Vascular Biology of Cold Injuries

…and why we should care!

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Disclosures

- Arctic Hematology LLC: independent consultant in hematology
- Tunnell Government Services: SME consultant supporting HHS/ASPR/BARDA/CBRN
- Velico Medical: Chief Scientific Officer, Board of Directors

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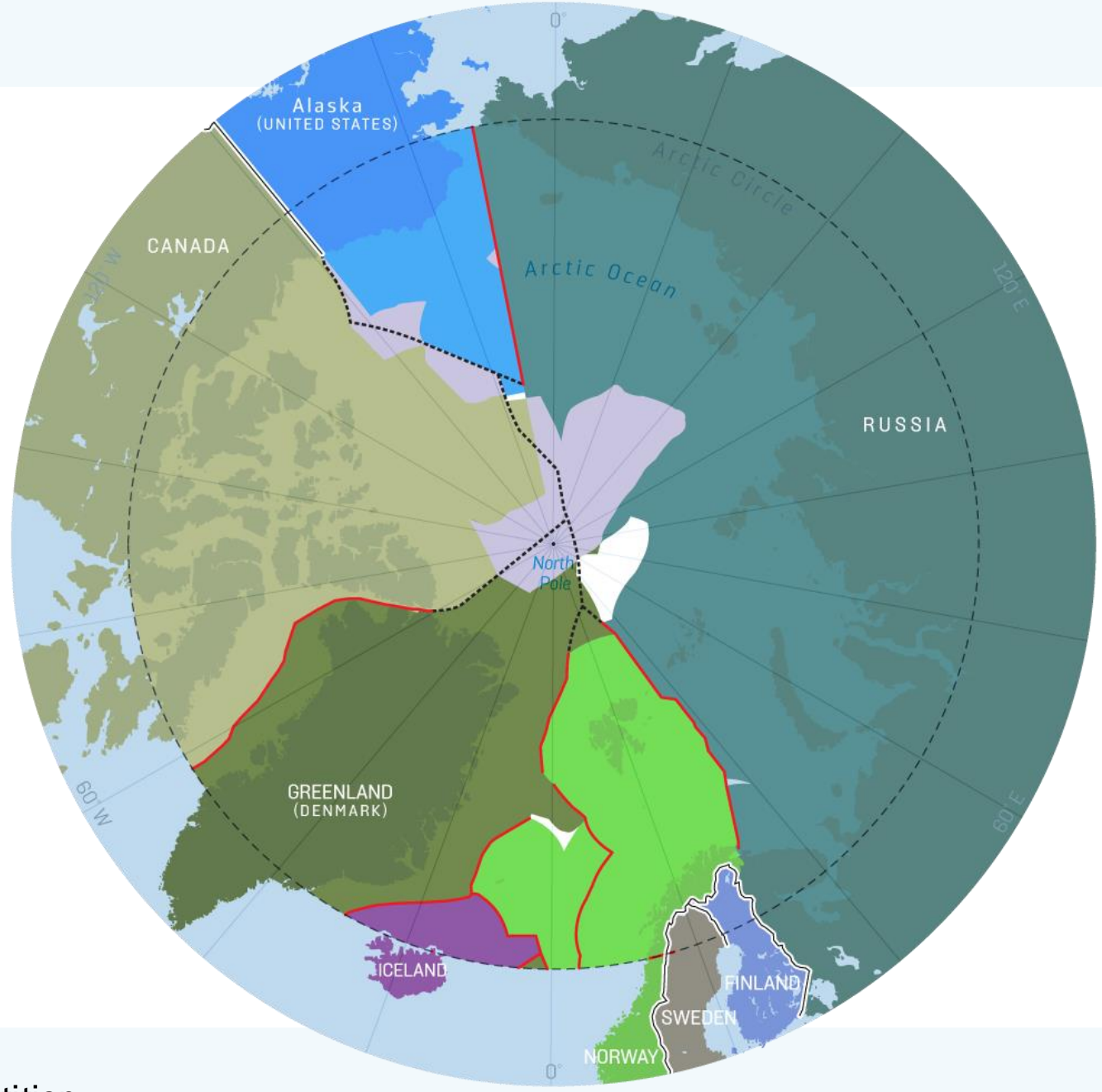
Arctic great power competition is happening now!

“We may not be interested in Arctic warfare, but Arctic warfare is going to be our problem.”

