Do we need diagnostic strategies enhanced with genetic information for ischemic heart disease?

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Although reliable information on left ventricular (LV) perfusion can be provided at stress with several imaging techniques, myocardial perfusion SPECT imaging (MPI) has the major advantages of being both relatively simple to perform and analyze, with very rare contraindications, and of providing a wide variety of stress and injection protocols, hence allowing this technique to be adapted to each patient and to different indications.[1,2] To these advantages, we can add its current high image quality owing to recent technical and methodological advances—i.e., semiconductor detectors, new collimation systems, and/or novel reconstruction software [1,2]—thus making MPI more reliable and relevant compared to the past. Moreover, as it can now be performed with a much lower radiation exposure, this evolution is particularly favorable for the growing number of patients referred for repeated ionizing procedures throughout the course of their life.[3]

However, in spite of these major advances, MPI and other imaging stress techniques are far from being widely recommended for the detection of stable ischemic heart disease (IHD), especially in low-risk and/or asymptomatic populations, at least in short- or medium-term analysis. According to recent reports from the American College of Cardiology Foundation,[4] referral to stress MPI is primarily deemed appropriate in symptomatic patients (i.e., those with chest pain or ischemic equivalents such as newly diagnosed heart failure, arrhythmias, or syncope) whereas it is only considered as possibly appropriate or rarely appropriate for most asymptomatic individuals, except for certain very limited high-risk subgroups. However, these recommendations lead to the selection of a limited population with a certain stage of symptoms and thus relatively advanced IHD, whereas an earlier stage of IHD development might also constitute a useful therapeutic target group from a longer-term perspective.

Several improvements in medical therapies, in diagnostic techniques, and in controlling certain risk factors have resulted in a marked decrease in IHD-related mortality in developed countries.[5] However, IHD and other forms of atherosclerotic diseases still remain the leading cause of death worldwide and have been projected to remain as such until at least the year 2030.[6] Thus, further progress is now needed (1) to decrease the number of individuals being detected too late, as well as to detect those individuals who do not reach their treatment goals;[7,8] and (2) focused on tailored prevention strategies and early risk prediction with the help of dedicated risk algorithms and diagnostic techniques.

In asymptomatic or poorly symptomatic patients, current diagnostic and preventive strategies are based on potentially modifiable risk factors[5] such as hypertension, diabetes, chronic kidney disease, inflammatory diseases, obesity, 'abnormal' blood lipid levels (total cholesterol; LDL and HDL cholesterol; Lp(a), and ApoB/ApoA1)

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and certain lifestyle parameters (smoking, physical activity, socioeconomic and psychological factors). Other conventional risk factors are extracted from demographic data (age, gender) and, finally, also involve family history, one of the strongest risk factors for IHD although the latter does not reflect the totality of the overall high heritability of cardiovascular diseases.[8] This heritability has indeed been estimated to correspond to range from 40% to 60% with a large proportion being independent of conventional risk factors.[9]

Much progress has been observed in recent years regarding enhancement of our knowledge of this heritability and more precisely, on the genetics of IHD and of other atherosclerotic diseases.[8] It is even expected that in the future, a further improvement in this genetic knowledge will help predict one's individual response to a particular drug treatment (pharmacogenomics), as well as help develop novel preventive therapies and novel stratifications of the risk of IHD and other atherosclerotic diseases.

However, IHD is a multifactorial disease (pure monogenic diseases leading to IHD, such as certain familial hypercholesterolemia, are very rare), and quantifying its heritability (definitely important) is highly complex, depending on interactions between a multitude of environmental factors and a large number of common genetic variants [9] including insertion/deletion of nucleotides, variable number of copies of a particular DNA sequence (i.e., copy number variations—CNVs), and variations in single base pairs (i.e., single nucleotide polymorphisms—SNPs).

