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Review Article

Genetics paired with CT angiography in the setting of atherosclerosis

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ABSTRACT

Coronary artery disease (CAD) continues to be the leading cause of morbidity and mortality globally. Although the etiological mechanisms for CAD have not been fully elucidated, however, most would agree that atherosclerotic plaques progressively narrow the coronary arteries are the earliest manifestations and the principal cause of CAD. The emergence of revolutionary imaging technologies such as cardiac CT angiography, noninvasive computed fractional flow reserve and intravascular ultrasound provided the possibility of detecting and monitoring phenotypes associated with subclinical atherosclerosis. Meanwhile, with the widespread use of high-throughput genotyping pipeline such as next-generation sequencing, combined with big data-driven solutions in bioinformatics, translating the emerging genetic technologies into clinical practice and, therefore, provide valuable insight into the CAD study. In this review, we briefly describe the latest noninvasive cardiac imaging techniques for atherosclerosis-related phenotypes' detection, mainly focusing on the coronary artery calcification, plaque burden and stenosis. Furthermore, we highlight the state-of-the-art genotyping techniques and its application in the field of CAD translational study. Finally, we discuss the clinical relevance of genetics paired with noninvasive imaging in the setting of coronary artery atherosclerosis.

1. Introduction

To date, coronary artery disease (CAD) has become an enormous public health problem in the United States. Approximately 1.1 million American adults have at least one major adverse cardiac event in 2014 [1,2]. Furthermore, by 2030, the prevalence of CAD in the United States is predicted to be 9.5% [2]. Atherosclerosis is a condition in which plaque forms in the arteries, and finally, impaired myocardial blood flow is the primary pathogenic mechanisms of obstructive CAD. Atherosclerosis is a typical complex disease process caused by multiple genetic and environmental factors' interactions. Over the past decade, genetics paired with cardiac imaging tools in the setting of atherosclerosis have made considerable progress. Rather than presenting an exhaustive review of atherosclerosis-related phenotypes for translational study, in this review, we focus on the latest applications of cardiac CT angiography (CTA)-based noninvasive imaging techniques in subclinical atherosclerotic plaque detection (qualitative and quantitative) and the challenge of treatment and prevention of CAD. Besides, we also highlight the state of knowledge of high-throughput genotyping, which has been given a tremendous boost in translational studies of atherosclerosis.

Twenty years ago, even an experienced physician also faced the frustrating situation when a patient has chest pain but with a "normal" Electrocardiogram (EKG) or normal cardiac enzyme readings. Indeed, at that time, few robust imaging tools are available for the morphological information of the coronary arteries, as well as the presence and severity of CAD evaluation in addition to the EKG-based tests. Today, advances in noninvasive cardiac imaging technologies, represented by coronary CTA, have provided unprecedented opportunities for plaque burden composition measurements, quantification and validation, stenosis and risk assessment and even the determinants of stent implantation with faster, more reliable and accurate ones than ever before.

As a matter of fact, early identification and effective monitoring plaque burden progression have a remarkable prognostic value in CAD patients. The coronary artery atherosclerosis phenotypes comprise qualitative and quantitative artery calcification, plaque burden and discriminate degrees of stenosis. To date, CTA can offer a high-resolution, three-dimensional (or 3D) digital imaging and visualization of the coronary arteries and other adjacent structures. Particularly worth mentioning is that the noncalcified atherosclerotic plaque burden can be recognized as an earlier manifestation of atherosclerosis than calcified plaque, previously required significant radiation dose exposure to obtain and now can be accurately assessed by CTA with very low radiation dose exposure without loss of image quality [3–5]. Relying on the innovative hardware–software architecture, today's CTA can accurately assess the vulnerable nonobstructive plaque and the native vessel lesions even in asymptomatic high-risk patients with satisfactory sensitivity and specificity at average 0.29-mSv radiation dose exposure [6,7], which is almost comparable with a chest X-ray [8]. In comparison with traditional angiography, the latest CTA can evaluate asymptomatic patients for CAD screening just taking less than 30 min and coronary artery calcium scan less than 5 min. These features make CTA increasingly

