**Testing for coronary artery spasm non-invasively – Potentially “ideal”, but safe?**

Editorial article

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Current strategies for the assessment of obstructive coronary artery disease (CAD) are based on anatomical (i.e. angiography) and functional tests able to elicit myocardial ischemia by increasing myocardial oxygen demand (i.e. exercise stress or dobutamine testing) or diverting blood away from areas affected by severely stenosed arteries onto unaffected myocardial regions (i.e. adenosine or dipyridamole infusion). These conventional tests for CAD-induced myocardial ischaemia, however, are not useful for the diagnosis of epicardial or microvascular coronary artery spasm, which require the use of provocative tests such as the intracoronary injection of acetylcholine (ACh) or intravenous or intracoronary ergonovine. Tests for coronary artery spasm are commonly carried out in Asian countries but rarely performed by European or USA cardiologists (1) perhaps due to an erroneous belief that epicardial and/or coronary microvascular spasm, is less prevalent in the Western world. Evidence gathered over the past 20 years, however, has shown that coronary vasospasm is also highly prevalent in the West. Indeed, in a recent study involving over 300 White stable angina patients undergoing diagnostic angiography, nearly 50% had angiographically normal or near normal coronary arteriograms and two-thirds had ACh-induced epicardial or microvascular coronary spasm. (2)

**Diagnosis of coronary artery spasm**

The objective diagnosis of coronary artery spasm is important, as effective treatments exist that can eliminate symptoms, prevent recurrent episodes and reduce the risk of acute myocardial infarction, life-threatening arrhythmias and sudden cardiac death. Due to its unpredictable occurrence and often short duration, coronary spasm is difficult to diagnose without resorting to provocative testing. Intracoronary ACh infusion and intravenous or intracoronary ergonovine are the most sensitive and specific tests available at present. (1,3) ACh and ergonovine can trigger spasm in susceptible patients acting via muscarinic receptors and serotonergic receptors, respectively. Provocation tests are rarely performed in the clinical setting in the United States and Europe but are carried out frequently in Asian countries.(1) In addition to the erroneous perception in the West that coronary spasm is a less frequent condition in Whites than in Asian individuals, other reasons exist for the reduced utilization of tests in Europe and the US, including a lack of understanding of the important pathogenic role of vasospasm in angina, little if any availability of ergonovine or ACh in the catheter laboratory, concerns about prolonging the diagnostic procedure excessively and fear of complications.

**Safety of provocative testing**

Concerns regarding the safety of provocative testing is a major clinical issue. Following a report by Buxton et al. in 1980 (4) of three deaths during intravenous ergonovine testing, Asian researchers and clinicians proposed the use of selective intracoronary ergonovine or ACh testing, as a safer alternative. (1) Recent review articles by Sueda et al. (1), and Ciliberti et al (5) showed that provocative tests are safe when carried out in the appropriate setting and performed by trained teams. Rate of major complications (i.e. death, urgent revascularization, life-threatening arrhythmias) with intravenous ergonovine testing is in the region of 0.31% (26 cases in 8,419 tested) while intracoronary ergonovine and ACh testing rates are 0.51% (11 instances out of 2,173 tests) and 0.95% (148 cases among 15,527 patients tested), respectively. (1) Selective intracoronary testing had an incidence of major complications of 0.89%, including one death (0.006%) and two acute myocardial infarctions (0.01%), according to Sueda and Kohno (1). Major complications occur in 0.62% of patients, with death, urgent revascularization, and acute myocardial infarction seen in 0.01%, 0.003% and 0.02% of patients, respectively. Of interest, complications of intravenous or intracoronary ergonovine are similar in in Western and Asian studies, but major complication rates during ACh testing are significantly higher in Asian compared with Western reports (1.03% vs. 0.25%, *p* < 0.01). (1) Ong et al (6)reported an overall incidence of epicardial spasm of 33.4%, and microvascular spasm of 24.2%, in 921 consecutive European patients with unobstructed coronary arteries undergoing intracoronary ACh administration during diagnostic angiography. Nine patients (1%) experienced only minor complications. Similarly, in a systematic review to evaluate safety of intracoronary testing with ACh or ergonovine in 9,444 patients, the prevalence of provoked spasm varied from 2.3% to 54.7%. Overall, the occurrence of major (0.8%) and minor (4.7%) complications for intracoronary testing was low and no deaths were reported. (5) Compared to ergonovine, ACh showed a significantly higher rate of major (1.09% vs 0.15%; p < 0.001) and minor complications (5.87% vs 2.36%; p < 0.001). (5)

