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COMMENTARY

Hypertension and C-reactive protein

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The recently released World Health Statistics report revealed that one in every 3–4 adults aged ⩾25 worldwide has hypertension.[1] According to this report, hypertension is singlehandedly responsible for 13% of all global deaths, 51% of stroke deaths, and 45% of coronary heart disease deaths. Hypertension therefore remains a major public health concern that is associated with substantial healthcare costs. The majority of hypertension (with the exception of secondary hypertension) has no direct identifiable cause. The discovery of novel causal factors of hypertension, or its downstream effects, can lead to more effective therapeutic interventions, which has the potential to translate into millions of lives and money saved. Despite the frequently used but misleading terms of 'essential' and 'idiopathic' hypertension, much is known about its pathophysiology. Vascular inflammation indeed has an important role in the genesis and progression of hypertension as recently reviewed by Androulakis *et al.*[2]

C-reactive protein (CRP) is a pentraxin whose level in the circulation has been used as an indicator of the acute-phase inflammatory state for decades.[3] The introduction of high-sensitivity CRP assays capable of measuring serum concentration of the protein previously considered in the normal range quickly led to the recognition that levels of CRP in otherwise healthy individuals track closely and independently with future cardiovascular risk. For example, in a meta-analysis of more than 160 000 individuals without a history of vascular disease from 54 long-term prospective studies fully adjusted risk ratios per 1-s.d. higher log(e) CRP concentration were 1.37 (1.27–1.48) for coronary heart disease, 1.27 (1.15–1.40) for ischemic stroke and 1.55 (1.37–1.76) for vascular mortality.[4] Despite initial skepticism with regards to the association of CRP with cardiovascular disease risk due to the variability of the strength of this association between studies, it is now widely accepted that CRP, independent of other risk factors and behaviors, not only associates with risk but correctly reclassifies risk among a substantial proportion of the population when added to risk algorithms that do not include CRP. In a landmark, large prospective randomized clinical trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin or JUPITER), Ridker *et al.*[5] demonstrated that CRP levels can be used to identify a population that will derive significant benefit from an intervention (in this case statin therapy) in the absence of other indications for treatment. Furthermore, analyses from multiple trials now suggest that reduction in CRP levels associated with statin therapy is an important indicator of successful treatment independent of reduction in lipid levels.[6–8]

CRP has been shown to be associated with the development of hypertension. In the Women's Health Study, out of 20 525 women with normal blood pressure at baseline, 5365 women developed hypertension during a median follow-up of 7.8 years. Even after controlling for multiple risk factors, CRP levels at baseline were independently predictive of the development of incident hypertension.[9] Other studies have confirmed that an elevated CRP level precedes the onset of elevated blood pressure.[10,11] Although these epidemiological data are compelling, a direct cause-effect relationship between CRP and hypertension is difficult to ascertain in these studies, as by definition hypertension uses an arbitrary cutoff for elevated blood pressure. It remains plausible that CRP elevation is a reflection of vascular inflammation secondary to elevated blood pressure and is not in itself responsible for the development of future hypertension.

Serum CRP levels are influenced by multiple environmental and behavioral factors that include age, gender, blood pressure, cholesterol level, body-mass index, insulin resistance, tobacco exposure and sleep deprivation. Nevertheless, almost 50% of the inter-individual variability in circulating CRP levels has been attributed to genetic background.[12] Several single-nucleotide polymorphisms (SNPs) in the *CRP* gene have been shown to influence steady-state CRP values.[12,13] As (1) these SNPs presumably influence the CRP level of an individual throughout lifetime and (2) they are inherited in a manner that is not related to the risk factors discussed above that may influence both CRP level and cardiovascular outcomes, the association between *CRP* SNPs and cardiovascular outcomes have been proposed as a method to study whether CRP is pathogenic or merely a risk marker that tracks with other causal factors. Early studies that used this methodology, termed Mendelian randomization, showed conflicting results,[12,13] but more recent larger studies have been consistent in showing no association between CRP SNPs and cardiovascular disease.[14,15]

