used, the tests are expensive and operator-dependent. This, however, should not discourage the cardiologist. Simply measuring diastolic thickening should at least provide an idea of which patients need further sophisticated testing; finally and, perhaps most importantly, the study stressed the importance of the fact that the extent of viability is related to better survival — the bigger the area of hibernation, the better the survival. This point is clinically critical, as a small area of viable myocardium was related to a higher incidence of cell death. Therefore, the cardiologist should aim to reperfuse only when there is enough hibernating myocardium able to recover.

I have only one concern regarding the study and this relates to its acronym ‘VIDA’ (Viability Identification with Dipyridamole Administration). I am, as are the main authors, Italian and, in Italian, ‘vita’ means ‘life: perhaps a ‘t’ instead of a ‘d’ would have been more appropriate!

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References


Polymorphism in coronary artery vasoconstriction

See page 845 for the article to which this Editorial refers

Coronary artery disease is a major cause of death in industrialized countries. Although processes leading to plaque development and progression (lipid and monocyte infiltration, smooth muscle cell proliferation and migration, synthesis and destruction of extracellular matrix proteins, thrombosis) are key players in the pathogenesis of the disease, abnormal coronary vasoemotion may also play an important role. Occlusive coronary spasm is the mechanism of spastic angina, which may occur in arteries with or without significant stenoses; by triggering plaque rupture or reducing the arterial lumen, abnormal vasoemotion (vasoconstriction) may also be implicated in the pathogenesis of acute coronary syndromes (unstable angina and acute myocardial infarction). The in vivo reactivity of human coronary arteries to vasoactive substances has been extensively studied; this response may vary widely among individuals, raising the question that at least some of its determinants may be genetically determined. A recent paper by Pristipino et al. supports this hypothesis. In this study, the response to acetylcholine injection of coronary arteries soon after myocardial infarction was compared between Caucasian and Japanese patients. Japanese patients exhibited a three-fold greater incidence of spasm and greater vasoconstriction of non-spastic segments after acetylcholine than Caucasians. The causes of such differences are unknown, but genetic factors may well play a role.

In the present issue, Meirhaeghe et al. suggest that a polymorphism located in the G protein β3 subunit may partly determine the response of human coronary arteries to the administration of methyl-ergonovine maleate (a vasoconstrictor): subjects bearing at least one T allele had greater vasoconstriction than CC subjects. G proteins are heterotrimers composed of three subunits, alpha, beta and gamma and are implicated in signal transduction in response to vasoactive substances. A polymorphism has been
described in the G protein β3 subunit[7]; the T allele is associated with the occurrence of a splice variant, GNB3-s in which the nucleotides 498-620 of exon 9 are deleted. An association between the T allele and hypertension has been reported[7]. The T allele thus appears as an interesting candidate for genetic modulation of the response of human coronary arteries to vasoactive substances.

Although Meirhaeghe et al. needed to be congratulated for their interesting observation, several points are not elucidated in the present study. First, these results were obtained in patients who were admitted for diagnostic angiography and had normal coronary arteries. Thus, the results of the present study cannot be extrapolated to patients with coronary artery disease. Indeed, due to endothelial dysfunction or to differences in receptor function, the response of diseased arteries may differ from that of normal vessels. Further studies should be designed to examine whether the T allele is also associated with higher vasoconstriction in patients with coronary artery disease; it would also be interesting to test the hypothesis that the T allele may be a risk factor for spastic or variant angina, as already suggested, for example, for the D allele of the ACE gene polymorphism[8]. Second, subjects with the T allele had significantly higher vasoconstriction in proximal segments but not in distal segments. There is no clear explanation for this apparent discrepancy, but it may be related to differences in receptor density or coupling in distal vs proximal vessels. Third, although the use of methyl-ergonovine maleate may be justified by the fact that it is widely used in clinical practice as a diagnostic test for spastic angina, its lack of specificity for a single family of receptors makes the results more difficult to interpret. As acknowledged by the authors, the vasoconstriction induced by methyl-ergonovine may be related to alpha adrenergic and/or serotoninergic stimulation. The use of a more specific stimulus, such as previously described by Henrion et al.[9], may allow a better understanding of the mechanisms underlying the higher vasoconstrictive response of subjects with the T allele.