Arctic Governance

- Complex & contested
- **China** also investing massively in energy & minerals projects, Arctic force projection capabilities

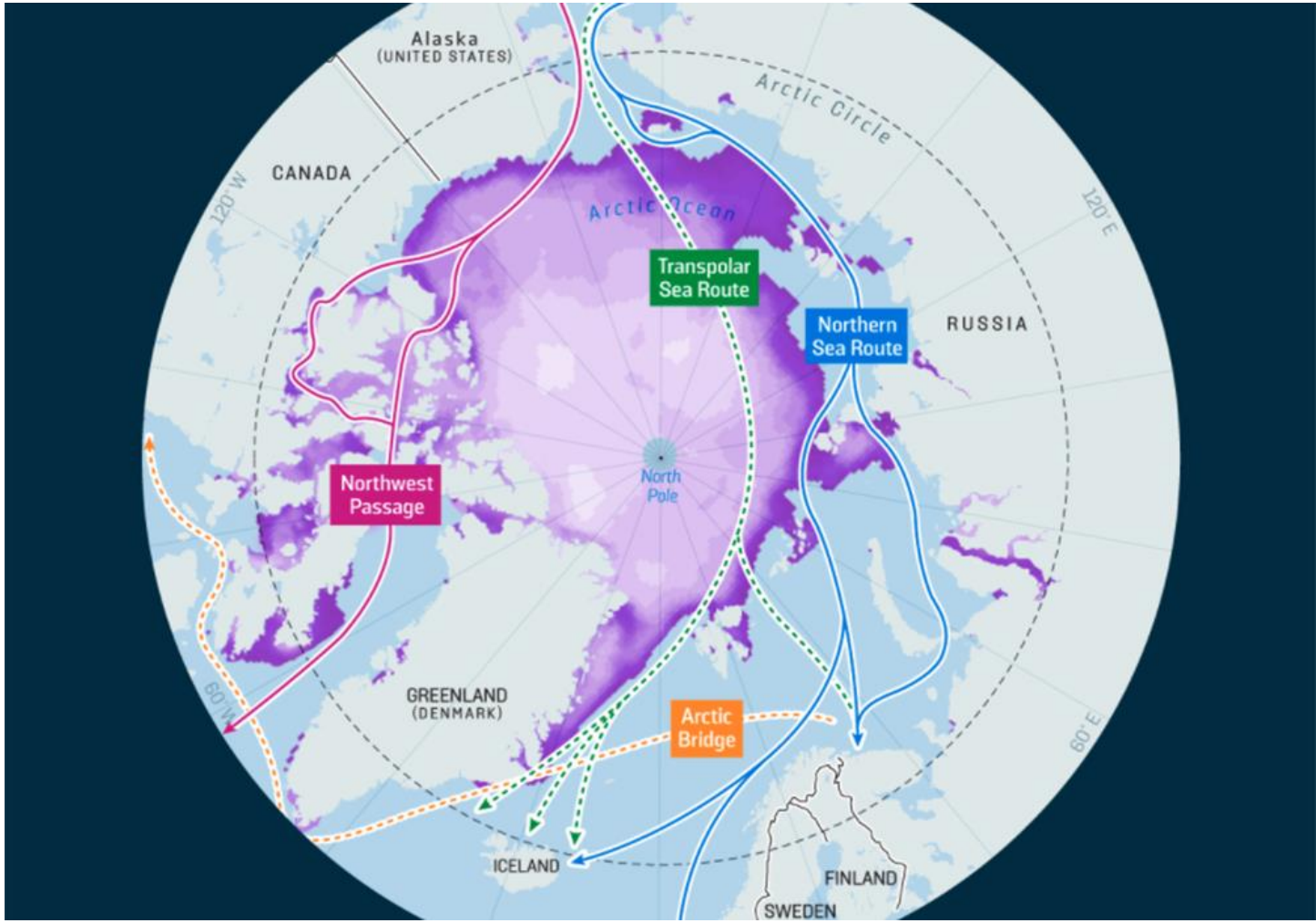


Foreign Policy 2020: FP Analytics Special Report – Arctic Competition

Receding Sea Ice

- Opening sea lanes
- Increased military & commercial traffic
- Undersea telecommunications cables