**Moving from invasive to non-invasive testing?**

The current gold standard method for spasm testing involves the administration of intracoronary ACh or ergonovine by experienced teams during invasive coronary angiography with the monitoring of patient symptoms, ECG and angiographic documentation of coronary artery spasm.(3)  In this issue of the Journal, however, Song et al (7) suggest that testing for coronary artery spasm non-invasively with “ergonovine echocardiography” is safe, even without angiographic documentation of the patient’s coronary anatomy, and that “ergonovine echocardiography” can replace invasive spasm provocation testing. This contrasts with recommendations by Japanese authors that intravenous ergonovine should not be employed as a spasm provocation test (1) and recommendations by COVADIS (3) and several authors and itnernational guidelines that tests should be carried out in the catheter laboratory.

Song et al’s data however, suggest that non-invasive testing for coronary artery spasm is as safe as invasive testing in the cath lab. (7). They assessed 14,012 patients (mean age, 52.8 years; 6,213 women [44.3%]) who underwent intravenous ergonovine echocardiography testing in three hospitals in South Korea. “Significant” coronary stenosis was ruled out by functional or anatomic tests. There were no deaths or myocardial infarctions during the test. The 10-year overall death and cardiovascular mortality-free survival rates were lower in patients with positive tests and a positive test was also predictive of major cardiovascular events over time. These results are intriguing, raising the possibility that provocative tests for spasm could be carried out safely in the non-invasive setting, without the need for cardiac catheterization. This is certainly an attractive proposition but there are several issues that need to be considered when interpreting the results of the Song study:

1. The study is retrospective in nature and the provocative test protocol may have differed in the three participating centres. Moreover, no data are provided as to the inter- and intra-operator variability regarding the interpretation of echocardiographic changes and the echocardiographic results were not analysed blindly or by a central core laboratory. Importantly, a positive test result was more commonly found in patients with a clinical diagnosis of coronary artery spasm raising the possibility of bias.
2. The importance of reproducing the patient’s usual symptoms of angina was not studied specifically in the trial, nor was the correlation or lack of correlation between echocardiographic and electrocardiographic changes.
3. The prevalence of coronary spasm was lower in the Song study compared with other invasive studies carried out in White and Asian patients. This apparently lower sensitivity of the echocardiography ergonovine test needs to be explored further in prospective, head to head, studies to establish the true yield of non-invasive echocardiographic coronary spasm testing and to allow clinicians to make sound decisions regarding which patients to refer for testing.
4. Although the study showed an encouragingly low incidence of major side effects, more prospective, multicentre, multinational data are required to further validate Song et al’s findings regarding safety.

Song et al. (7) make an important point, namely that non-invasive ergonovine testing using the echocardiogram to identify ischemia caused by coronary artery spasm, is safe and this testing strategy may help assessing larger numbers of patients in clinical practice, as well as increasing the feasibility of re-testing patients if necessary (i.e. to assess the efficacy of treatment in high risk patients). These are extremely important issues that deserve to be assessed in prospective clinical studies, involving large numbers of centres, worldwide.

Non-invasive spasm provocation testing, albeit promising, warrants further safety, sensitivity and specificity and clinical outcomes data, to determine its true role in the routine diagnosis and management of vasospasm. Only solid evidence confirming the safety, sensitivity and specificity of provocative testing in the non-invasive laboratory will encourage clinicians and patients alike, to embrace non-invasive testing for spasm.

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