Candidate gene and genomewide association studies (GWAS) have shown SNPs to be associated with the increasing risk of IHD, although this increase is generally estimated to be weak for a SNP considered individually.[9] It is important to note, however, that common SNPs, located on chromosome 9, were shown to lead to an increased risk level of IHD comparable to levels documented for conventional cardiovascular risk factors in population-based analyses (see the population-attributable risks (PARs) in Figure 1).[9]

In the present issue of the Journal of Nuclear Cardiology, the association between gene polymorphisms and myocardial perfusion, investigated through SPECT-derived parameters, has been addressed by Angelidis et al.[10] The assessed polymorphisms were those of genes coding for the renin–angiotensin–aldosterone system (RAAS). The RAAS system is indeed known to have a significant impact on IHD development, as well as on several risk factors (hypertension, diabetes, and dyslipidemia). Several polymorphisms were found to be associated with an abnormal myocardial perfusion and/or with indirect signs of severity (transient ischemic dilation, low heart-to-lung ratio), while the strongest association was found for the deletion allele of the gene coding for angiotensin-converting enzyme (*ACE*), especially in its homozygote form (D/D). Furthermore, these original data were found to be at least partly independent of conventional risk factors and still remained significant in the subgroup of asymptomatic patients. In this subgroup, abnormal SPECT was documented in 73.5% of the subjects who were homozygous for the deletion allele and in 63.1% of those who had the heterozygote form, compared with only 42% of those who did not have the deletion allele ($P = 0.005$).

Although these results should be confirmed on other study populations, they nevertheless strengthen the hypothesis that, in the not so distant future, genetics may constitute a useful stratification tool to help predict the risk of developing an IHD at the individual level.

This is still not the case till now, however, given the lack of sufficient accuracy in the assessment of genetic-related risks at the individual level. One of the challenges is that the genetic variants discovered to date allow explaining only 10% of the heritability for IHD.[9]

One of the main drawbacks of the results of genetic association studies in general is that the identified factors explain a much lower percentage of the phenotype/trait variability than that initially expected. Such observation occurs in all complex human diseases and related traits and has been described under the term ''*missing heritability*.''[11]

A variety of explanations for this ''missing heritability'' have been suggested in the literature, and new approaches have been proposed to predict the genetic risk:

1. *Gene–gene and gene–environment interactions* might explain a significant proportion of ''missing heritability.''[11] It is likely that a better risk assessment would be provided by a better understanding of how the genetic variants interact with each other as well as with environmental factors, with a comprehensive modeling of this complex multifactorial system.[9,11,12]
2. ''*Missing causality*.'' Although recent GWAS assays offer high SNP densities and sometimes even encompass structural variations (e.g., copy number variations), they do not include the total variation of the genome, and they have not been successfully used to determine molecular causality.[13] This causality may be better identified by

    - *Next-generation sequencing* methods that are very promising and are expected to (i) enable the detection of rare variants (both SNPs and structural variants) that may have functional properties,[14] (ii) enhance the analyses of the regulation of gene expression (transcriptomics); and (iii) better assess

