

Metabolic inertia in contracting skeletal muscle: a novel approach for pharmacological intervention in peripheral vascular disease.

Reference: Br J Clin Pharmacol. 2004 Mar;57(3):237.

Peripheral vascular disease (PVD) is generally accepted to result in the failure of skeletal muscle blood flow to increase adequately at the onset of muscular work. There are currently no routine pharmacological interventions towards the treatment of PVD, however, recent Phase III trials in the USA have demonstrated the clinical potential of the phosphodiesterase III inhibitor Cilostazol for pain-free and maximal walking distances in patients with intermittent claudication. PVD is characterized by a marked reliance on oxygen-independent routes of ATP regeneration (phosphocreatine hydrolysis and glycolysis) in skeletal muscle during contraction and the rapid onset of muscular pain and fatigue. The accumulation of metabolic by-products of oxygen-independent ATP production (hydrogen and lactate ions and inorganic phosphate) has long been associated with an inhibition in contractile function in both healthy volunteers and PVD patients. Therefore, any strategy that could reduce the reliance upon ATP re-synthesis from oxygen-independent routes, and increase the contribution of oxygen-dependent (mitochondrial) ATP re-synthesis, particularly at the onset of exercise, might be expected to improve functional capacity and be of considerable therapeutic value. Historically, the increased contribution of oxygen-independent ATP re-synthesis to total ATP generation at the onset of exercise has been attributed to a lag in muscle blood flow limiting oxygen delivery during this period. However, recent evidence suggests that limited inertia is present at the level of oxygen delivery, whilst considerable inertia exists at the level of mitochondrial enzyme activation and substrate supply. In support of this latter hypothesis, we have reported on a number of occasions that activation of the pyruvate dehydrogenase complex, using pharmacological interventions, can markedly reduce the dependence on ATP re-synthesis from oxygen-independent routes at the onset of muscle contraction. This review will focus on these findings and will highlight the pyruvate dehydrogenase complex as a novel therapeutic target towards the treatment of peripheral vascular disease, or any other disease state where premature muscular fatigue is prevalent due to metabolite accumulation.

Management of peripheral arterial disease of the lower extremities in elderly patients.

Reference: J Gerontol A Biol Sci Med Sci. 2004 Feb;59(2):172-7.

The prevalence of peripheral arterial disease (PAD) increases with age. PAD in elderly persons may be asymptomatic, may be associated with intermittent claudication, or may be associated with critical limb ischemia. Other atherosclerotic vascular disorders, especially coronary artery disease (CAD), may coexist with PAD. Elderly persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from CAD. Modifiable risk factors should be treated in persons with PAD such as cessation of cigarette smoking and control of hypertension, dyslipidemia, and diabetes. Statins have been shown to reduce the incidence of intermittent claudication and to improve treadmill exercise duration until the onset of intermittent claudication in persons with PAD and hypercholesterolemia. Antiplatelet drugs such as aspirin or clopidogrel, especially clopidogrel, should be administered to all persons with PAD. Persons with PAD should be treated with angiotensin-converting enzyme inhibitors and also with beta blockers if CAD is present. Cilostazol should be given to persons with intermittent claudication to improve exercise capacity unless heart failure is present. Exercise rehabilitation programs improve exercise time until claudication. Indications for lower extremity angioplasty, preferably with stenting, or bypass surgery are 1) incapacitating claudication in persons interfering with work or lifestyle; 2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence. However, amputation should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations obviate the benefit of limb salvage.

J Wound Care. 2004 Feb;13(2):45-7.

Foot ulceration due to arterial insufficiency: role of cilostazol.

Left untreated, peripheral arterial disease can lead to chronic leg ischaemia, causing pain, foot ulcers and gangrene, and increasing the risk of amputation. The ulcers of two patients treated with cilostazol after revascularisation healed completely.

Renal Insufficiency and the Risk of Lower Extremity Peripheral Arterial Disease: Results from the Heart and Estrogen /Progestin Replacement Study (HERS).

Reference: J Am Soc Nephrol. 2004 Apr;15(4):1046-51.