- NOTE: the Arctic is still **COLD (-40℃ to 0℃)** … despite global warming



Foreign Policy 2020: FP Analytics Special Report – Arctic Competition

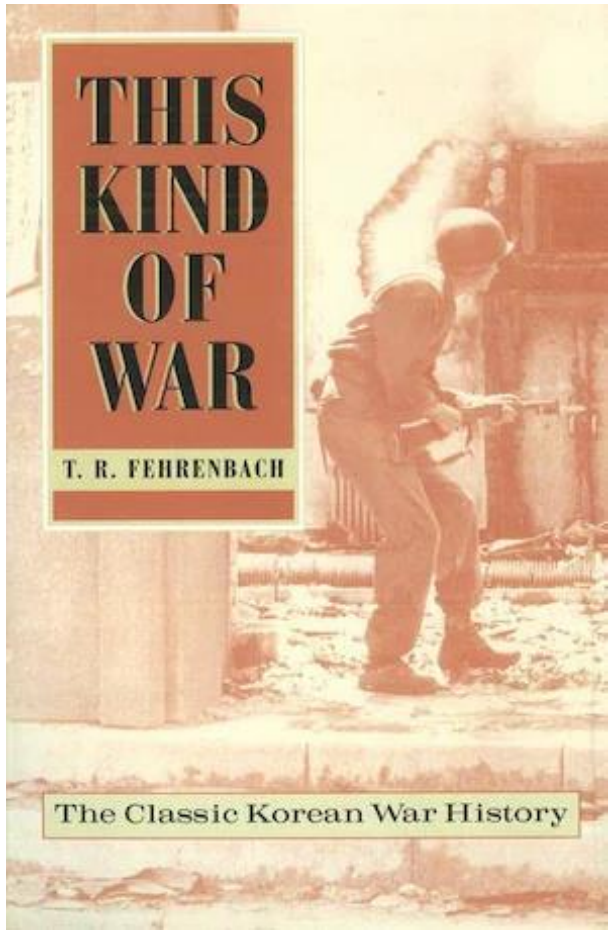
Oil & Gas Fields

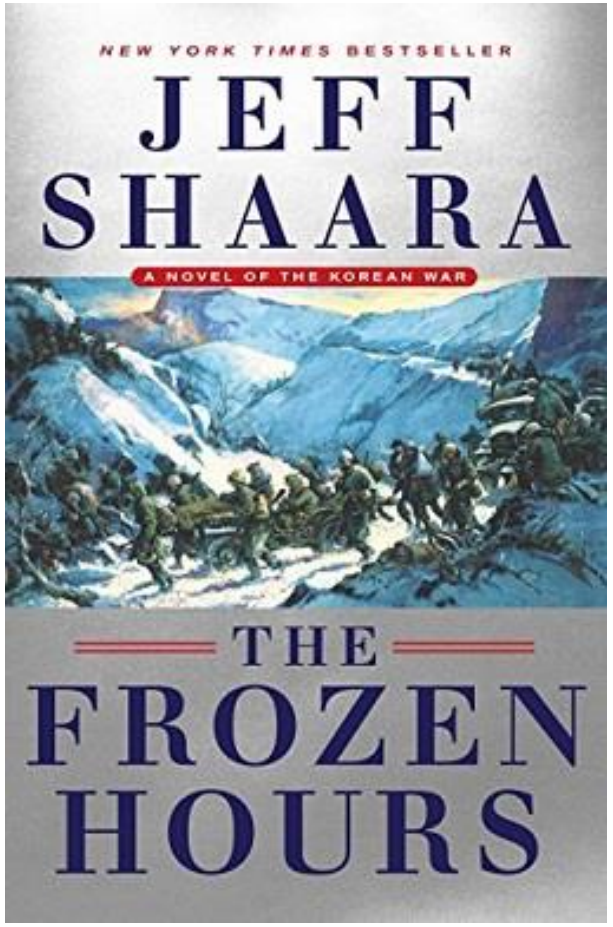
- 95% untapped
- Arctic oil & gas: major strategic priorities for Russia, China

- *There will be claims, counter-claims and violence…*

Foreign Policy 2020: FP Analytics Special Report – Arctic Competition

Read about Korea; it's instructive





Cold injuries were a **huge** problem for commanders on both sides.

Cold is the ancient enemy of armies…

- Frostbite on 5000 yo Chilean mummy
- Red Army, Finnish War: 17,867 frostbite injuries; est. 7920 Finnish
- German Army 1942: >15000 amputations on Russian Front
- US Military >6300 cold weather injuries in Korean War

Overall: 2-4% of all surgical trauma for Soviets

Soviet Frostbite Injuries WWII	**% Total Injuries**	**% RTD**	**Anatomic location**	**Mortality**
1st Degree	70-90%	100	83-91% lower limbs	NA
2nd Degree		100		NA
3d Degree		98.5		NA
4th Degree		60.5	4.5-8.4% hands 12.3-26.4% lower limbs	0.2-0.3%

Hall et al. J Surg Educ. 2010.

