Safety of provocative tests of coronary artery spasm and prediction of long-term outcome: need for an innovative clinical research strategy

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This editorial refers to ‘Clinical implications of provocative tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: Multicentre Registry Study of the Japanese Coronary Spasm Association†, by Y. Takagi et al., on page 258

Takagi et al.,† have reported the findings of a nationwide multicentre Japanese registry on the arrhythmic risk of provocative tests of coronary artery spasm (CAS) in all comers with angiographically documented vasospastic angina (VSA). They recruited a total of 1246 patients who, after the test, were followed for a median period of 32 months in order to quantify major acute cardiac events (MACEs). Although largely retrospective and with an incomplete clinical characterization of patients (no information on onset, duration, and severity of symptoms in patients with focal, diffuse, or microvascular constriction), this study has two major practical clinical implications and suggests that continuing to consider only the most common features of the ‘average’ patient with VSA is unlikely to produce relevant additional novel information; thus the time has come to implement novel clinical research strategies.

This report proves the following conclusively, in agreement with previous smaller, single-centre studies: (i) In an unselected spectrum of patients with VSA, the global acute arrhythmogenic risk of provocative tests for CAS was quite low, comparable with that observed during spontaneous anginal episodes [with or without pain or electrocardiogram (ECG) changes]; moreover, the risk of life-threatening events was quite small and unpredictable, on the basis of the descriptors tested. (ii) In the broad range of patients studied, the risk of MACEs during a median follow-up of nearly 3 years was also quite low, and the predictive value of available descriptors for MACEs appears poor.

Therefore, innovative clinical research strategies must be developed in order to identify: (i) new, more specific, and more accurate combined predictors of life-threatening events, in carefully characterized subgroups of patients, rather than in all comers; and (ii) the various underlying causal mechanisms of spasm and their specific diagnostic and therapeutic targets.

Acute arrhythmogenic risk

The examination of the composition of the 6.8% total arrhythmic events, included in the global risk calculation, reveals that they were widely heterogeneous and that at least 50% of these were not life threatening. Indeed they were represented by premature ventricular contractions (PVCs; 1%), by bradycardia/sinus pause (2.3%), by atrioventricular block (0.6%), and by the sum of ventricular tachycardia (VT)/ventricular fibrillation (VF) (3.2%, but without a distinction between VF and VT or between sustained and non-sustained VT).

An arrhythmic response was statistically more common among patients with diffuse right coronary and multivessel spasm, lower prevalence of organic stenoses, and female sex. However, these differences, though statistically significant, were of negligible importance for everyday clinical practice. Conversely, the incidence of both VT/VF and bradarrhythmias was about three-fold greater following acetylcholine than ergonovine, indicative of a direct major arrhythmogenic effect of this drug, possibly unrelated to the severity and extension of ischaemia.

This important arrhythmogenic difference between the two tests suggests the need for a conclusive study of their relative sensitivity and specificity for the diagnosis of spasm in order to compare their respective advantages and disadvantages, but unfortunately the registry included only cases with angiographically demonstrated spasm, without information on the clinical indications for the test.

Thus, lumping together a broad spectrum of VSA patients in order to obtain a statistically significant prediction of ‘global’ risk...
It appears remarkable that not even the history of out-of-hospital cardiac arrest (OHCA) was, by itself, a predictor of an arrhythmic response (at variance with its predictive value for MACEs previously reported). The lack of predictive arrhythmic response of OHCA strongly suggests that the triggers of life-threatening arrhythmias are multiple and combined with responses which may vary at different times. The identification of the sequence of potential adverse responses and their combinations could shed light on the various mechanisms of ischaemia-induced arrhythmias, and suggest specific, personalized treatments.

This research target should be based on careful observation of the distinctive features that consistently characterize those patients who do develop a given type of life-threatening arrhythmia, focusing on phenotypically homogeneous subgroups with an inquisitive mind and a 'detective' attitude, rather than on statistically significant differences in the average behaviour of all comers.

**Long-term outcome**

In a broad spectrum of Japanese patients with angiographically diagnosed VSA, on standard treatment, the outcome, over a median period of 32 months, was fairly good.