ABSTRACT. Renal insufficiency is a risk factor for coronary heart disease and stroke, but whether it predicts lower extremity peripheral arterial disease (PAD) is unknown. The authors evaluated the association of baseline renal insufficiency with future PAD events in the Heart and Estrogen/Progestin Replacement Study (HERS) and follow-up study (HERS II). A total of 2763 postmenopausal women with known coronary heart disease were enrolled in HERS and randomly assigned to receive hormone therapy with conjugated estrogens and medroxyprogesterone acetate or placebo and followed for up to 8 yr for clinical end points. The outcome was time from randomization to first occurrence of either a lower extremity amputation, revascularization (surgical or percutaneous), or lumbar sympathectomy during follow-up. Incident lower extremity PAD event rates among women with creatinine clearances ≥ 60 , 30 to 59, and <30 ml/min/1.73 m² were, respectively, 0.55%, 0.92%, and 2.73% per year. After multivariable proportional-hazard adjustment for potential confounders and other known risk factors for PAD, women with a creatinine clearance 30 to 59 ml/min/1.73 m² (hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.04 to 2.54, $P = 0.032$) and <30 ml/min/1.73 m² (HR, 3.24; 95% CI, 1.20 to 8.78, $P = 0.021$) had a significantly increased risk of PAD compared with participants with a creatinine clearance ≥ 60 ml/min/1.73 m². Renal insufficiency was independently associated with future PAD events among postmenopausal women with coronary heart disease. Future studies should determine whether this association is present in other populations and investigate its potential mechanisms.

Nutr Rev. 2004 Jan;62(1):33-8.

New support for branched-chain amino acid supplementation in advanced hepatic failure.

Nutritional supplementation with branched-chain amino acids (BCAA) has been a topic of considerable debate for more than two decades. Several studies have demonstrated that supplementation with BCAA is associated with improvement of the catabolic state commonly seen in people with cirrhosis, whereas other studies have showed an improvement in portosystemic encephalopathy in patients with liver disease. Some studies have also shown there to be no benefit in BCAA supplementation in advanced cirrhosis. A recent large clinical trial showed that long-term BCAA supplementation may be useful in preventing progressive hepatic failure and improving liver function in some patients.

Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment.

Reference: J Am Coll Cardiol. 2004 Mar 17;43(6):1122.

OBJECTIVES: We sought to investigate the effect of aspirin resistance on the incidence of myonecrosis after non-urgent percutaneous coronary intervention (PCI) among patients pretreated with clopidogrel. **BACKGROUND:** Oral antiplatelet therapy using aspirin and a thienopyridine is the standard of care for preventing thrombotic complications of PCI. The effect of aspirin resistance on the outcomes of patients undergoing PCI is unknown. **METHODS:** We used the Ultegra Rapid Platelet Function Assay-ASA (Accumetrics Inc., San Diego, California) to determine aspirin responsiveness of 151 patients scheduled for non-urgent PCI. All patients received a 300-mg loading dose of clopidogrel >12 h before and a 75-mg maintenance dose in the morning of the PCI. The incidence of myonecrosis was measured by creatine kinase-myocardial band (CK-MB) and by troponin I (TnI) elevations after PCI. **RESULTS:** A total of 29 (19.2%) patients were noted to be aspirin-resistant. There was a significantly higher incidence of female subjects in the aspirin-resistant versus aspirin-sensitive groups. The incidence of any CK-MB elevation was 51.7% in aspirin-resistant patients and 24.6% in aspirin-sensitive patients ($p = 0.006$). Elevation of TnI was observed in 65.5% of aspirin-resistant patients and 38.5% of aspirin-sensitive patients ($p = 0.012$). Multivariate analysis revealed aspirin resistance (odds ratio [OR] 2.9; 95% confidence interval [CI] 1.2 to 6.9; $p = 0.015$) and bifurcation lesion (OR 2.8; 95% CI 1.3 to 6.0; $p = 0.007$) to be independent predictors of CK-MB elevation after PCI. **CONCLUSIONS:** Despite adequate pretreatment with clopidogrel, patients with aspirin resistance as measured by a point-of-care assay have an increased risk of myonecrosis following non-urgent PCI.

Am J Med. 2004 Feb 15;116(4):236-40.

Effect of type 2 diabetes and its duration on the risk of peripheral arterial disease among men.

The relative risk of developing peripheral arterial disease among men with diabetes compared with men without diabetes was 2.61 (95% confidence interval [CI]: 1.98 to 3.45). Peripheral arterial disease among men with diabetes increased with duration of disease. These results indicate that **duration of type 2 diabetes is associated strongly with the risk of developing peripheral arterial disease.**

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