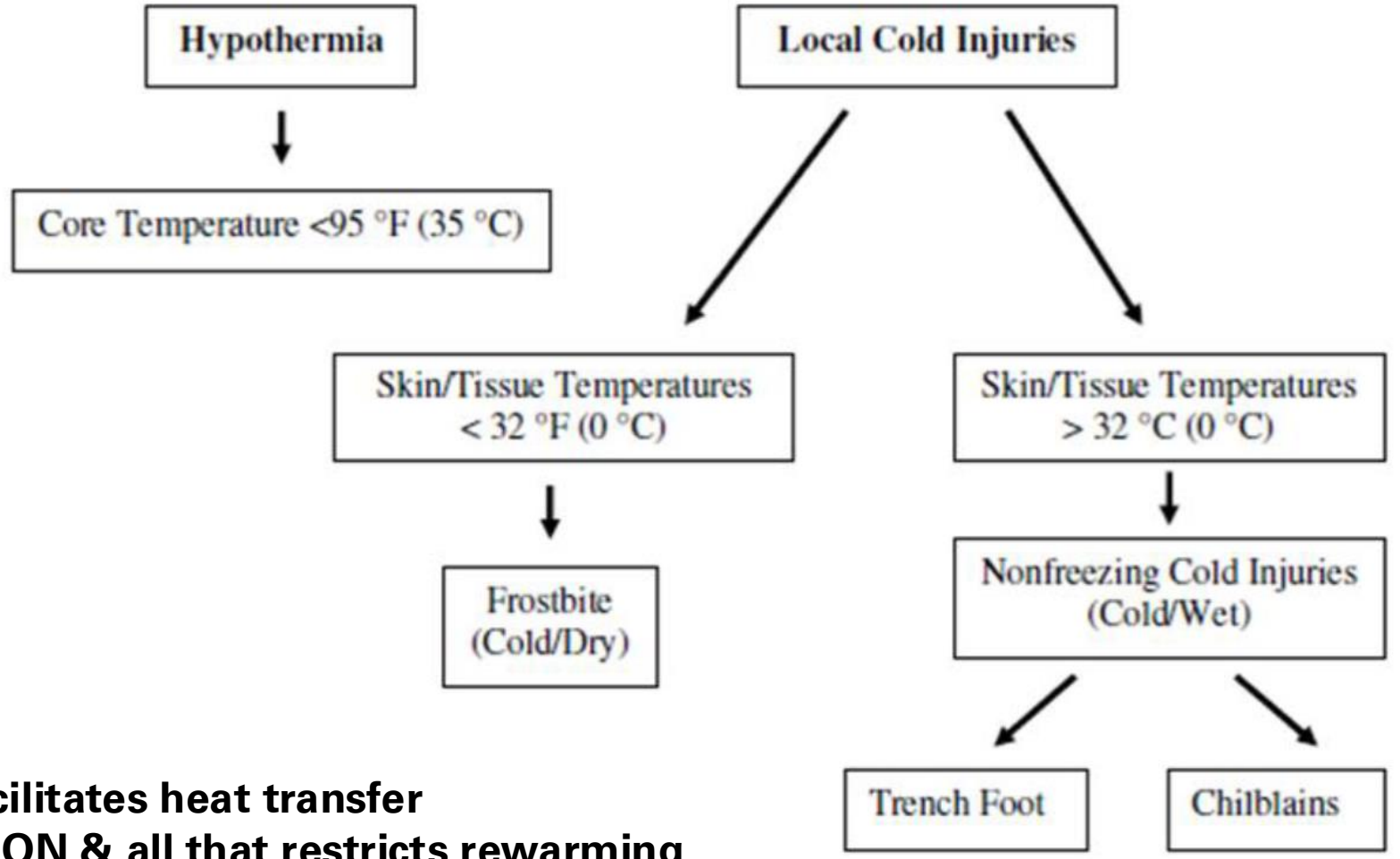
Sokolov et al. Mil Med Res 2017.

CCC in the Arctic — *combined injury in a "denied" environment*

- **Cold analogous to radiation:** the environment can kill **you** and your patient!
- **Trauma + direct cold injury/hypothermia:** all trauma patients will have combined injury → combined management approach (no separating the problems)
  - Troop status assessment; TCCC/ TACEVAC
  - DCR/DCS @ R2 (rewarming, re-bleeding, cold injury assessment, timing of surgery, patient holding)
  - STRATEVAC/R4 (evac triage, delayed cold injury surgery, rehab)

Cold Injury is not just freezing!

Cold injury continuum



Risk factors:
COLD & all that facilitates heat transfer
VASOCONSTRICTION & all that restricts rewarming

Cold injury overlap syndrome: **vascular** & nerve injury

Anesthesia & edema → hyperemic stage: edema, paresthesia & anhydrosis

Meryman *J Physiologic Rev* 1957.

