the use of existing and evolving tests for coronary spasm. In Asian practice, where the incidence of symptomatic vasospasm seems more common [21], there remains considerable interest in invasive and non-invasive provocation testing. This review examines the role of provocation testing in the diagnosis and management of coronary artery spasm.

2. Background

Coronary artery spasm is a heterogeneous condition. In some patients spasm occurs in association with atheromatous vascular disease. This may manifest as a spastic segment superimposed on a fixed coronary stenosis visible on epicardial coronary angiography. Spasm may occur at sites of intimal plaque which do not impinge on luminal diameter (due to negative remodelling) but which can be

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identified with intravascular ultrasound [22,23]. Coronary artery spasm can also occur in normal or near-normal coronary arteries[24,25] and in arterial segments without demonstrable intimal atheromatous disease[26]. This is usually referred to as (Prinzmetal's) variant angina [27] (although strictly speaking Prinzmetal's original publication referred to 'increased tonus at the site of atherosclerotic plaque'). Coronary artery spasm may therefore account for a proportion of patients with chest pain syndromes and normal epicardial coronary arteries, including those with documented ischaemia on stress testing (syndrome X) [28]. The common factor in these patients is thought to be endothelial dysfunction. The endothelium is a paracrine regulator of vascular smooth muscle tone. Endothelial cells respond to changes in shear stress, myogenic constriction and vasoactive factors such as acetylcholine, by releasing nitric oxide, prostoglandins and other vasorelaxant substances such as EDHF (endothelial derived hyperpolarising factor) [29–34]. Deficiencies of nitric oxide mediated endothelial function have been reported in the coronary arteries of patients with coronary vasospasm in some [35] but not all [36] studies. Endothelial production of the potent vasoconstrictor endothelin may also be abnormal in these patients [37]. These local changes in endothelial function are triggered either by the development of intimal atheromatous plaque or by other unidentified factors. This then leads to supersensitivity of focal coronary segments to a range of spasm provoking stimuli [38]. The predisposing factors which lead to endothelial dysfunction and render patients susceptible to coronary vasospasm are the subject of ongoing investigation [39,40].

3. Incidence

The incidence of symptomatic coronary artery spasm is difficult to calculate precisely as it depends on the population of patients studied, the diagnostic test used and the criteria used to define spasm. There may also be racial variations in incidence [21]. In a large French cohort study [41], 1089 patients underwent provocation testing with 0.4 mg intravenous bolus methylergonovine maleate during routine coronary angiography. One hundred thirty-four (12.3%) of these patients developed coronary spasm (defined as: 1—total occlusion of a coronary artery segment either normal or at the site of atherosclerotic narrowing; 2—the appearance of significant narrowing (<75%) of a segment of coronary artery that was initially or subsequently considered to be normal; 3—the disappearance either spontaneous or induced by pharmacologic agents of the narrowing or occlusion). Subgroup analysis indicated provoked spasm was most common in patients with rest angina (38%) and recent myocardial infarction (20%). It was rarer in patients with atypical chest pain (1.2%) and exertional symptoms only (4.3%). Fifty-nine percent of spastic episodes occurred on pre-existing fixed stenoses.

In a North American cohort of 3447 patients with angiographically insignificant (<50%) or no coronary disease, excluding those with clinical Prinzmetal's variant angina, only 4% had positive ergonovine testing (defined as ≥75% focal stenosis) [42]. Ergonovine was administered to these patients intravenously in three sequential doses of 0.05, 0.1 and 0.15 mg. This is a lower dose than that used by Bertrand et al. [41]. Independent predictors of a positive test in this study were the extent of visible coronary artery disease at angiography and smoking.

A smaller Japanese study of 685 patients [43] demonstrated positive provocation testing with intracoronary acetylcholine in a much larger proportion of patients. Incremental doses of 20, 50 and 80 μg were administered to the right coronary artery with 20, 50 and 100 μg in the left coronary artery. A total of 221 patients (32.3%) developed coronary spasm (defined as total or near total coronary occlusion focally). Of the 252 patients with no ischaemic heart disease 23, (9.1%) developed spasm in response to intracoronary acetylcholine. Possible explanations for the higher incidence of a positive provocation test in this study include the patient's racial origin and the use of intracoronary acetylcholine as the spasm provoking agent.

The variability in the incidence of positive provocation testing in these three large studies demonstrates the differences between patient populations and with different provocation stimuli.

4. Methods of provoking and identifying coronary spasm

Coronary spasm may be induced in susceptible patients by a number of physiological manoeuvres and pharmacological agents. This reflects the lack of specificity of the hyper-reactivity found in the coronary arteries of these patients [38]. Several of these methods for coronary spasm provocation have been investigated as potential diagnostic tests in this context. Exercise testing [44], hyperventilation testing [5,6,45,46] and a combination of both [3,4] have been assessed. These tests have the advantage of being non-invasive and as such would be most useful for excluding patients from more invasive testing. The specificity of the combined test (when compared with a gold standard provocation test of intracoronary acetylcholine followed if negative by intracoronary ergonovine) has been reported as 100%. However the sensitivity of ECG changes during the test (in patients with organic stenoses greater than 75% but less than 90%) was 85% [4]. This reduced further in patients with less coronary disease [3]. This relatively high false negative rate would preclude using this test as a screen to exclude patients from more invasive testing. The high specificity is less clinically useful as patients with positive tests would probably need angiography anyway to exclude clinically important fixed stenoses. Other physiological manoeuvres which have been shown to provoke vasospasm are probably even less sensitive [38].