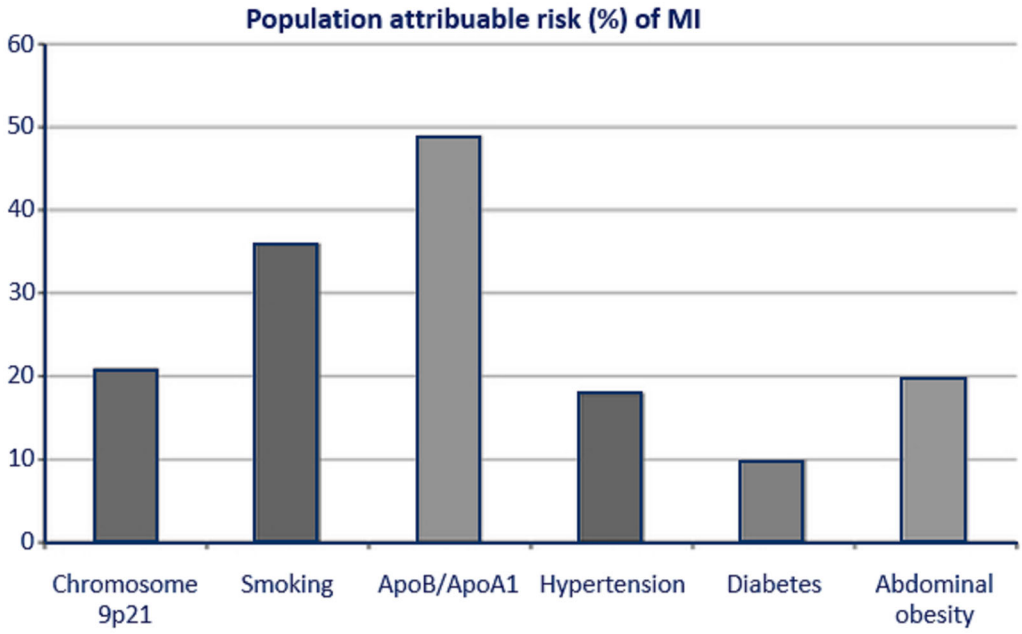

Figure 1. Population-attributable risk (PAR) of myocardial infarction conferred by common single nucleotide polymorphisms on chromosome 9p21, compared to those conferred by conventional risk factors[8].

the significance of markers located in untranslated regions and noncoding RNAs, such as microRNAs.[11]

- *Proteomics analyses* that provide essential insight into protein expression profiles and posttranslation modifications (which represent a key biological regulator of protein function).[15]
- *Epigenetics analyses* corresponding to the mechanisms that enable cells to respond quickly to environmental factors. Epigenetic modifications commonly include the study of DNA methylation and of histone modification, which play key roles in transcription profiles, regulation of DNA replication, and organization of DNA structure within the cell.[16] These modifications are likely to explain a larger portion of the phenotypic variation than differences in genotype alone [17] and are strongly associated with cardiovascular risk factors (including nutrition, smoking) as well as with subclinical and clinical cardiovascular diseases.[11]
- *The aging-related impairment of our genetic material*, since aging is known to progressively affect the telomeres, which protect the extremities of our chromosomes.[18] The variable shortening of our telomeres with age is related to the rate with which the biological aging takes place in individuals and also to the risk of cardiovascular diseases, especially in older individuals.[18]

Given the above explanations, new challenges have arisen such as the extent of the medical information to be analyzed (which goes beyond our human reckoning) and how to mine the data (Big Data). Since the human mind is incapable of concurrently collecting all of the available data, integrating the information and deducing relevant decisions, *new statistical procedures and software tools* [19] are needed. The aim of such new methods is to integrate the vast amount of «-omics», clinical, and environmental data, as well as their interactions, in order to establish biological networks that will (i) improve our understanding of the pathophysiology of complex diseases, (ii) identify groups of patients with similar molecular and disease profiles, and (iii) ultimately develop and validate predictive models in order to be used for decision-making in clinical practice.

Nevertheless, it can be speculated that genetic-related risk will be assessed much more accurately in the future. In this more or less distant area of highly personalized medicine, information regarding the risk of cardiovascular diseases would be made available very early in life, much earlier than the presence of conventional risk factors and well before the detection stage of any atherosclerosis marker. This could allow planning early preventive strategies for higher-risk subjects, especially regarding lifestyle and education.[9] This also leads us to ponder over how to adapt current diagnostic strategies for those subjects showing the highest genetic-

related risks with diagnostic tests starting earlier in life, and adapted to each patient. For MPI, this may presumably require further reductions in radiation doses and further enhancements in diagnostic accuracy, with lower rates of artifactual defects together with a higher sensitivity for detecting the early stages of IHD.

It is likely that these properties are not very distant from those of the current PET imaging of cardiac flow tracers (^{82}Rb or ^{13}N-ammonia, ^{15}O-water). This PET imaging may indeed be associated with fairly low radiation doses, with effective attenuation correction processes and with a possible identification of early abnormalities of coronary flow reserve.[20] However, at present, individual monitoring through serial PET exams on large populations is neither realistic nor suitable, at least from a medico-economic standpoint. Further significant progress is hence needed for adapting PET imaging to this setting, and/or to further improve diagnostic accuracy and dosimetry for cardiac SPECT imaging.

Disclosure

The authors declare that they have no conflict of interest.

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