Tissue Freezing and Local Cold Injury

HAROLD T. MERYMAN

From the Department of Internal Medicine, Yale University, New Haven, Connecticut

well. Trenchfoot, like immersion foot, upon rewarming is characterized by a pre-hyperemic stage with anesthesia and edema, paresthesia and anhydrosis. More severe cases may show muscular weakness or atrophy and ulceration or gangrene on distal superficial areas. In a matter of days or weeks a post-hyperemic stage develops in which hypersensitivity to cold and to weight bearing may be the principal complaint and may last for years.

and the other cold injuries. So-called first and second degree frostbites are mild injuries showing anesthesia and edema followed by a hyperemic stage with edema, paresthesia and anhydrosis, a clinical course identical to that of mild immersion foot.

Mechanisms of Cold Injury

- YES: Ice crystals break cell membranes… *BUT ALSO:*

- **VASOCONSTRICTION**: conserve heat but accelerate cold injury, tissue hypoperfusion
- Intracellular dehydration, increased intracellular **calcium**, cellular activation *(cold platelets!)*
- Cellular **anoxia** (5℃ to freeze) – even in non-freeze injuries
- Environmental freezing: most crystals form in extravascular space
- Freeze-thaw
- Vascular stasis → **thrombosis**
- Ischemia-reperfusion