In this issue of the Journal, Kong *et al.*[16] study the association of *CRP* SNPs, circulating CRP levels and hypertension in a population of Han Chinese descent. The population included a random sample of 2000 subjects (909 with hypertension at study entry) recruited in 2008 when a total of eight *CRP* SNPs (rs1205, rs1800947, rs3093059, rs2211321, rs2027469, rs12031749, rs1130864 and rs2246469) were genotyped, circulating CRP levels measured in plasma samples, blood pressure measured on three occasions and hypertension status determined. Of the normotensive controls, 968 participants with complete CRP levels and genotyping were followed for 2 years during which 71 partici-

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pants developed hypertension. As expected, plasma CRP levels in the entire population associated with increasing systolic and diastolic blood pressures and with prevalent hypertension (adjusted odds ratio for hypertension per CRP quartile 1.39, 95% confidence interval 1.22–1.58, $P<0.001$). Furthermore, baseline CRP levels were associated with changes in systolic blood pressure from baseline to follow-up and with the development of hypertension in the normotensive population (adjusted odds ratio for incident hypertension per CRP quartile 1.64, 95% confidence interval 1.18–2.26, $P<0.001$). Some of the *CRP* SNPs associated with plasma CRP levels, but none of the SNPs was significantly associated with prevalent hypertension, systolic or diastolic blood pressure, change in blood pressure over the follow-up period or incident hypertension.

Despite its relatively small sample size with only 71 subjects developing hypertension over a 2-year period, this study raises a very important question of whether CRP is directly involved in vascular pathology. Similar to the Mendelian randomization studies discussed previously, an association between *CRP* SNPs and pathology is not apparent despite a clear association of CRP plasma level and pathology. This data seems to suggest that CRP elevation is a reflection of other risk factors that associate with disease (confounding) or alternatively, it is elevated in pre-clinical disease and it is therefore a marker of disease activity. It is important to point out, however, that the conclusions drawn from these genetic studies are limited by the phenotype that is examined. In the study by Kong *et al.*[16] the phenotype is development of hypertension in participants who are normotensive at the study entry. As previously pointed out, the cutoff for the diagnosis of hypertension is artificial and therefore the lack of association with the development of hypertension does not exclude the possibility that CRP is directly involved in the disease process. The phenotype in the study by Zacho *et al.*[14] was ischemic heart disease, which included fatal or nonfatal myocardial infarction, symptoms of angina pectoris, revascularization procedures and obstructive coronary disease on angiography. The study by Wensley *et al.*[15] also used a combined phenotype of fatal coronary heart disease, nonfatal myocardial infarction and obstructive coronary stenosis by angiography. These composite phenotypes constituted an attempt at increasing the statistical power of the studies to detect an association, but they also increase the possibility of obscuring a relationship between CRP and a distictive phenotype (for example: myocardial infarction or, alternatively, the development of atherosclerosis). Thus, although these data cast doubt on the previous studies showing a relationship between *CRP* SNPs and cardiovascular disease, and the use of these SNPs for risk pridiction, they do not categorically prove that CRP is not a mediator of cardiovascular disease. In fact, the involvement of CRP in the disease process could be independent of the plasma concentration of the protein as CRP is known to be locally present at the atherosclerotic lesion site.[17]

Is there any direct evidence that CRP is pathogenic? There is substantial epidemiological, *in vitro* and *in vivo* biological evidence that implicates CRP as a direct mediator of vascular disease.[18] For example, elegant mouse studies performed by independent investigators have shown that CRP impairs endothelial function,[19,20] induces hypertension,[21] exacerbates vascular remodeling after acute vascular injury,[22,23] accelerates the progression of atherosclerosis,[24] exacerbates cardiac remodeling secondary to pressure overload,[25] angiotensin II,[26] diabetic cardiomyopathy[27] and myocardial infarction.[28] Important questions remain as to the implications of these studies to human pathology and one needs to be cautious in extrapolating the findings of these mechanistic studies to human disease.[29] The hope is that future studies that critically examine the role of CRP would enhance our understanding of the pathobiology of cardiovascular disease and pave the way for development of novel therapeutic strategies with great impact on cardiovascular health. It is clear that the controversy regarding CRP as a risk factor for cardiovascular disease remains, and is unlikely to be resolved without direct human experiments using a specific intervention that targets CRP or its downstream effects.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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