# Boosting Temperature, Heat Shock Proteins and Nitric Oxide as Potential Strategies Against RNA Viruses

Dr. James J. DiNicolantonio

**Affiliation:** Saint Luke's Mid America Heart Institute

**Abstract**

Sauna use has been associated with a lower risk of numerous infections including the common cold, influenza and pneumonia. Fever is the body's first line defense against an infection and sauna sessions artificially induce fevers by increasing core body temperature. By boosting core body temperature, sauna therapy activates heat shock proteins, which have been shown to bind to viral ribonucleoprotein complexes preventing their export and reducing viral replication. Sauna sessions also stimulate the immune system and increase the cytotoxicity of immune cells. This paper will review the mechanistic, observational and clinical data surrounding the antiviral effects of sauna and other heat therapies.

## Introduction: Common cold, influenza and coronaviruses

On average, children have six to eight colds per year and adults have two to four.[1] This has a significant economic and personal cost. Influenza causes up to 500,000 deaths worldwide annually, 90% of which occur in the elderly (65 and older).[2] The common cold, influenza, and coronavirus are all RNA viruses. However, the difference between influenza and SARS-CoV-2, is that the latter is more contagious (1.3 vs. 2-2.5 individuals infected per person). Considering that millions of people are infected with RNA viruses annually and hundreds of thousands of people die every year from them, strategies that could reduce the incidence and/or severity of common colds, influenza and coronaviruses would be welcomed.

## Fever: An ancient ally against infections

Fever has been a conserved response to infections in both warm and cold-blooded vertebrates for over 600 million years of evolution.[3] Animals infected with viruses or bacteria have better survival rates when a fever is elicited.[4] Elevation in body temperature, for example, an infection-induced fever, enhances the immune system by increasing white blood cell mobility, lymphocyte transformation and interferon production, which helps to produce antiviral antibodies. Additionally, fever stimulates the production of heat shock proteins to help inhibit viral replication[5-7] and decrease proinflammatory cytokines.[8] Thus, fever, or moderate elevations in body temperature, are beneficial to the infected host.[4] Indeed, temperatures of ~ 104° Fahrenheit can reduce the replication of poliovirus in mammalian cells by 200-fold and increase the susceptibility of Gram-negative bacteria to serum-induced lysis.[3]

Animals infected with viruses have an approximate 4-fold increase in mortality when fever is inhibited with antipyretic medications.[3] In humans, inhibiting a fever with the use of antipyretic medications is associated with an increased risk of influenza infections and mortality and an increased risk of death in patients in the intensive care unit.[9, 10] However, it should be noted that fever is not universally beneficial, especially in out of control fevers (generally above 104° Fahrenheit) or fever in septic shock. [3] Thus, there is a delicate balance in the fever response as being a friend or foe during an infection. Even so, in general, the overall data suggests that a moderate fever is beneficial during an infection and that inhibiting a fever worsens outcomes.

**Hyperthermia: Inducing an exogenous fever with sauna therapy to reduce viral replication and activate the immune system**

Hyperthermia is a rise in body temperature above normal but unlike a fever there is not an increase in the thermoregulatory set-point. While there is no standard definition or cut-off for hyperthermia, typically a body temperature > 99.5° Fahrenheit constitutes hyperthermia.[11] Similarly, any rise in body temperature above normal technically constitutes as a fever. However, from a clinical perspective, fevers are not considered significant until they reach a level of ~ 100.5° Fahrenheit. Thus, hyperthermia is a way to mimic a fever by artificially raising one's core body temperature. And the most efficient way to induce hyperthermia would be through the use of sauna therapy. Thus, there is sound reasoning that inducing hyperthermia with sauna therapy to raise core body temperature to mimic a fever can have benefits on the immune system. Furthermore, the clinical evidence in humans supports this idea.

