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Invited commentary

Simplicity is the ultimate sophistication. PR electrocardiographic intervals for smart forecasting of decline in renal function

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Leonardo da Vinci is quoted as saying that simplicity is the ultimate sophistication. The truth of this axiom becomes apparent when considering the original, elegant and, above all, intellectually and scientifically sound study published by Saori Majima et al. in the previous issue of Atherosclerosis [1]. Although using measures of the function of one of two such distant organs as the kidney and heart to predict, by correlation, the function or prognosis of the other may at first seem counterintuitive, the authors show that nevertheless it appears possible. Indeed, in their community-based cohort, after an adequate period of follow-up, they demonstrate that electrocardiography PR interval (iPR) and QRS duration (dQRS) are not only independent predictors of cardiovascular disease and events – which has long been known – but that they can also be used to predict a deterioration in renal function.

On the Electrocardiogram (ECG), the PR interval reflects atrial depolarization and atrioventricular node delay, which can be partially differentiated by P-wave duration and the PR segment, respectively. It is noteworthy that genetic associations of the PR interval seem to be mainly driven by genetic determinants of the PR segment [2]. It has recently been reported that both prolonged PR interval and prolonged QTc (but not prolonged QRS) are independently associated with nearly twice the risk of all-cause mortality, as compared with patients with renal failure without PR or QTc ECG interval prolongation [3]. This is particularly important since the cardiological reference measure used in these studies is extremely cheap, objective, reproducible and not subject to any bias stemming from operator skill, or lack thereof.

Elsewhere it has been claimed that the erratic, arbitrary, unreliable and complex information seemingly provided by lung ultrasound artifacts may be suitable for predicting prognosis in chronic kidney disease patients [4]. In my view, promotion of such questionable putative markers not only wastes time and money [5,6], but also represents a step on the slippery slope away from sound scientific procedure. It is therefore very timely that Majima et al. [1] are able to show that the prolongation of ECG PR interval and, to a lesser extent, the duration of ECG QRS, are the most powerful predictors of estimated Glomerular Filtration Rate (eGFR) decline among the variables studied in their multiple regression analysis. Indeed, they show that neither blood pressure, smoking, fasting plasma glucose, LDL cholesterol, triglycerides nor uric acid are significant predictors of eGFR decline, but, alongside gender (male) and high body mass index, the ECG PR interval and duration of ECG QRS are (Fig. 1).

Of course, this relationship is not proof of causation, but there is very compelling evidence that both phenotypic changes may have a common background of progressive functional impairment. Naturally the relative components are conjectural at this stage, but if there are common genetic factors, it may be conceivable that they and more conventional associated risk factors operate through a shared atherosclerotic pathway. Indeed, the suggestion of a concealed shared mechanism behind the commonly recognized risk factors for cardiovascular and renal diseases is implicit in these findings. Although the Authors acknowledge the lack of sodium, potassium and calcium serological assays among the limitations of their study, in my view these factors are not in any case able to significantly affect iPR in normal subjects [7].

Despite the recent major advances in genomic science and technology having opened new avenues of investigation in the pathogenesis of coronary heart disease (CHD), some of which are being translated into clinical practice [8], the complexity of outcomes and phenotypic indicators are likely to cause uncertainty

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Fig. 1. Saori Majima et al. [1] show a convincing link between the progression of renal failure, and hence of glomerular injury, and the duration of the PR interval – the component of the electrocardiogram most strongly influenced by genetic factors [2]. In a field where others' attempts to paint castles in the air are increasingly clouding the eye, this novel, fresh and simple yet sophisticated return to solid, scientific evidence-gathering helps to clarify the picture and generates much food for thought (drawing by Giuliano Cangiano).

regarding the clinical utility of novel genome-wide association study (GWAS) findings. Indeed, thus far the relative contributions of common variants of modest effect, and rare variants of greater effects, in terms of the risk of CHD or response to drugs remain unclear [8]. It is refreshing then that, despite its apparently simplicity, the use of recorded ECG intervals [1], which are mainly modulated by heart rate [2,7] and are not subject to arbitrary interpretation, appear to indicate a fruitful area of research.

Though there is concern that awareness of the role of genetics in the aetiology of chronic disease may undermine efforts to improve lifestyle, and therefore adversely affect public health, the interactions between genetics, lifestyle and environment cannot be ignored. In fact, there is evidence that recognition of the influence of genetics on chronic disease risk can prompt individuals to reassess their lifestyles, flying in the face of the belief that the public takes an 'either/or' approach to such potentially preventable diseases [9]. Hence the genetic "threat", if used appropriately as an easy-to-obtain surrogate marker, could be seen as a pivotal tool for empowering lifestyle changes and modification of dietary and exercising habits [10,11].

Therefore, unlike the "red herrings" furnished by woolly criteria or procedures, which may be prejudicial to more robust and reliable approaches [5,6], this finding by Majima et al. [1] is a welcome step in the right direction. Indeed, it is only thorough, scientifically sound investigation that will elucidate the shared basis of such pathologies, enabling us to raise awareness about the role of comorbidities in chronic disease, and foster the development of targeted and effective clinical practice.

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