10–41%, respectively) and offer no real advantage over our model.[3–5]

Cardiac biomarkers such as troponins and brain natriuretic peptides (BNPs) have a high negative predictive value (>93%) for mortality in patients with PE.[5] However, the ability of cardiac biomarkers to identify low-risk patients is currently unclear because prognostic studies for PE using troponins or BNPs with or without echocardiography are limited by relatively small sample sizes from single hospitals, inconsistent results, and different testing methods (e.g. troponin I or T, BNP or NT-proBNP) and cut-off values to define abnormal results.[4,6] Moreover, echocardiography may not be available 24 h a day in smaller community hospitals. Thus, although our 11-variable model is more complex than a single laboratory parameter, its usefulness to identify low-risk patients with PE has been proved in almost 16 000 patients from 305 European and US hospitals.[1,2]

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Drahomir Aujesky
Service de Médecine Interne
BH10-622,
Centre Hospitalier Universitaire Vaudois
1011 Lausanne
Switzerland
Tel: +41 21 314 04 81
Fax: +41 21 314 08 71
E-mail address: drahomir.aujesky@chuv.ch

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Exercise and inflammation

Low-grade systemic inflammation is present in subjects with insulin resistance, obesity, type-2 diabetes mellitus, hypertension, hyperlipidaemia, and metabolic syndrome X.[1–3] The results of the study reported by Lakka *et al*.[4] suggest that exercise reduces the concentrations of pro-inflammatory molecule C-reactive protein. These results are in support of my earlier proposition that exercise is anti-inflammatory in nature.[5]

Studies revealed that exercise not only decreased the levels of pro-inflammatory cytokines IL-6, TNF-α, and C-reactive protein but also simultaneously enhanced the concentrations of anti-inflammatory cytokines IL-4, IL-10 and TGF-β compared when with controls. IL-4, IL-10 and TGF-β are not only anti-inflammatory in nature but also suppress the production of pro-inflammatory cytokines IL-1, IL-2, and TNF-α.[5] In experimental animals, exercise significantly reduced the magnitude of myocardial infarction and this cardioprotective action paralleled the increase in manganese superoxide dismutase (Mn-SOD) activity.[6] The administration of antisense oligodeoxyribonucleotide to Mn-SOD abolished this cardioprotective action implying that ability of exercise to enhance the activity of Mn-SOD is crucial to this protective action. Obviously, this increase in Mn-SOD activity is in response to exercise-induced free radical generation suggesting that under certain circumstances free radicals have highly beneficial actions, especially when they are produced in response to physiological stimulus such as exercise. Even pro-inflammatory cytokines enhance free radical generation. It is interesting to note that administration of antibodies to TNF-α and IL-1 abolished the cardioprotective action of exercise and activation of Mn-SOD. These results indicate that exercise-induced increase in the production of pro-inflammatory cytokines augment the production of free radicals that, in turn, augment Mn-SOD activity, which is ultimately responsible for the cardioprotective action of exercise. This is supported by the observation that circulating levels of extracellular SOD are lower in subjects with CHD.[7] Furthermore, SOD enhances the half-life of nitric oxide, a potent vasodilator, platelet anti-aggregator, and anti-atherosclerotic molecule. It is noteworthy that supplementation of anti-oxidant vitamin E counteracted the beneficial effects of exercise, suggesting that stimulation of endogenous anti-oxidants such as Mn-SOD is more critical to the beneficial actions of exercise and this benefit cannot be imitated by exogenous administration of anti-oxidants. Thus, regular exercise ensures adequate expression of endogenous anti-oxidants and anti-inflammatory cytokines and thus, brings about its cardioprotective action. In this context, the ability of exercise to suppress C-reactive protein levels is interesting and re-emphasizes the anti-inflammatory nature of exercise. A better understanding of the molecular mechanism(s) of the beneficial actions of exercise could lead to development of more precise therapeutic strategies both in the prevention and treatment of cardiovascular and other diseases.