Trauma & cold injury final common pathways are common

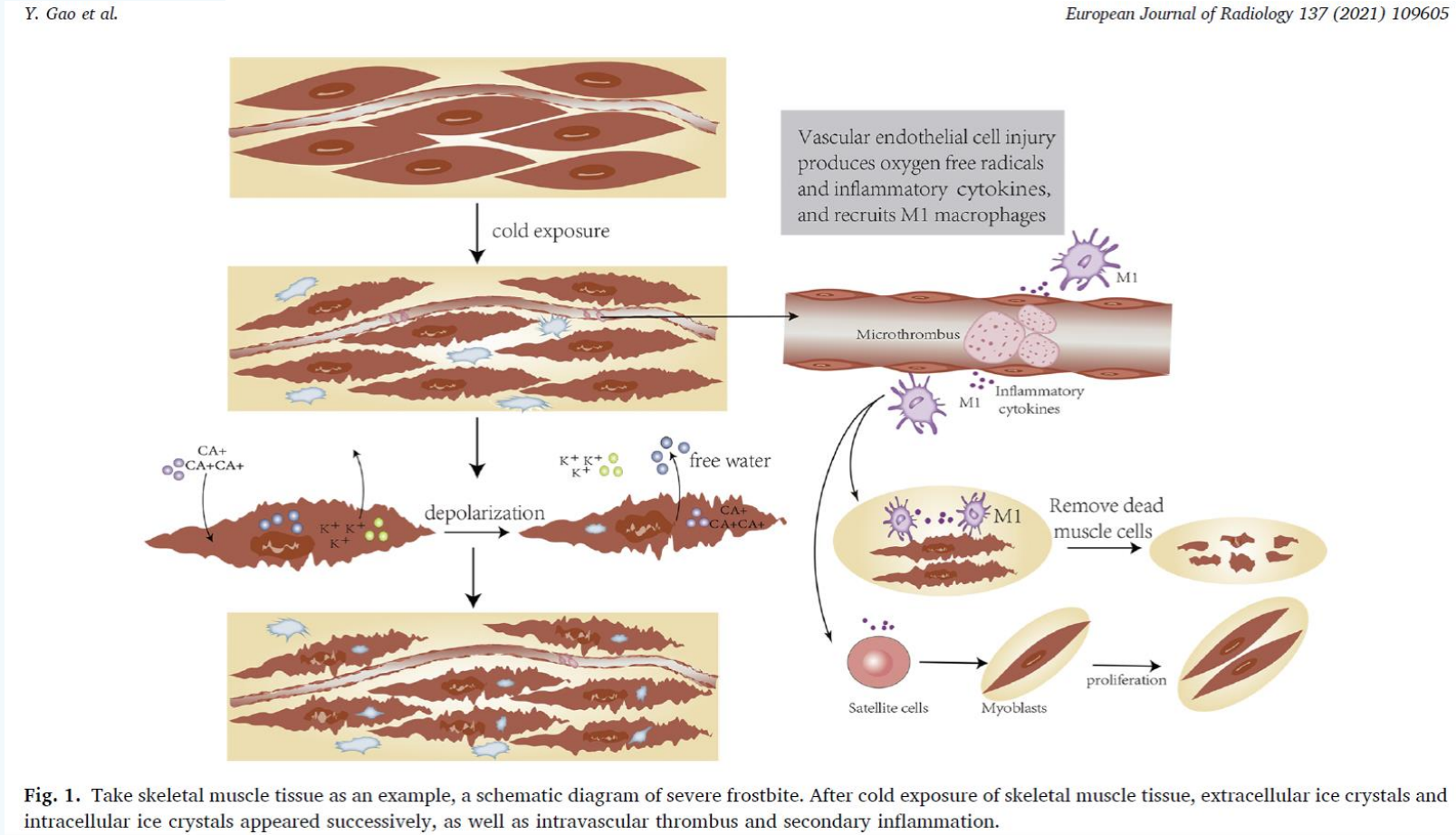


Fig. 1. Take skeletal muscle tissue as an example, a schematic diagram of severe frostbite. After cold exposure of skeletal muscle tissue, extracellular ice crystals and intracellular ice crystals appeared successively, as well as intravascular thrombus and secondary inflammation.

- Vasospasm
- Physical disruption
- Ion imbalances
- Endothelial injury
- Platelet activation
- Thrombosis (microemboli in 5min – 1hr of reperfusion)
- Ischemia/reperfusion /oxidant stress
- Vascular leak/edema
- Neural injury
- Inflammation
- Fibrosis, decreased angiogenesis

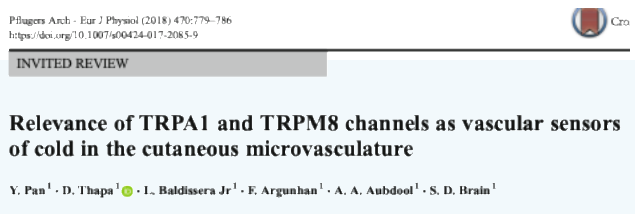
Many processes make this complicated, but this also implies opportunities for druggable targets!

Target for intervention?

- **Vasoconstriction** & Vasodilation (pallor & hyperemia); “hunting reaction”
  - How do we sense cold? **TRPA1, TRPM8 – cold receptors**; directly drive vasoconstriction and vasodilation
    - Can block constriction with dual antagonists
  - Acute cold: catecholamines increased, decreased NO: druggable targets?

➢***Strategy of early detection coupled to treatment to rewarm & reduce vasoconstriction & platelet activation?***

➢***Catch before irreversible, cold/hypoxic/thrombotic complications?***


Pflugers Arch - Eur J Physiol (2018) 470:779–786
https://doi.org/10.1007/s00424-017-2085-9

INVITED REVIEW

Relevance of TRPA1 and TRPM8 channels as vascular sensors of cold in the cutaneous microvasculature

Y. Pan[1] · D. Thapa[1] · L. Baldissera Jr[1] · F. Argunhan[1] · A. A. Aubdool[1] · S. D. Brain[1]

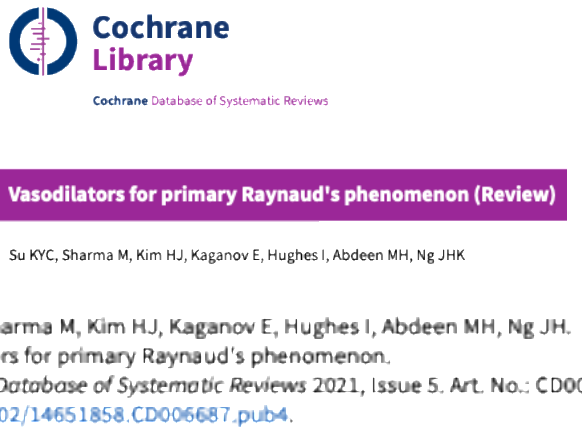
Raynaud's as a model of cold injury?

- Can we learn from similar pathophysiology to identify useful drugs?
- Do vasodilators prevent symptoms?
  - Alpha blockers: maybe some benefit
  - Prostacyclin analogues (vasodilator & antiplatelet): no benefit for beraprost (iloprost not included)
  - Phosphodiesterase inhibitors: no benefit, just headaches
  - Thromboxane synthase inhibitor: no benefit
  - Nitrates: no benefit
  - SSRIs: no benefit
  - ACEi: increase frequency of attacks!
- Current treatment (moderately effective): CCBs

➢*Is it really a good model?*

➢*Overall data quality weak…*

➢*Need to do more studies in COLD INJURY!*



Drugs for vasoconstriction?

