Editorial

CRP and Risk of Coronary Heart Disease
Can Exercise Training Cool Down the Flames?

Jean-Pierre Després

Although epidemiological and clinical studies conducted over the last 40 years have identified variables which became well accepted “classical” coronary heart disease (CHD) risk factors (such as increased cholesterol and low-density lipoprotein (LDL) cholesterol levels, diabetes, hypertension, smoking, etc.), it was also obvious that these parameters had limited ability to discriminate for CHD events. Therefore, which additional lifestyle or biological variables could help identify, at reasonable costs in clinical practice, individuals at increased risk of CHD remains a question of considerable importance.

In this regard, we have moved in lipidology beyond the following simple sequence of events (hyperlipidemia, atherosclerosis, CHD) as it is now recognized that acute coronary syndromes are the consequence of a complex interplay between the presence of known or unknown risk factors and atherosclerosis. For instance, factors modulating the balance between fibrinolysis and thrombosis are also involved, and considerable evidence has been published over the last decade to support the notion that CHD also has an inflammatory component.

Largely driven by the pioneering work of Ridker and colleagues, results of epidemiological studies, of primary and secondary prevention studies as well as of trials conducted in patients with acute coronary syndromes, have revealed that the plasma concentration of a relatively simple marker of inflammation, C-reactive protein (CRP), could predict the risk of a first or a recurrent coronary event, beyond the contribution of classical risk factors. Whether CRP, an acute phase protein, plays a direct role in the etiology of CHD or whether it is only a marker of a dysmetabolic milieu that contributes to the patient’s inflammatory profile is under investigation, but it is clear that CRP is currently the hottest new marker of CHD risk. Therefore, the study of factors responsible for elevated CRP concentrations is an important topic both from public health and clinical perspectives. Accordingly, which therapeutic modalities may optimally reduce inflammation (and its most popular marker, CRP) is the object of considerable attention.

Among the documented correlates of an inflammatory profile, it has become evident that obesity, especially abdominal obesity, is associated with elevated CRP concentrations. This situation could be explained by the increased production of inflammatory cytokines (interleukin [IL]-6 and tumor necrosis factor [TNF]-α) by the expanded abdominal adipose depot of overweight/obese patients. For instance, the production of CRP by the liver is stimulated by IL-6, and adipose tissue becomes a major source of circulating IL-6 in abdominally obese patients. Accordingly, intervention studies have shown that weight loss can indeed reduce circulating CRP levels, the reduction being proportionate to the magnitude of weight loss.

Another identified correlate of CRP concentrations is the level of physical activity/fitness. It has been shown that individuals with low levels of cardiorespiratory fitness (who are also often sedentary) have increased CRP levels compared with fit individuals, such difference remaining significant even after adjustment for the level of adiposity crudely assessed by the body mass index (BMI). Because of the extensive and well documented effects of endurance exercise training on risk factors for CHD (body composition, plasma lipoprotein levels, glucose tolerance and insulin action, fibrinolysis and thrombosis, endothelial function, etc.), it is of course relevant to examine to what extent exercise training could affect inflammation and, if so, what are the parameters affected by exercise training that could explain its beneficial effect of CRP levels.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, two relevant articles are published. In the article by Okita et al., 199 healthy women participated in a 2-month exercise training program in which individuals lost on average ~3 kg. At baseline, the BMI and waist circumference were again found to be the best predictors of CRP levels, confirming the very significant contribution of abdominal obesity as possibly the strongest correlate of individual differences in CRP levels. Whereas many metabolic parameters related to the risk of CHD and type 2 diabetes were improved and correlated with the magnitude of weight loss, the reduction in CRP levels observed in this exercise training protocol was not related to the magnitude of weight loss. This finding could be due to the fact that these women were quite healthy and at fairly low risk of CHD at baseline. In addition, the magnitude of weight loss was clearly greater than what could be expected from the estimated energy deficit generated by the exercise program. Thus, some of these women may have been under rather severe caloric restriction, a phenomenon that, for an inflammation marker,
may have obscured this relationship. For instance, we cannot exclude the possibility that a severe energy deficit (created by diet and/or by exercise) may have transient harmful consequences on inflammation, such deleterious response being no longer observed once body weight is stabilized at a reduced level and energy balance reestablished. Finally, another possibility is that women with the largest accumulation of visceral adipose tissue at baseline had the highest initial CRP levels, and that women with the most substantial loss of visceral adipose tissue with exercise training were also those who showed the most substantial reduction in CRP concentrations. Unfortunately, only an imaging technique such as computed tomography could have precisely measured visceral adipose tissue, and additional studies will have to be conducted to explore this possibility.

