SA9

Epidemiology of intermittent claudication, myocardial infarction and stroke

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SA10

Inflammation and cardiovascular disease

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There now exists overwhelming evidence supporting the inflammatory hypothesis of atherosclerotic vascular disease. Cellular interactions between leukocytes, platelets and endothelial cells are critical in the initiation and progression of atherosclerotic disease. Acute coronary syndromes, namely unstable angina and acute myocardial infarction, and thromboembolic stroke represent acute unstable phases of atherosclerotic vascular disease that are associated with significant morbidity and mortality. Atherosclerotic plaque disruption, with consequent platelet aggregation and thrombosis, is the principal mechanism by which atherosclerosis leads to the acute ischaemic syndromes of acute myocardial infarction, stroke and sudden cardiac death. Pathophysiological studies have confirmed the importance of inflammation in the pathogenesis of these acute vascular events by demonstrating (i) acute inflammatory reaction in unstable atherosclerotic plaques, (ii) a systemically detectable acute inflammatory response, and (iii) elevated levels of circulating inflammatory markers. The clinical importance of inflammation in atherosclerotic cardiovascular disease can be seen in the development of novel screening programs for detecting asymptomatic disease and designing novel anti-inflammatory therapies for established disease.

SA11

Inflammation in intermittent claudication

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Atherosclerosis is not merely a degenerative disease of the circulation and vasculature. It receives profound contributions from various inflammatory mechanisms. Early work looking at the white cell count (WCC) as a predictor of vascular events confirmed that WCCs in the high normal range confer a significant risk of future myocardial infarction and stroke. Our own work in critical limb ischaemia also showed the WCC to predict those destined for future amputation. Evidence suggests that for each $1.0 \times 10^9\ l^{-1}$ cell difference there was an increase in cardiovascular disease risk of 32 % for men and 17 % for women.

The white blood cell may contribute to vascular disease in the patient with claudication through both physical and chemical means. White blood cell (WBC) adhesion and aggregation are increased in these patients and predict those patients with claudication who will subsequently develop critical limb ischaemia (CLI).

WBCs release many cytokines and other inflammatory mediators such as free radicals. These latter are profoundly active chemicals which can be both directly and indirectly prothrombotic and atherogenic. Of particular relevance to the patient with intermittent claudication is reperfusion injury. The generation of superoxide during reperfusion may cause significant vascular injury. Oxidative stress is clearly linked to endothelial cell dysfunction in the patient with intermittent claudication and once again appears to be predictive within the patient group in terms of those patients with intermittent claudication who will subsequently progress to develop CLI.

Thus it has been recognised for some years that the WBC and inflammatory processes are important mediators of the Atherosclerotic process. The oxidative stress generated from the WBC, along with its increased aggregation and adhesion, have the potential to be deleterious in patients with intermittent claudication. Not only is there evidence of increased inflammatory markers in such patients but the higher the levels the more likely the patient is to proceed to critical limb ischaemia. Inflammation appears to be important in atherogenesis in the patient with intermittent claudication. We must focus future studies and evolving therapies in this area.

SA12

Exercise, skeletal muscle and inflammation: is interleukin-6 the 'exercise factor' for good health

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Physical activity offers protection against cardiovascular disease, type 2 diabetes. Physical training is also effective in the treatment of a number of medical disorders including ischemic heart disease, heart failure, chronic obstructive lung disease, type 2 diabetes and intermittent claudication. Although the beneficial effects of exercise are related somewhat to its positive effects on the lipid profile, insulin sensitivity and blood pressure, it is still unclear as to how muscle activity improves cardiovascular health. For years the search for the stimulus that initiates and maintains the change of excitability or sensibility of the regulating centres in exercise has been progressing. For lack of more precise knowledge, this stimulus has been called the 'work stimulus', 'the work factor' or 'the exercise factor'. In other terms, one big challenge for muscle and exercise physiologists has been to determine how muscles signal to central and peripheral organs. In this talk, I suggest the possibility that interleukin-6 (IL-6) could mediate some of the beneficial health effects of exercise. In resting muscle, the IL-6 gene is silent, but it is rapidly activated by contractions. The transcription rate is very fast, the changes in muscle IL-6 mRNA are marked, and IL-6 is released from working muscles into the circulation in high amounts. IL-6 production is modulated by the glycogen content in muscles and, thus, IL-6 works as an energy sensor. IL-6 exerts its effect on adipose tissue, inducing lipolysis and gene transcription in abdominal subcutaneous fat and increases whole body lipid oxidation. Furthermore, IL-6 inhibits low-grade TNF-α-production and may thereby inhibit TNF-α-induced insulin resistance and contribute to an improvement in cardiovascular health. Thus, I suggest that IL-6 and other cytokines, which are produced and released by skeletal muscles, and which exert their effects in other organs of the body, should be named 'myokines'.

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SA13

Exercise, skeletal muscle and oxidative stress

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Exercise has been recognised to cause changes in indicators of oxidative stress for 25 years. More recently, it has become apparent that contracting skeletal muscle is a major source of oxidant generation. The main source of intracellular oxidant generation appears to be mitochondria, but contracting skeletal muscle is recognised to release superoxide anions and nitric oxide to the interstitial fluid where hydroxyl radical activity is also increased. The functions of these extracellular species are unclear; nitric oxide released from skeletal muscle may exert a vasodilatory role, but the effects of other reactive oxygen and nitrogen species have not been characterised. Many investigators have suggested that these species might mediate the tissue damage that can accompany excessive or unaccustomed exercise, but there is little data in support of this. Increasingly, there is evidence that these species act as local signals to influence changes in redox-regulated gene expression leading to some adaptive responses to exercise.

SA14

Exercise-induced cardioprotection against ischaemia–reperfusion injury

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Myocardial ischaemia–reperfusion (I–R) injury is the major contributor to the morbidity and mortality associated with coronary artery disease. Although several factors contribute to I–R-mediated myocardial injury, strong evidence indicates that production of radicals and other reactive oxygen species are important mediators of this type of cardiac damage. It follows that increasing myocardial levels of antioxidants could provide cardioprotection against an I–R insult. This tutorial lecture will discuss recent experiments examining the effects of exercise training in providing cardiac protection against I–R injury. In this regard, new evidence suggests that both short term (days) and long-term (weeks) endurance exercise training reduces I–R-induced myocardial injury. Recent experiments investigating the role of exercise-induced increases in cardiac manganese superoxide activity and glutathione levels in this exercise-mediated cardioprotection will be discussed.

SA15

Exercise, inflammation and cardiovascular disease

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