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Undurti N. Das
UND Life Sciences
13800 Fairhill Road
No. 321 Shaker Heights
OH 44120
USA
E-mail address: undurti@hotmail.com

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Exercise and inflammation: reply

Our recent report from the HERITAGE Family Study showed that moderate to high-intensity exercise training reduced plasma levels of C-reactive protein, an important pro-inflammatory biomarker, in sedentary healthy adults with initial C-reactive protein levels >3.0 mg/L.[1] This finding is

potentially important from both a public health and a clinical point of view, because individuals with C-reactive protein >3.0 mg/L represent about one-fourth of all adults and are thought to have a markedly increased risk of cardiovascular disease and type-2 diabetes. A number of studies with different designs support the view that regular physical activity suppresses the inflammatory process,[2,3] an observation that could partly explain the effectiveness of regular exercise in the prevention and treatment of cardiovascular disease and type-2 diabetes.

Dr Das discussed some of the evidence that exercise reduces the levels of pro-inflammatory cytokines but increases the levels of anti-inflammatory cytokines, which in turn suppress the production of pro-inflammatory cytokines. He suggested that the exercise-induced increase in the production of pro-inflammatory cytokines augments the production of free radicals, which increases the activity of the endogenous antioxidant, manganese superoxide dismutase, ultimately responsible for the cardioprotective effect of exercise. He concluded that regular exercise ensures adequate expression of anti-inflammatory cytokines and endogenous antioxidants for the prevention of coronary heart disease.

Indeed, there is evidence for the inflammation-suppressing effects of exercise. A recent review concluded that a single bout of strenuous exercise produces a short-term, transient increase in plasma levels of C-reactive protein. The C-reactive protein increase is due to an exercise-induced acute phase response, mediated by the cytokine system and mainly IL-6.[2] In contrast, exercise training may blunt the acute pro-inflammatory response, and even suppress the inflammatory process, thereby contributing to the beneficial effects of habitual physical activity.[2] There also appears to be an acute homeostatic anti-inflammatory response after a bout of strenuous exercise that counteracts the pro-inflammatory response.[2]

A Danish research group has suggested that the inflammation-suppressing effect of exercise training is explained by the anti-inflammatory response elicited by a bout of exercise, which is partly mediated by an increase in IL-6 in skeletal muscle.[3] They have shown that physiological increases in plasma levels of IL-6, produced by the contraction of skeletal muscles during exercise, stimulate the production of anti-inflammatory cytokines IL-1ra and IL-10 but inhibit the production of a pro-inflammatory cytokine TNF-α. Thus, the inflammation-suppressing effect of exercise training may protect against TNF-α-induced insulin resistance, one of the important pathophysiological mechanisms of type-2 diabetes.

More research is needed to better understand the molecular mechanisms by which physical activity suppresses inflammation. Randomized controlled trials are warranted to investigate the dose of regular physical activity needed for an inflammation-suppressing effect, whether moderate intensity physical activity, as currently recommended, is sufficient for the effect, and whether there are dose and intensity thresholds above which no further benefits are gained or even harmful effects occur.

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Timo A. Lakka
Institute of Biomedicine
Unit of Physiology
University of Kuopio
POB 1627
Kuopio 70210
Finland
Tel: +358 40 5776914
Fax: +358 17 163112
E-mail address: timo.lakka@uku.fi

Pennington Biomedical Research Center
Louisiana State University
Baton Rouge, LA
USA

Kuopio Research Institute of
Exercise Medicine
Kuopio
Finland

Hanna-Maaria Lakka
Department of Public Health and
Clinical Nutrition
University of Kuopio
Kuopio
Finland

Pennington Biomedical Research Center
Louisiana State University
Baton Rouge, LA
USA

Tuomo Rankinen
Pennington Biomedical Research Center
Louisiana State University
Baton Rouge, LA
USA

Claude Bouchard
Pennington Biomedical Research Center
Louisiana State University
Baton Rouge, LA
USA