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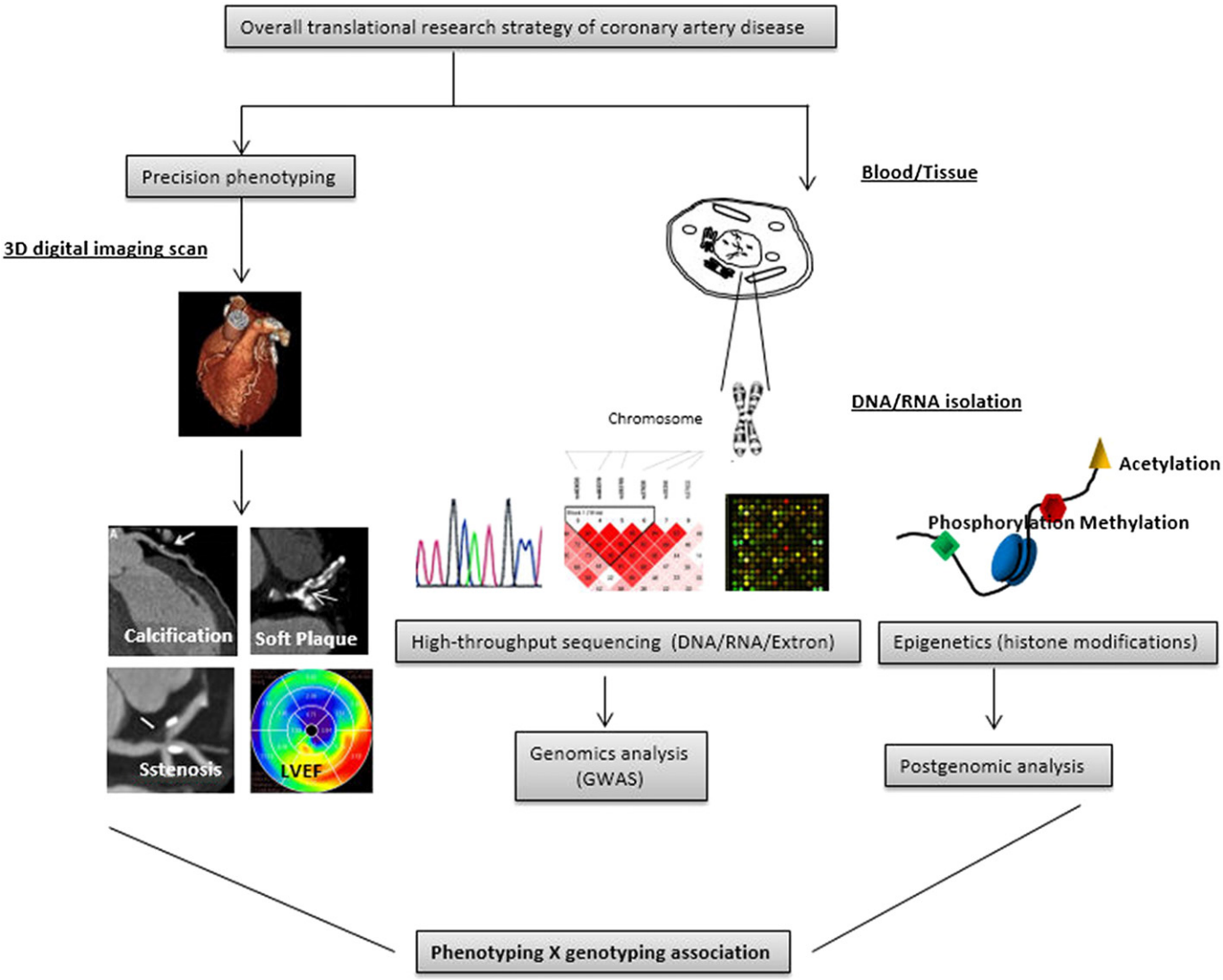

Fig. 1. Flowchart of CAD translational study.

being applied in translational studies of subclinical atherosclerosis and CAD for qualitative, quantitative and semiquantitative determination of phenotypes (Fig. 1).

Although there is a widespread use of CTA for the evaluation of atherosclerotic plaque, in vivo assessment of the progressive narrowing of the coronary arteries is a significant issue as well. In other words, whether the patient's stenosis will trigger a series of clinical syndrome due to the resistance to blood flow is a significant clinical question must be asked and answered. Today, in most of the clinical centers across the United States, the invasive cardiac catheterization in patients with chest pain and a clear history of CAD is preferentially examined after a stress test. However, this pattern remains controversial because a certain amount of patients were finally identified with no significant blockages. Therefore, in 2014, the U.S. Food and Drug Administration cleared Heart Flow fractional flow reserve (FFR) computed tomography software, a novel noninvasive technique to investigate CAD patient's coronary flow dynamics across a stenosis based on computed tomography (CT) scan data [9]. Today, the FFR management in stable CAD patients became Class I and Class IIa guideline recommendations [10,11]. Notably so far, evidence-based data for FFR_{CT} application is limited. Nevertheless, some initial studies have demonstrated that the value for FFR_{CT} in avoiding potential unnecessary angiography procedures [12] affects patient care and economic outcomes [13,14].

Beyond CTA, intravascular ultrasound (IVUS) is another promising in vivo technique for assessing plaque burden [15], lesion severity and lesion characteristics [16] and stent sizing [17]. IVUS can precisely detect arteries and luminal narrowing with an axial resolution of 150 μm, which is critical to stent implantation, as well as calcified stenosis treatment strategy selection. Although it is a well-validated modality compared to histopathology with an accuracy of 90% in detecting all types of plaque morphology [18], however, use of IVUS is limited due to its invasiveness and expense.

2. The dilemma and limitations of microsatellites or expressed sequence tags genetic markers atherosclerosis study

The interactions of genetic and environmental factors is responsible for the pathogenesis and progression of atherosclerosis. With the development and widespread application of noninvasive cardiac imaging techniques, a series of remarkable progress had been making toward unraveling the genetic basis of CAD and atherosclerosis.

Acute plaque rupture is the cause of most adverse CAD events [19]. Predicting the progress and prognosis of CAD by plaque volume and composition (fibrous, fibro-fatty, necrotic core, dense calcium) is a hotspot in the latest genetic research. Before Genome-Wide Association Study (GWAS) era, the candidate gene and linkage association are two