- Acute cold: catecholamines increased, decreased NO
  - Topical 10% nifedipine: may be useful to rewarm fingers but not toes (just dump more heat)
  - Oral nifedipine: lowers BP, increases edema, equivocal results on cold injury
  - Nerve block (medical sympathectomy): vasodilation and pain relief but limited data
  - **TRPA1 & TRPM8 antagonists** not yet available
  - Prostacyclin analogue (**iloprost** – vasodilates and prevents platelet activation): *now FDA approved for use in frostbite*

- Chronic effects of cold injury: exaggerated cold sensitivity and response to catecholamines
  - Botulinum toxin may be helpful: blocks sympathetic driven vascular smooth muscle contraction so vasodilates

RESEARCH OPPORTUNITY!

FDA approval for iloprost (frostbite)!

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AURLUMYN safely and effectively. See full prescribing information for AURLUMYN.

AURLUMYN™ (iloprost) injection, for intravenous use
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
AURLUMYN is a prostacyclin mimetic indicated for the treatment of severe frostbite in adults to reduce the risk of digit amputations. Effectiveness was established in young, healthy adults who suffered frostbite at high altitudes (1.1).

----------DOSAGE AND ADMINISTRATION----------
- Initiate intravenous infusion at 0.5 ng/kg/minute and titrate in 0.5 ng/kg/minute increments based on tolerability at intervals of 30 minutes to a maximum of 2 ng/kg/minute (2.1).
- Administer as continuous infusion for 6 hours each day up to a maximum of 8 consecutive days (2.1).
- Patients with moderate or severe hepatic impairment (Child-Pugh Class B or C): initiate infusion at 0.25 ng/kg/minute and titrate as described above (2.3).
- Patients with renal impairment with eGFR less than 30 mL/min: initiate infusion at 0.5 ng/kg/minute and titrate as described above. If the patient cannot tolerate the starting dose of 0.5 ng/kg/minute, the dose can be decreased to 0.25 ng/kg/minute (2.4).
- See Full Prescribing Information for instructions on preparation and administration (2.2).

14.1 Frostbite

The efficacy of intravenous (IV) iloprost for the treatment of severe frostbite to reduce the risk of digit amputations is derived from a published open-label, randomized controlled trial that enrolled patients with severe frostbite (Cauchy et al, 2011; Cheguillaume, 2011)[1]. Severe frostbite was defined as having at least one digit (finger or toe) with frostbite stage 3 (lesion extending just past the proximal phalanx) or stage 4 (lesion extending proximal to the metacarpal or metatarsal joint).

The trial randomized 47 patients at a single site between 1996 and 2008. At enrollment, all eligible patients (n=47) were treated with rapid rewarming of areas with frostbite, aspirin 250 mg IV, and buflomedil 400 mg IV and then randomized to Groups A, B or C. All patients continued to receive aspirin 250 mg IV daily up to 8 days. In addition, Group A (n=15) received buflomedil 400 mg IV for up to 8 days, Group B (n=16) received iloprost IV for 6 hours daily for up to 8 days, and Group C (n=16) received recombinant tissue plasminogen activator IV on Day 1 and iloprost IV for 6 hours daily for up to 8 days.

The mean age of the study population was 33 years (range: 18-55 years), 94% were men, 96% sustained frostbite during sports activities, 6% had history of smoking, and none had diabetes. At randomization,

[1] Cauchy, E., et al. (2011). A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. N Engl J Med 364, 189-190; Cheguillaume, B. (2011). Controlled trial of iloprost and iloprost and rt-PA in the treatment of severe frostbite. Grenoble School of Medicine Thesis. HAL, https://dumas.ccsd.cnrs.fr/dumas-00618697.