Since at least 1957 evidence has suggested that sauna therapy may help prevent influenza infection.[12] Since then, numerous studies have linked sauna bathing with a multitude of health benefits. For example, a prospective study in nearly 2,000 Caucasian men with nearly 26 years of follow-up found a 27% and 41% reduction in respiratory diseases, respectively, in participants who had 2-3 and $\geq$ 4 sauna sessions per week compared to those who had $\leq$ 1 sauna session per week.[13] The same authors also noted a 33% and a 47% reduction in the risk of pneumonia, respectively.[14] One review article concluded, "Regular visits to the sauna significantly reduce the frequency and severity of influenza infections in children and adults."[15] Even the mitigation of typhus fever in Finland during World War II was noted with sauna therapy, "The main method of typhus prevention in Finland consisted of regular sauna bathing, which was culturally acceptable and very efficient when combined with heating of the clothing. The Finnish troops remained virtually louse-free by ecological and traditional methods, and thus the spread of typhus fever in the army could be prevented."[16] Finally, a clinical study in 50 patients noted an approximate halving in the incidence of common cold episodes during the last three months of the study in those who were given sauna therapies for several months versus those who were not.[17] Thus, sauna therapy may reduce the incidence and severity of the common cold, influenza and pneumonia in humans.

**Hyperthermia induces heat shock proteins and increases type 1 interferon activity**

Mice that are heat shocked several times (placed in an incubator at 102.2° Fahrenheit) prior to being infected with H5N1 influenza virus have significant reductions in viral replication, lung pathology, and mortality.[18] These benefits appear to be due to upregulation of heat shock protein-70 (HSP70) levels in lung tissues and inhibition of viral replication by blocking the export of the viral ribonucleoprotein complex. Essentially, viral nucleoproteins combine with RNA polymerases to form a viral ribonucleoprotein complex which must be exported for viral replication.[5] However, hyperthermia-induced release of HSP70 inhibits the export of this complex and hence viral replication.[5-7] Thus, sauna therapy may help reduce the severity of RNA viral infections by inhibiting their replication. Even bacterial infections are improved when hyperthermia is used prior to infection.[19, 20]

The increase in heat shock proteins (HSPs) with hyperthermia stimulates both the innate and adaptive immunity. This helps to activate monocytes, dendritic cells, and macrophages, inducing the production of pro-inflammatory cytokines such as interleukin-6 and TNF-alpha secretion for killing pathogens and improves antigen presentation for cell-mediated immune killing.[18]

**Individuals susceptible to RNA viruses have reduced type 1 interferon activity, which may be rescued by hyperthermia**

When influenza infected blood monocytes are compared from young and old adults, both have intact proinflammatory cytokine but older adults have a reduced type 1 interferon response.[2] Type 1 interferons, such as interferon-alpha and beta, help our bodies make antiviral antibodies and activate our immune system. Thus, a hallmark of an aging or a dysfunctional immune system is elevated proinflammatory cytokines and decreased type 1 interferons. This is a recipe for a cytokine storm in the lungs and acute respiratory distress and death. However, hyperthermia, as with sauna therapy, may improve this defect.

For example, it has been known since 1978 that, “The antiviral/antiproliferative/antitumor properties of interferon are potentiated by a febrile temperature.”[21] Human cell culture studies have shown that mild hyperthermia increases the antiviral effect of interferon by 3 to 10 fold.[21] Moreover, hyperthermia has been shown to improve both the antiviral and antiproliferative activity of all three human interferons.[22] In fact, just 15 minutes in a sauna can dramatically stimulate the immune system, increasing the number of white blood cells, lymphocytes, neutrophils and basophil counts.[23] Local hyperthermia has been successfully used to treat viral warts; benefits which seem to be due to an increase in the expression of type 1 interferons and downstream antiviral enzymes.[24] The authors of the study concluded, “Local hyperthermia was proved effective in treating human papillomavirus-infected skin. These results suggested that hyperthermia took effect partly by inducing the expression of local endogenous interferons and partly by subsequent interferon-induced antiviral activity…”[24] Many viruses employ a range of mechanisms to avoid induction of type 1 interferons,[25, 26] hence strategies that can mitigate these effects, such as hyperthermia, may provide significant benefit.

The threshold for inducing thermal stress and eliciting many of the immune-stimulating benefits with hyperthermia seems to occur when the core body temperature reaches ~ 100.4° Fahrenheit, a temperature that can easily be reached with sauna therapy.[23] It should be stressed, that sauna therapy would have the greatest potential if utilized prior to an infection, or early in the course of an infection.

