Elevated Peri-Operative C-Reactive Protein Impedes Late Vein Graft Remodeling

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Objectives: Enhanced systemic inflammation, as measured by C-reactive protein (CRP), has been associated with reduced early outward remodeling and long-term vein graft (VG) failure. This study seeks to define the long-term changes in VG remodeling that are induced by this pro-inflammatory phenotype.

Methods: A prospective study was performed on 31 patients undergoing autogenous VG placement. CT scans, with computational analysis of wall shear stress (WSS), were performed at 1wk, 1m, and 6m to evaluate lumen remodeling. hsCRP was obtained pre-op and 1wk post-op.

Results: Late changes in VG lumen diameter (between 1m to 6m) were negatively correlated with CRP levels (P<0.04), while early changes in VG diameter (1wk and 1m) were independent of 1wk CRP (Fig B, P=NS). Adaptation of the lumen was positively correlated with WSS (Fig C, P<0.001) and was not influenced by the 1wk CRP level (Fig D, P=NS). Neither early or late geometric VG changes nor the adaptive response to WSS were correlated with pre-op CRP levels. Six (of 31) VG were revised or occluded within 1 year, and this was not dependent on either pre-op or 1wk CRP.

Conclusions: Late VG remodeling was significantly reduced by an enhanced peri-operative inflammatory response, while early VG adaptation was independent of this response. In contrast to published reports, we found no correlation between the baseline inflammatory state of the patient and WSS-dependent VG adaptation. The current studies suggest long-term structural modulation of the VG by the inflammatory system as the dominant determinant for these events.

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The Toll-like Receptor 2 Ligand HMGB-1 Contributes to Skeletal Muscle Damage in Critical Limb Ischemia

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Objectives: Inflammation and cell damage contribute to the pathophysiology of critical limb ischemia (CLI). Toll-like receptors (TLRs) play an important role in inflammation and tissue damage probably in response to the release of endogenous ligands. We hypothesize that the expression of TLRs and their endogenous ligands is upregulated in ischaemic skeletal muscle with consequent activation of their signaling pathway, which could lead to an increase in inflammatory cytokine release contributing to muscle damage.

Methods: TLR expression was studied in ischaemic and control human muscle biopsies and in C2C12 myotubes cultured in ischaemic conditions using RT-PCR and Western blot. Western blot was used to measure the expression of the endogenous ligand, high mobility group box protein-1 (HMGB-1). Functional effects of TLR2 antagonism on ischaemia-induced IL-6 release and cell death were studied by incubating myotubes with neutralizing TLR2 antibody. IL-6 release was assayed by ELISA. Apoptosis was assessed using cleaved caspase-3 and bax/bcl-2 ratio measurements.

Results: TLR2 mRNA and protein expression was significantly upregulated in ischaemic muscle and in C2C12 myotubes cultured in ischaemic conditions (p<0.05). Raised levels of HMGB1 were demonstrated in ischaemic human muscle biopsies and in ischaemic C2C12 myotubes. TLR2 antagonism reduced ischaemia-induced IL-6 production and apoptosis in culture.