Although coronary artery spasm (CAS) has been linked with acute coronary syndromes (ACS) and vulnerable plaque (1), thrombosis (2), percutaneous coronary intervention (PCI), and stenting (3–7), very limited attention is given to CAS in the current era. This may be related to assumptions that the frequency of CAS is decreasing and if present it will be eliminated with calcium antagonist (8) or nitrate use. However, concerns about adverse outcomes in hypertensive and angina patients over the past decade have diminished calcium antagonist use, particularly in ACS. Long-acting nitrates, once a standard discharge order, are not recommended discharge medications in recent ACS guidelines (9–11). Important to the perception that CAS is decreasing is the lack of testing to detect spasm as a possible mechanism for ACS when other causes are not apparent. Except for Prinzmetal angina and cocaine use, CAS testing is either not mentioned (9,10) or is given only a IIb recommendation (11) among patients without obstructive coronary artery disease (CAD) in recent guidelines. Therefore, among ACS patients the frequency of CAS was unknown, and it was uncertain whether it was simply a mediator of ischemia among other factors, a marker predicting adverse outcome, or both.

This is the setting for 2 provocative reports on coronary spasm in ACS published in this issue of the Journal. Using a prospective cohort design, Wakabayashi et al. (12) tested consecutive Japanese patients for CAS 10 to 20 days after acute myocardial infarction (MI) treated by PCI. Spasm was provoked in about 70% of cases, and almost one-half of these had an event (death, ACS, or revascularization) over follow-up. Spasm was provoked in the majority of arteries examined; occurring in approximately 70% of infarct-related arteries and about one-half of noninfarct-related arteries.

Finding CAS in these latter cases indicates that spasm was not related to vascular injury associated with the PCI. Provoked spasm was an independent predictor of adverse outcome, and although exploratory, their analysis suggests that CAS may be linked with early nonobstructive vulnerable plaque as a precursor to recurrent ACS in multiple arteries rather than only the infarct-related lesion. Ong et al. (13) continued this theme of spasm testing in ACS patients without obstructive lesions. Spasm was provoked in approximately 50% of these marker-positive (electrocardiographic [ECG] and/or biochemical) Caucasian cases. Interestingly, smoking history, long recognized as a risk condition for spasm (14), was present in only about one-fourth of these cases and did not differ significantly comparing those with and without spasm. This also held true for other factors previously linked with CAS, such as female gender and hypertension.

Although these data, indicating a very high frequency of multivessel CAS in ACS patients possibly linked with adverse outcomes, are very interesting, there are some limitations. The Wakabayashi et al. (12) study conclusions would be stronger if the outcome included only death or MI. These were Japanese patients in whom smoking prevalence exceeded 60% and spasm prevalence is higher than in Caucasians (15). Although Ong et al. (13) identified spasm in one-half of the ACS cases without obstructive CAD, we do not know whether this finding also portends a high risk for adverse outcome in Caucasian patients with less smoking history versus Japanese patients. Therefore conclusions linking spasm after MI with adverse outcomes require confirmation in non-Asian patients. Also the frequency of classified spasm may vary with the provocation test (agent, route of administration) and the definition (from total to near-total occlusion with or without symptoms, and so on). Both studies used intracoronary acetylcholine and an angiographic diagnosis of spasm associated with clinical findings. Wakabayashi et al. (12) defined CAS as transient total or subtotal occlusion with ECG changes and/or typical chest symptoms. Ong et al. (13) defined CAS when quantitative analysis confirmed ≥75% narrowing (compared with the relaxed state after nitroglycerin) and symptom reproduction. These subtle differences in CAS definition would not be expected to influence the conclusions in an important manner.

**Questions on the Theme of Spasm in ACS and Some Future Areas for Development**

What is the prevalence of nonobstructive lesions in ACS where CAS could play a role in ischemia? Although past reports suggested nonobstructive CAD in about 25% of ECG and/or biomarker-positive ACS patients (16), our experience suggests that the frequency now approximates 40% to 50%. This likely relates to improved biomarker diagnosis of ACS (17) as well as increased use of atherothrombosis-preventative treatments.
What is the prevalence of CAS in these ACS patients without obstructive lesions? Although ACS patients undergo risk stratification, consideration is not routinely given to CAS among cases without obstructive lesions. Although the association between ST-segment elevation and CAS in patients with chest pain is well documented, it should be emphasized that most patients with CAS do not have ST-segment elevation when seen in the emergency department or office with chest pain (18,19). The important clinical point is that absence of ST-segment elevation during chest pain should not exclude CAS. Noninvasive tests can document ischemia and further quantify risk, but the reference standard for CAS is visualization during angiography in association with symptoms and/or signs of ischemia.

Why does the frequency of CAS seem to be decreasing? Modification of atherosclerosis risk factors, in particular cigarette smoking, which has been strongly associated with CAS (14), and statin and calcium antagonist use (8) account for some reduction. But with the increase in diabetes (20), hypertension, obesity, drug-eluting stent use (4,5,7), and methamphetamines or cocaine use (11), it would be unlikely that the incidence of spasm is truly declining. It is more likely that the decline in testing accounts for the perception that spasm has declined. If the high CAS prevalence noted above can be reproduced but the frequency of CAS may actually be increasing, it remains to be determined whether provoked CAS portends high risk for adverse outcomes in a Caucasian ACS population.

Is spasm testing of value in the management of ACS patients? This is the critical question and would require an adequately powered, randomized study assessing the outcomes impact of a routine CAS detection and management strategy in ACS compared with the prevailing strategy of very restricted attempts at CAS detection and management. The vast majority of patients with either spontaneous or provoked CAS have coronary atherosclerosis (obstructive or nonobstructive) as do those with ACS, and with over 1.5 million ACS patients (primary and secondary diagnoses) (21), the population exists to properly address this question.

Some Thoughts on the Mechanism(s) of Coronal Spasm

Focus has been on a defect that spontaneously increases coronary tone, narrowing the lumen to limit flow and result in ischemia. Although perceived as a disorder of epicardial arteries, intramyocardial vessels are also likely involved (22). While the final pathway is associated with the KATP channels in smooth muscle cells, it is likely that processes extrinsic to smooth muscle also participate (23,24). These include endothelial cells, where KATP channel opening by adenosine and alpha2-adrenergic receptor stimulation contributes to nitric oxide generation and vasodilation. Endothelial dysfunction with loss of KATP channels and attenuated nitric oxide production and/or bioavailability promotes smooth muscle hypercontractility. Another possibility includes the sympathetic neurons, where opening of presynaptic KATP channels attenuates norepinephrine release enhancing smooth muscle relaxation to dilate coronary arteries. A defect in these channels decreasing the threshold for norepinephrine release may be associated with spasm. Another possibility relates to bone marrow-derived cells recruited to the vessel wall and their products (25,26). Indeed, identification of specific mechanisms of CAS and ischemia-related adverse outcomes requires further study in experimental models and patients. Considerable species variability exists in atherosclerosis models, so mechanisms for CAS in humans and experimental models might not be the same. Nevertheless, smooth muscle and extrinsic processes are likely to be important in CAS pathogenesis, and investigations in this area could yield new therapies for these ACS patients.

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