Such a study raises the question of the assessment of genetic susceptibilities for complex phenotypes. A recent editorial[10] considered that several conditions were necessary to prove that a genetic polymorphism was a risk factor: large population samples, family studies, several studies in independent populations, a functional mutation, large relative risks or odds ratios. But how do we fit all these conditions into a study on coronary vasomotion? Due to their complexity, such clinical tests are difficult to develop in a large population, and it is almost impossible to perform coronary angiography in several members of the same family. Thus, association studies, as proposed by Meirhaeghe et al. remain the most appropriate means by which to approach this question. But, like most epidemiological studies, which are mainly based on statistical correlations, these analyses may lead to spurious results if not run properly. This is the reason why a strict design, with strong a priori hypotheses, should be followed and cautious conclusions drawn. This study was performed in a scientific context that strongly argued for the potential involvement of the GNB3-s variant in artery vasomotion. In such association studies, candidate gene reasoning is the only possible reasoning method. Meirhaeghe et al.’s results, consistent with this hypothesis, reinforce the initial finding of Siffert et al. on the involvement of this protein in the vascular system and can be considered as a confirmation study with an intermediate phenotype.

Given the increasing complexity of cardiovascular physiopathology, which involves multiple biological pathways which interact with environmental influences throughout life, and includes numerous proteins whose genes may present subtle variations, it is less and less probable that a strong effect of a single genetic polymorphism could be discovered. As inherent in monogenic diseases, if we seek too large an effect from a single major gene, we risk losing other interesting ways of deciphering this complexity. On the other hand, boosted by the Human Genome Project, the densification of the single nucleotide polymorphism map and the dramatic development of high throughput technologies, the hunt for genetic susceptibility factors of complex diseases is increasing to a crescendo. This will involve the discovery of hundreds of genes, known or unknown, whose place in the physiopathology of cardiovascular diseases will not be obvious. Thus, within these two extremes, there is a place for well designed association studies, such as that by Meirhaeghe et al., which will establish, step by step, solid concepts and models useful to physicians in the management of cardiovascular diseases at the most accurate and efficient level.

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References
Management of syncope: head-up tilt test or electrophysiological study?

See page 857 for the article to which this Editorial refers

Syncope accounts for up to 3% of emergency room visits and 6% of hospital admissions. The Framingham study reported that approximately 3% of individuals have a syncopal episode during their lives, although lifetime incidence in the elderly may be as high as 23%. Mortality is generally low but may be up to 33% at 1 year in patients with a cardiac aetiology[1]. The differential diagnosis is wide. Diagnosis may be made difficult by the intermittent nature of the symptoms, the large number of potential aetiologies, and the lack of a gold standard for clinical investigation. The cost of investigation of recurrent unexplained syncope can be high, particularly if a relatively benign cause of syncope is overlooked in the process of excluding life-threatening disorders. Recurrences are common after the index event, occurring in up to a third of patients. The search for an underlying cause in patients with syncope often poses a clinical dilemma and even after extensive evaluation, the specific cause can remain unknown in up to 50% of patients. In selected patients the diagnostic yield may be improved with the use of specialized studies such as head-up tilt testing and electrophysiological studies.

Head up tilt table testing

Head-up tilt testing is a widely accepted tool in the investigation of syncope, particularly where there is no evidence of structural heart disease. It is a provocative test, which uses orthostatic stress to determine susceptibility to vasovagal (neurocardiogenic) syncope. Patients are tilted head-up on a table, with straps and a footplate, at an angle between 60–80 degrees for 20–45 min. Head-up tilt testing may be helpful in differentiating convulsive syncope from true seizures, evaluating recurrent falls in the elderly, and investigating near syncope or syncope in patients with autonomic neuropathy.

Electrophysiology study

Electrophysiology studies use programmed electrical stimulation and monitoring with intracardiac (and surface ECG) electrodes to assess cardiac impulse formation, conduction abnormalities and the propensity for developing tachyarrhythmias. Although relatively safe, electrophysiology is invasive and expensive, but it can be useful for evaluating sinus node function. However, most patients with sick sinus syndrome and syncope have clear evidence of sinus node dysfunction on the 12 lead ECG or ambulatory monitoring. Ativoventricular nodal and His-Purkinje conduction may also be assessed. Supraventricular and ventricular tachycardia may be induced by electrophysiological study.

Use of head-up tilt testing and electrophysiological study in the diagnostic work-up of syncope

The clinical question is always when and on whom to use these investigations. The paper by Sagristá-