Abstracts

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STATEMENT OF ASSURANCES:

All authors affirm that any animal studies conform with the "Position of the American Heart Association on Research Animal Use" (*Circulation* 1985;71:849A–850A), and that any human experimentation has been conducted according to a protocol approved by the institutional committee on ethics of human investigation or, if no such committee exists, that it conforms with the principles of the "World Medical Association Declaration of Helsinki" (*Cardiovascular Research* 1997;35:2–3).

Abstracts are in order of the Primary Author's last name.

A COLLAGEN GEL-BASED WOUND DRESSING RESOLVES INFLAMMATION THROUGH MIR-21 INDUCED M2 MACROPHAGE POLARIZATION

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Our previous work has demonstrated improved wound healing outcomes in excisional and ischemic porcine wounds following the use of a modified collagen gel (MCG) dressing. The objective of the current work was to elucidate the mechanism of action of MCG on the host wound inflammatory cells in early and late inflammatory phase. Polyvinyl alcohol sponges containing either MCG or saline were implanted on the dorsal side of mice, and inflammatory wound cells were harvested on day 3 (early phase) or day 7 (late phase). Flow cytometry data from harvested sponges on day 3 and day 7 post wounding showed markedly higher infiltration of macrophages (F4/80+) to the wound site in the MCG-treated group. On treatment with MCG, wound-site macrophages showed significantly lower abundance of the pro-inflammatory M1 phenotype at the early inflammatory phase but higher expression of M2 macrophage markers during the late inflammatory phase. RNA extracted from the inflammatory wound cells showed significantly up-regulated anti-inflammatory cytokines IL-4 and IL-10 at both early and late time-points in the MCG treated group. In vitro studies in THP-1 derived macrophages confirmed MCG's ability to induce an anti-inflammatory response. Engulfment of apoptotic cells by macrophages (efferocytosis) has been reported to induce miR-21 and switch macrophage from pro-inflammatory to anti-inflammatory phenotype leading to resolution of wound inflammation, which was bolstered by MCG. MCG was also found to support wound angiogenesis by increased VEGF production. Taken together, MCG promotes efferocytosis which induces miR-21 leading to M2 Macrophage Polarization and improved wound healing outcomes.

RELIABILITY AND VALIDITY STUDY OF A SMARTPHONE WOUND HEALING APP

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The purpose of this study was to describe inter- and intra-observer agreement for a Smartphone Wound Healing App and measure criterion-validity using the Silhouette Star wound imaging system as the criterion standard. Twenty consecutive patients with lower extremity wounds were asked to enroll in a cross-sectional reliability and validity study. Four examiners took wound images of the same wound on the same day. For each patient, each examiner used the wound healing application to take a baseline image followed by a wound image (for a total of 80 wound images to be used for inter-observer reliability evaluation). The wound image was traced with a stylus, allowing the application software to automatically calculate the surface area of the wound. For each patient, one examiner was randomly selected to image the wound ten times for evaluation of intra-observer reliability. Each examiner repeated this process on five patients for a total of 50 images per examiner (and a total of 200 images to be used for intra-observer reliability evaluation). A stratified approach was used for enrollment based on the time of day to help account for fatigue accumulated throughout the day. Intraclass correlation coefficients using a two-way mixed effects model, coefficient of variation, and kappa coefficients were calculated. Time of day differences were assessed using coefficients of variation and a paired *T*-test assuming equal variance. We found the overall criterion validity with the Silhouette Star was 90.43%. Test-retest reliability was 0.999. We found no differences in time of day for the coefficient of variation ($p = 0.0997$). In conclusion, we found the wound care application to demonstrate high criterion validity with the gold standard and high test-retest reliability. We recommend further testing in a busy wound clinic.

ENVIRONMENTAL TOBACCO TOXINS ALTER RESPONSE TO INJURY IN SKELETAL MUSCLE BY ALTERING MITOCHONDRIAL FUNCTION

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Third-hand smoke (THS) is the accumulation of second-hand smoke on environmental surfaces; it ages with time becoming progressively more toxic. THS can be found in the clothing/hair of smokers as well as in their homes and cars and where smoking has occurred. Exposure to THS can occur by ingestion, inhalation, and dermal absorption. We show here that mice exposed to THS under conditions that mimic exposure of children in the homes of smokers have an altered response to injury in skeletal muscle due to increased oxidative stress and pro-inflammatory cytokines/chemokines, and down-regulation of anti-inflammatory cytokines/chemokines. We also show that THS regulates several genes involved in mitochondrial biogenesis and function. In particular, PGC1-a, which is a master regulator of mitochondrial biogenesis. This suggests that muscle of THS-exposed mice contains fewer mitochondria. We also show that Sirtuins 1 and 3 (SIRT 1,3) are down-regulated. This class of histone deacetylases are involved in the activation of PGC1-a and of proteins involved in oxidative phosphorylation and beta-oxidation. With lower levels of SIRT 1 and 3, THS exposed mice suffer from mitochondria that have reduced function. Furthermore, several classes of ATP synthases are also down-regulated resulting in reduced oxidative phosphorylation, ATP production is reduced and the cells use anaerobic respiration that results in lactate accumulation causing cell damage. Lastly, proteins involved in the proper fission and fusion of mitochondria such as mfn2, OPA1, and UCP 1 and 2 are also down-regulated. The down-regulation of these proteins indicates that mitochondria are dysfunctional and cannot properly fuse or fission during fasting and fed states, and as a result cannot meet the energy demands of the cell. Our studies provide mechanistic data on how environmental tobacco smoke toxins cause mitochondrial dysfunction that can lead to an altered response to injury in the skeletal muscle.