Indeed of the 66 patients (5.5%) who had a MACE, 55 had admissions for ‘unstable angina’, 7 for infarction, 4 had cardiac death, and 2, out of 14 who received an implantable cardioverter defibrillator (ICD), an appropriate discharge. Death from all causes occurred in 16 (1.3%). A statistical but weak correlation was found between overall MACEs (which included very heterogeneous events), multivessel spasm, and organic stenosis; no correlation was found with arrhythmic response to provocative tests (which included very heterogeneous events).

Considering the very low incidence of irreversible life events in all-comer Japanese patients with VSA, a prediction of major life events, useful in clinical practice, appears unlikely to be achievable without the identification of novel distinctive features which specifically characterize those patients who suffer major life events. Only a combination of clinical, angiographic, and biological distinctive events of very different clinical relevance) fails to provide useful indications for clinical practice.

Figure 1 VSA is a broad syndrome with multiple causes and outcomes, like anaemia. In severe anaemia a blood transfusion is effective in all cases, just like dilators for spasm, but prevention requires the identification of the specific underlying causes. Occlusive spasm may result from even mild constrictor stimuli (in the presence of an enhanced postreceptoral constrictor response to a variety of stimuli acting on different receptors, possibly mediated by Rho-kinase), or from very powerful stimuli, not blocked or prevented by usual doses of dilators. The search for a single common cause of spasm and a single prevailing pattern of response has provided useful average information, but now we should try to discover new specific diagnostic and therapeutic targets. This goal should be pursued by focusing the attention on phenotypically homogeneous subgroups of patients characterized by the same distinctive features in their presentation, course, response to tests and treatments and biological profile. These patients with their most striking findings that deviate most from the common patterns (outliers) are the most likely to provide clues of the mechanisms that make them different and thus may suggest novel working hypotheses and potential diagnostic and therapeutic targets (like it happened for anaemia).
features can open the way to the identification of carefully characterized and phenotypically homogeneous subgroups of patients which are most likely to have the same pathogenetic components, and benefit from the same treatment.3,4

**The multiple, complex mechanisms of spasm**

The syndrome of VSA may present with different angiographic characteristics of CAS: focal, diffuse, mixed, and multifocal, with an apparent prevalence of the focal pattern among Caucasians and of the diffuse patterns among Japanese, with an atherosclerotic component, greater on average among Caucasians. These different angiographic presentations may be associated with a different clinical course, prognosis, response to tests, and treatments, with a different prevalence of causal mechanisms.3,4

Among Caucasian patients with typical, clinically documented VSA, spasm is commonly focal and occurs at the site of an atherosclerotic stenosis of variable severity, and in these patients prognosis is more severe than in those with angiographically normal coronaries. In these patients, spasm can be induced by a variety of constrictor substances acting on different surface receptors on the coronary smooth muscle (acetylcholine, ergonovine, hystamine, serotonin, and pitressin) and by non-pharmacological stress (exercise, hard grip cold test, and hyperventilation). Thus it appears that in these patients an enhanced post-receptor smooth muscle constrictor response is a major, common underlying causal mechanisms of spasm, quite variable in time, with hot phases during which stimuli of minimal intensity are sufficient to trigger spasm, alternating with cold phases during which spasm cannot be elicited by the usual triggers. The variability of this enhanced constrictor response combined with the intensity and duration of constrictor stimuli determines the severity and duration of the coronary artery constriction and thus contributes to the possible development of arrhythmias and of infarct.

Shimokawa’s group demonstrated in an animal model that local contraction hyperactivity can be related to a Rho kinase-dependent mechanism, blocked by fasudil. Preliminary studies suggest that this drug can also prevent spasm in some patients. Thus it could be a useful tool for the identification of responders and non-responders, and open up a new avenue for a systematic study of the mechanism responsible for focal coronary smooth muscle or diffuse or microvascular contractile response.4

At the other, opposite extreme, strong constrictor stimuli, such as high doses of acetylcholine (but not of ergonovine), neuropeptide Y, or endothelin, can induce severe coronary constriction and ischaemia in patients with mild chronic stable effort angina, without any evidence of variant angina or of a focal smooth muscle hypersensitivity.3,4

Wall vessel damage at the site of occlusive spasm may cause a mural thrombosis which becomes a powerful positive feedback mechanism for persistent coronary occlusion. The key features of this complex scenario3,4 are illustrated schematically in Figure 1.

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**References**