Mechanisms of Action of Active Esophageal Cooling During Left Atrial Radiofrequency Ablation: A Multidisciplinary Review

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Purpose

To determine possible mechanisms of action underpinning the protective effects of active esophageal cooling.

Background: Active esophageal cooling is increasingly used as a protective strategy during left atrial radiofrequency (RF) ablation for the treatment of atrial fibrillation (AF). Endoscopic data show an 83% reduction in esophageal lesions with active esophageal cooling, but to date, with over 22,000 ablation cases completed with a dedicated esophageal cooling device, there has been no reported atrioesophageal fistula (and only one pericardio-esophageal fistula has been reported). Thus, additional protective mechanisms beyond acute thermal injury reduction from cooling are likely to be involved.

Methods

We reviewed the literature on burn injury progression, fibrosis, fistula formation, and therapeutic hypothermia, focusing on studies that identified molecular factors involved in these processes. Common mediators were cataloged, and the effects of temperature on the activity of these mediators were then determined from additional literature searches.

Results

We identified more than 135 relevant articles and found that a wide range of molecular mediators are implicated in the pathophysiology of burn injury progression, fibrosis, and fistula development. Both fibrosis and epithelial-to-mesenchymal transition (EMT) are potential drivers of fistula development after an initial thermal injury. The soluble mediators of these processes are also implicated in burn wound conversion, which further facilitates progression of a thermal injury. Importantly, the activity of many pro-inflammatory markers have been shown to be inhibited by cooling, while some anti-inflammatory mediators are activated. (Table 1)

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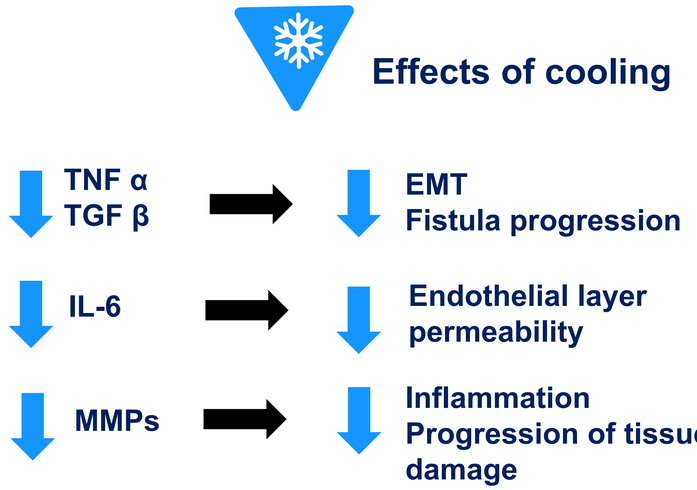
Results

	Action in burns	Action in fistula formation	Action in fibrosis	Temperature effects	Effect of cooling on activity or expression
TNF- α	Pro-inflammatory cytokine.	Triggers EMT, onset and progression of fistula formation.	Induces apoptosis of fibrotic progenitors.	Cooling significantly reduces activity.	↓
TGF-β	Worsens scar formation.	Triggers EMT, onset and progression of fistula formation.	Induces fibrosis.	Cooling reduces mRNA expression.	↓
Angiotensin II	Possible synergistic signal to TGF-B in burn scarring.	Unclear actions.	Expression of genes related to fibrosis.	Lowers body temperature when administered systemically.	?
IL-1	Pro-inflammatory cytokine (inhibited by IL-1ra).	Inhibition alleviates severe fistulae in hidradenitis suppurativa.	Profibrotic cytokine; induces apoptosis of fibrotic progenitors.	Downregulated or unchanged with cooling.	↔
IL-4	Anti-inflammatory cytokine.	Implicated in oronasal fistula formation.	Facilitates muscle regeneration.	Expression levels of IL-4 anti-inflammatory cytokines increased.	↑
IL-6	Pro-inflammatory cytokine associated with mortality.	Induced by TNF-alpha, increases permeability of endothelial layer.	Triggers cardiac fibrogenic signalling cascade.	Reduces IL-6 expression.	↓
IL-7	Pro-inflammatory cytokine.	Unclear actions.	May inhibit high glucose-induced renal proximal tubular fibrosis.	Uncertain.	?
IL-8	Enhances neutrophil transmigration; pro-inflammatory cytokine, associated with ARDS.	Putative role in pathogenesis of cryptoglandular anal fistula.	Dominates the inflammatory profile in cystic fibrosis.	Higher levels may determine severity hypoxic ischemia.	?
IL-10	Anti-inflammatory cytokine, associated with burn mortality.	Impaired IL-10 signaling implicated in inflammatory bowel fistulas.	Profibrotic cytokine.	Elevations delayed with hypothermia.	↑
IL-12	Pro-inflammatory cytokine, stimulates production of TNF-alpha.	Elevated levels linked to entercutaneous fistulas.	Induces apoptosis of fibrotic progenitors.	Reduced expression with hypothermia.	↓
IL-13	Anti-inflammatory cytokine, induces metaplasia.	Triggers EMT, onset and progression of fistula formation.	Effects muscle regeneration by resident mesenchymal progenitor cells.	Expression levels increased with hypothermia.	↑
IL-17	Pro-inflammatory cytokine increased during burn injuries.	Pro-inflammatory mediator; key role in fistula formation in hidradenitis suppurativa.	Mediator in foreign body response and fibrosis.	Gene expression levels significantly down-regulated with local cryotherapy.	↓
Matrix metalloproteinases (MMPs); MMP-1, MMP-3, MMP-9	Upregulated in vascular inflammation.	Activated by EMT, causing further tissue damage and inflammation.	Associated with fibrotic processes underlying right ventricular remodeling.	Down-regulatory effects on expression.	↓
Histamine	Increases wound edema, microvascular permeability.	Unclear actions.	Unclear actions.	Decreases or prevents histamine release.	↓
Reactive oxygen species	Induce burn progression, edema formation, and microvascular permeability.	Implicated in enterocutaneous fistula development.	Associated with severity of cystic fibrosis.	Reduced with hypothermia.	↓

Table 1

Conflicts of interest: SO: None, JZ: BioSense Webster, Attune Medical, RS: None, JH: None; BL: None, EK: equity and employment in Attune Medical, AC: None

Results



Conclusions

Thermal injury triggers an inflammatory cascade that may result in further progression of injury, leading to fibrosis and fistula formation. Cooling affects the activity of most of the molecular mediators of this inflammatory cascade. This may explain the safety benefits seen clinically with active esophageal cooling and suggests an important direction for further investigation.

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