Conclusions: Current CMS physiologic high-risk CEA criteria place patients at increased risk for adverse events for CAS. This warrants the need to reconsider patient selection criteria for CAS vs CEA in physiologically high-risk patients.

Short-term Dietary Manipulations can Attenuate the Adipose Inflammatory Response to Surgical Trauma

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Introduction and objectives: Morbid obesity is frequently associated with increased surgical morbidity and mortality, and adipose is increasingly recognized as an organ that plays an important mechanistic role in host inflammation. We thus hypothesized that diet-induced obesity drives an accentuated proinflammatory adipose response to surgical trauma and that short-term dietary intervention by switching from a high-fat diet to a normal diet can attenuate this response.

Methods: Standard surgical manipulations were performed on the left flank fat pad of 26-week-old C57Bl6 male mice fed normal chow for 20 weeks (n = 6), high-fat chow for 20 weeks (60% Kcal; n = 6), or high-fat chow for 17 weeks reversed to normal chow for 3 weeks (n = 6). Day 1 adipose was collected and the expression of the proinflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor(TNF)-α, and of the anti-inflammatory cytokine IL-10 was assessed using quantitative RT-PCR (individually normalized to day 0 adipose).

Results: Expression of all assayed mediators was induced by surgical trauma. Adipose from the group fed high-fat chow yielded an exaggerated proinflammatory cytokine signature compared with controls fed normal chow ($P = .002$ for IL-1βa and IL-6). Short-term dietary reversal significantly attenuated the IL-1β ($P = .002$) and IL-6 induction ($P = .015$).

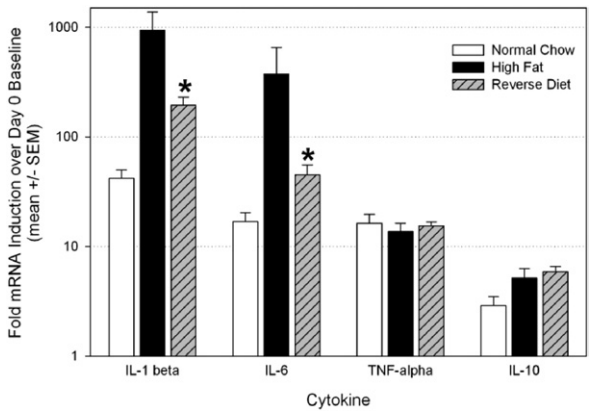

Fig.

Conclusion: Surgery induces proinflammatory and anti-inflammatory cytokine expression, and diet-induced obesity is associated with an accentuated proinflammatory cytokine response to surgical trauma. Short-term dietary switch to a normal chow diet attenuates this response. These results support a nimble adipose phenotype and suggest that periprocedural dietary interventions could affect surgical outcomes (Fig).

A Novel Model of Hind Limb Ischemia to Test Human Therapeutic Angiogenesis

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Introduction and objectives: Clinical trials injecting bone marrow-derived mononuclear cells (MNC) for therapeutic angiogenesis in patients with critical limb ischemia are currently underway. However, there are limited animal models available that adequately model human disease to allow direction of the human studies.

Methods: C57BL/6 male mice (aged 6-8 weeks) underwent unilateral high femoral artery ligation and excision; the contralateral leg was used as a control. MNC were isolated from donor mice, suspended in Roswell Park Memorial Institute 1640, and injected into the gastrocnemius. Control injections used an equal volume of medium without cells. MNC were characterized using fluorescence-activated cell-sorting analysis. Muscle blood flow was measured with "deep probe" laser Doppler. Functional Tarlov, ischemia, and modified ischemia scales were recorded at intervals before the operation and to 4 weeks after. Mice were euthanized at 1, 2, and 4 weeks for histologic analysis. Statistics were based on five random fields of view at original magnification ×40.

Results: Blood flow was significantly higher in MNC-injected mice than in controls ($P < .0001$). Tarlov scores were statistically higher throughout the first week postoperatively in MNC mice ($P = .0064$). Ischemia scores were significantly higher in MNC mice ($P = .0269$). Average number of muscle fibers was lower and fiber area was higher in MNC mice (n = 3) at all intervals ($P < .01$).

