

10–41%, respectively) and offer no real advantage over our model.<sup>3–5</sup>

Cardiac biomarkers such as troponins and brain natriuretic peptides (BNPs) have a high negative predictive value (>93%) for mortality in patients with PE.<sup>5</sup> 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.<sup>4,6</sup> 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.<sup>1,2</sup>

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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.<sup>1–3</sup> The results of the study reported by Lakka *et al.*<sup>4</sup> 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.<sup>5</sup>
- Studies revealed that exercise not only decreased the levels of pro-inflammatory cytokines IL-6, TNF- $\alpha$ , and C-reactive protein but also simultaneously enhanced the concentrations of anti-inflammatory cytokines IL-4, IL-10 and TGF- $\beta$  compared when with controls. IL-4, IL-10 and TGF- $\beta$  are not only anti-inflammatory in nature but also suppress the production of pro-inflammatory cytokines IL-1, IL-2, and TNF- $\alpha$ .<sup>5</sup> 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.<sup>6</sup> 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- $\alpha$  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.<sup>7</sup> 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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- ### 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.<sup>1</sup> This finding is