Combined cold & trauma DCR

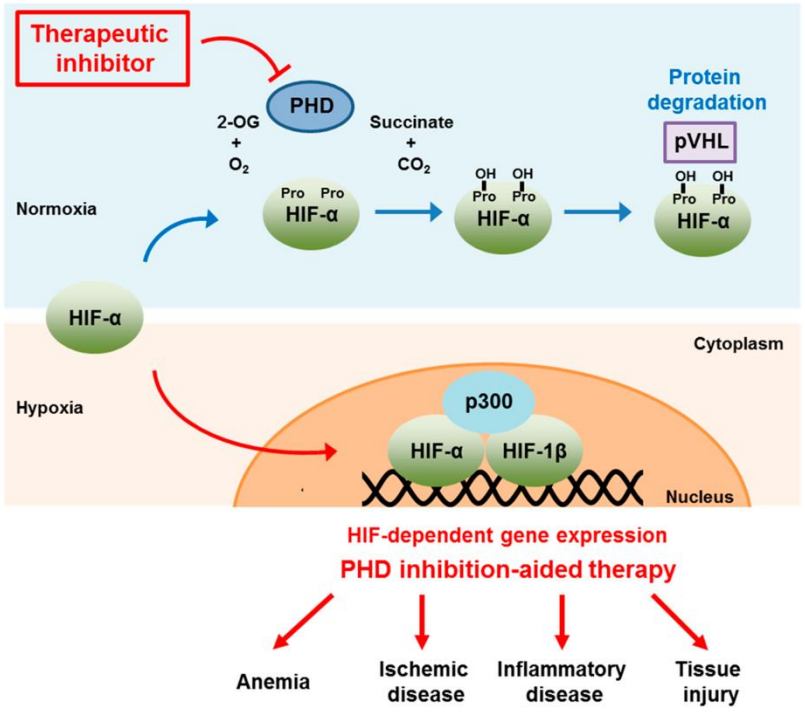
- **Immediate hemostasis due to freezing but rebleed from cold damaged tissue**
  - Hypothermia-induced coagulopathy
  - Bradycardia and systemic vasoconstriction complicate resuscitation
  - V-fib risk at body temp <30 ° C
  - Apnea = death
  - Trauma-induced Coagulopathy, endotheliopathy
- **ECMO** shows promise for organ support and rewarming
  - Anticoagulation challenge in trauma, far forward care
- **Major component of combined injury is tissue hypoxia & endothelial injury**
  - **Shock drugs** for metabolic reprogramming, stabilization (PHDi, others)
  - **Vascular integrity stabilizers** (TIE2 agonists, bradykinin & histamine blockade, protein C)

Cold-Induced Multi-organ Failure

- Cardiac instability frequently lethal
  - Optimal combination of rewarming and pharmaceutical stabilization?
- Cold pulmonary injury? Treat like inhalation injury?
- CNS hypothermia management? Cerebral edema with IRI?
- **Severe mismatch between TCCC → Role2/3 capabilities and challenges!**
  - Military fieldable diagnostics
  - Optimized drug therapy
  - Decision support

Treating cold metabolic failure

- HIF stabilizers?
- Tissue anoxia a major driver cold injury…



scientific reports

Check for updates

OPEN

Prolyl hydroxylase domain inhibitor is an effective pre-hospital pharmaceutical intervention for trauma and hemorrhagic shock

Xiaowu Wu[1,2], Andrew P. Cap[1], James A. Bynum[2], Tiffani C. Chance[3], Daniel N. Darlington[1] & Michael A. Meledeo[1]

Pre-hospital potentially preventable trauma related deaths are mainly due to hypoperfusion-induced tissue hypoxia leading to irreversible organ dysfunction at or near the point of injury or during transportation prior to receiving definitive therapy. The prolyl hydroxylase domain (PHD) is an oxygen sensor that regulates tissue adaptation to hypoxia by stabilizing hypoxia inducible factor (HIF). The benefit of PHD inhibitors (PHDi) in the treatment of anemia and lactatemia arises from HIF stabilization, which stimulates endogenous production of erythropoietin and activates lactate recycling through gluconeogenesis. The results of this study provide insight into the therapeutic roles of MK-8617, a pan-inhibitor of PHD-1, 2, and 3, in the mitigation of lactatemia in anesthetized rats with polytrauma and hemorrhagic shock. Additionally, in an anesthetized rat model of lethal decompensated hemorrhagic shock, acute administration of MK-8617 significantly improves one-hour survival and maintains survival at least until 4 h following limited resuscitation with whole blood (20% EBV) at one hour after hemorrhage. This study suggests that pharmaceutical interventions to inhibit prolyl hydroxylase activity can be used as a potential pre-hospital countermeasure for trauma and hemorrhage at or near the point of injury.

Molecules **2015**, *20*(11), 20551-20568; https://doi.org/10.3390/molecules201119717

Need an integrated approach to combined injury

Prevent, Detect, Early Intervention, Salvage Treatment→ RTD

- Prevent (mitigate) what? [**PPE/shelter**/transport modalities]
  - Injury to prehospital providers
  - Iatrogenic cold injury to patient (on top of shock)
- Detect progressive cold injury/hypothermia in healthy & injured
  - **Thermography, wearable sensors,** etc.?
- Early intervention to prevent progression
  - **Rewarming** plus **meds: target vascular dysfunction & metabolic failure**
  - **Tourniquet**: when? how? management of limb?
  - Effects of TCCC drugs (ketamine, TXA)

Need more research!


Questions?