The second article on CRP reported in this issue of the Journal examines another aspect of its variability which should receive more attention: genetic susceptibility to inflammation. Obisesan et al23 have examined some CRP gene variants at baseline and tested whether they could be related to the exercise training–induced changes in CRP levels. As previously reported, they found CRP levels to decrease with exercise training. Furthermore, they found that subjects homozygous for the common A/G–732/+219 haplotype exhibited the highest CRP levels at baseline. However, the CRP genotypes and haplotypes that they studied did not appear to be related to changes in CRP levels induced by exercise training.

Although these results are potentially important, the rather limited sample size of this study cannot allow us to derive firm conclusions on this question. For instance, the study sample included men and women, various ethnic groups, as well as postmenopausal women with or without hormone replacement therapy, all factors that could modulate body composition for any given BMI value, as well as the susceptibility to develop metabolic complications for any given level of abdominal fat. In this regard, several genes involved in lipoprotein metabolism have been shown to have a significant impact on the relationship between the amount of abdominal fat and plasma lipoprotein-lipid levels.24 In this regard, it would be interesting to precisely measure abdominal fat accumulation (especially the level of visceral adipose tissue) and to measure the possible interaction between the studied CRP genotypes/haplotypes and CRP levels. Furthermore, proper control for concomitant factors and subgroup analyses will require a much larger sample. Thus, the study by Obisesan et al23 should pave the way to larger intervention studies on this topic.

Nevertheless, the challenge with genetic markers of CHD risk will be to integrate this information in clinical practice. Although the proper quantification of their influence remains a challenge, clinicians who are familiar with assessment of CHD risk have known for years that it is important to pay attention to the family history of early premature manifestations of CHD when assessing a patient’s absolute level of risk. Because many genes have subtle influences on several markers, the quantification of the ultimate contribution of all these gene variants to global CHD risk represents a remarkable challenge for which we currently do not have appropriate algorithms ready for implementation in clinical practice. For the time being, the family history of premature CHD represents the best-integrated marker of genetic susceptibility available to physicians.

In summary, these two interesting studies confirm that endurance exercise training can reduce CRP levels. Part of this effect appears to be mediated by the concomitant weight loss. In this regard, the specific contribution of the reported selective loss of visceral adipose tissue25 associated with endurance exercise training will have to be examined. Because pharmacotherapy of atherogenic dyslipidemias with statins and fibrates can also reduce CRP levels,26–29 and considering the epidemic proportions reached by abdominal obesity, type 2 diabetes, and the metabolic syndrome (which are major correlates of elevated CRP concentrations), we should emphasize further the importance of targeting the sedentary lifestyle that has unfortunately been adopted by a large segment of our population. However, we have engineered for ourselves a “toxic” environment that does not promote physical activity (suburbs with no sidewalks, no opportunity for physical activity at work, cities designed to be friendly for car drivers and not for walkers, bikers, etc.). Beyond the classical medical model, it is hoped that we will reshape our living environment to favor the promotion of an active lifestyle, which by itself may reduce the burden of CHD through its favorable impact on many risk factors, among which we should now also include inflammation.

References


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