Conclusions: High femoral ligation and excision is a reproducible model of limb ischemia in C57BL/6 mice that shows response to MNC injection. These studies suggest several parameters of human trials can be tested in a small animal model in a cost-effective manner, allowing optimization of human trial parameters.

Nitrosylative Stress During Ischemia–Reperfusion Injury: Implications For Poly (Adenosine Diphosphate-Ribose) Polymerase and Nitric Oxide Synthase Activity

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Introduction and objectives: Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibition is cytoprotective during limb ischemia–reperfusion (IR) injury. Paradoxically, PARP activation may be triggered by dysfunctional nitric oxide synthase (NOS) activity. These experiments were undertaken to assess whether NOS inhibition will ameliorate skeletal muscle injury and alter PARP activity during the acute and early chronic phases of reperfusion in a mouse model of hind limb IR.

Methods: Two groups of C57BL6 mice were underwent to 1.5 hours of hind limb ischemia, followed by reperfusion. Mice were treated with the NOS inhibitor N^G-nitro-L-Arginine methyl ester (L-NAME, 50 mg/kg/d n = 10) or normal saline (n = 10) starting 1 day before IR. Hind limb muscles were harvested after 1 day or 7 days of reperfusion for histologic evaluation of skeletal muscle fiber injury and protein expression. PARP activity was assessed by Western blotting for poly-ADP-ribosylated (PAR) proteins. NOS activity was evaluated by measuring tissue nitrite, the expression of total-nNOS and the activating pS1412 and the inhibitory pS847-nNOS sites. Evidence of nitrosative stress was estimated by Western blotting for nitrotyrosine. Data were analyzed by Student *t* test.

Results: L-NAME treatment resulted in an 80% increase in the number of injured fibers compared with nitrotyrosine at day 1 IR ($P = .02$.) There was no difference in PARP activity at days 1 or 7 between the two groups. Furthermore, there was no significant difference in nitrite, nitrotyrosine, or the expression of total or pS1412-nNOS, but there was significantly less pS847-nNOS expression in the L-NAME group at day 7 ($P = .0003$).

Conclusions: L-NAME treatment exacerbates skeletal muscle fiber injury after IR but does not alter PARP activity. Because NOS inhibition (pharmacologic and through phosphorylation) does not alter nitrite or nitrotyrosine levels after injury, NOS and interactions may be partially NOS-independent during acute IR.

Western blotting data are expressed as average specific bands densities ± standard error. *$P < .001$ compared with NS.

Small Interfering RNA Coating of Prosthetic Arterial Graft Materials

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Introduction and objectives: Intimal hyperplasia (IH) remains the leading cause for prosthetic arterial graft failure. Electrospinning of the Dacron-based polymer, polyethylene terephthalate (ePET), is an appealing alternative to woven or knitted Dacron or polytetrafluoroethylene (PTFE) grafts. RNA interference is a promising tool to silence genes contributing to IH. Combining these technologies thus seemed logical. In this study, ePET and commercially available PTFE fabrics were dipped into various small interfering (si) RNA formulations, and adsorption of siRNA to the materials was investigated.

Methods: PTFE and ePET fabrics were incubated for 50 minutes in solutions containing unlabeled siRNA, siGLO Red (DyLight-547 tagged) transfection indicator siRNA, or cholesterol-siRNA-DyLight-547. siRNA was used without a transfection reagent or was complexed with JetPEI, a cationic polymer. siRNA concentrations were measured before and after fabric incubation to determine total adsorption. In a different experiment, ePET samples were dipped into siGLO Red/PEI solutions once for 50 minutes or repeatedly, 10 times for 5 minutes each, with intermittent washes in NaCl. Confocal microscopy was performed and red fluorescent density determined.

Results: Unlabeled siRNA was not adsorbed to fabrics unless complexed with PEI, whereas siGLO Red and Chol-siRNA-DyLight547 had some affinity to the materials. Overall, siRNA adsorption to ePET and PTFE