

## Topical Menthol Application Augments Cutaneous Microvascular Blood Flow

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**Purpose:** Menthol containing topical analgesic gels are used clinically to activate transient receptor potential melastatin 8 (TRPM8) receptors, which elicits a cold sensation that purportedly mimics cryotherapy. However, there is controversy as to the precise vascular effects of menthol containing topical analgesics. We sought to more fully characterize the mechanism(s) of action through which topical menthol application may alter skin blood flow (SkBF). **Methods:** Three distinct protocols were conducted in three groups of 10 young, healthy subjects. Red cell flux was measured via laser speckle contrast imaging in all protocols. Protocol 1: Menthol (4%) and placebo gels were applied to 45cm<sup>2</sup> of skin without thermal control and SkBF was measured until SkBF reached a stable plateau. Protocol 2: Menthol and placebo gels were applied to skin under local thermal control (33<sup>0</sup>C). Post-occlusive reactive hyperemia (PORH) and local heating (42<sup>0</sup>C) protocols were conducted to determine the contribution of endothelium derived hyperpolarizing factors (EDHFs) and nitric oxide, respectively. Protocol 2 was repeated with Lidocaine pretreatment to determine sensory nerve contribution. Protocol 3: Seven concentrations of menthol gel (0.04%, 0.4%, 1%, 2%, 4%, 7%, 8%) were applied to the skin to model the dose-response relation between menthol and SkBF. Data for all protocols were normalized to cutaneous vascular conductance (CVC: flux/mean pressure) and expressed as percent maximum CVC (%CVC<sub>max</sub>) where appropriate. **Results:** Protocol 1: menthol gel increased SkBF compared to placebo (3.4±0.3 v 1.1±0.2 CVC; p<0.001). Protocol 2: menthol augmented SkBF compared to placebo during baseline (63±7 v 20±2 %CVC<sub>max</sub>; p<0.001), PORH (90±4 v 69±5 %CVC<sub>max</sub>; p<0.001), and local heating (81±2 v 74±3 %CVC<sub>max</sub>; p=0.03). Sensory nerve inhibition attenuated menthol-mediated dilation at baseline (32±4 %CVC<sub>max</sub>; p<0.001) and PORH (70±5 %CVC<sub>max</sub>; p<0.001). Protocol 3: SkBF increased with increasing doses of menthol (main effect, p<0.05). Pharmacological curve modeling indicated that the ED<sub>50</sub> for menthol was a 1% concentration. **Conclusion:** Topically applied menthol dose-dependently increases blood flow in the cutaneous microvasculature. This increase in blood flow is mediated in part by EDHFs and sensory nerves.