**The antiviral benefits of sauna therapy may be partially mediated through nitric oxide**

Nitric oxide has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus (SARS) by inhibiting viral protein and RNA synthesis and SARS coronavirus replication cycle.[27] One study concluded, "Nitric oxide (NO) inhibits the replication of SARS-CoV by two distinct mechanisms. Firstly, nitric oxide or its derivatives cause a reduction in the palmitoylation of nascently expressed spike (S) protein which affects the fusion between the S protein and its cognate receptor, angiotensin converting enzyme 2. Secondly, nitric oxide or its derivatives cause a reduction in viral RNA production in the early steps of viral replication..."[28] In other words, nitric oxide inhibits the entry and replication of SARS-CoV. In fact, during the 2003 severe acute respiratory syndrome (SARS) outbreak, inhaled nitric oxide was used to rescue patients in Beijing, China, improving arterial oxygenation and reducing the need of inspired oxygen therapy and airway pressure support. More importantly, chest radiography showed a decreased spread of lung infiltrates with benefits persisting even after termination of inhaled nitric oxide therapy.[29]

Sauna therapy is well known for boosting nitric oxide.[30] The ability of sauna therapy to increase the expression of eNOS (and nitric oxide),[31, 32] endogenous antioxidant systems[33] and suppress oxidative stress[30, 34] would help to increase type 1 interferons[26] and lower the uncoupling of eNOS[35], the latter of which can lead to endothelial barrier dysfunction and acute lung injury during RNA viral infections.[35] Thus, sauna therapy may have additional antiviral effects via increased nitric oxide production.

**Inhaling hot air may help reduce common cold symptoms**

There also appears to be specific benefits of inhaling hot air. For example, in one randomized single-blind controlled trial in patients with a newly acquired common cold despite both groups being placed in a hot sauna at 194° Fahrenheit with winter coats on, inhaling hot dry sauna air through the mouth versus dry air from outside (75.2° Fahrenheit) showed significant benefits for symptoms severity score on Day 2, the proportion of participants who took medication for the common cold on Day 1 and participants rating of effectiveness on Day 7.[36] The overall findings on symptom severity of the common cold were not significantly improved, however, this may be due to several factors including sessions of just 3 minutes and both groups sitting in a hot sauna with winter coats on. Furthermore, inhaling the hot air through the mouth, instead of the nose, may have reduced the effectiveness of the therapy as many RNA viruses harbor in the nasal and sinus passages replicating in these cooler areas during the initial infection.

In a randomized, double-blind trial of cold sufferers, compared to inhaling fully humidified warm air from an apparatus for 20 minutes at 86° Fahrenheit, inhaling hot air at 109.4° Fahrenheit cut the score for acute nasal and upper respiratory symptoms roughly in half in the succeeding days.[37] In those treated for 30 minutes on three occasions when they were starting a cold an 18% reduction in symptoms occurred, whereas being treated for 20 minutes at onset of the cold and 10 minutes on succeeding days showed no difference between groups. The authors concluded, "Nasal hyperthermia can improve the course of the common cold and also give immediate relief of symptoms."[37]

The additional benefits of breathing high heat may be due to direct antiviral effects at high temperatures. Indeed, hyperthermic treatment at 20 minutes utilizing 113° Fahrenheit temperatures suppresses human rhinovirus replication by more than 90%.[7] And the World Health Organization has noted, "Heat at 56°C (113°F, *our insertion*) kills the SARS coronavirus at around 10,000 units per 15 minutes (quick reduction)."[38] Thus, sauna and other hyperthermic treatments may work via activation of heat shock proteins but also through direct antiviral effects of increased temperatures in the nose and throat.

**Conclusion**

Sauna, and other heat therapies, may have a significant role in improving immunity, especially in those who are most susceptible to RNA viruses by combating the defect in type 1 interferon response. Considering that sauna use has been found to reduce the number of common colds and is associated with a lower risk of influenza and pneumonia further interventional studies should be performed to ascertain its antiviral potential during the COVID-19 pandemic.

References:

1 Lissiman E, Bhasale AL, Cohen M. Garlic for the common cold. *The Cochrane database of systematic reviews* 2014:Cd006206.
2 Pillai PS, Molony RD, Martinod K, et al. Mx1 reveals innate pathways to antiviral resistance and lethal influenza disease. *Science* 2016;352:463-6.
3 Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat Rev Immunol* 2015;15:335-49.
4 Kluger MJ. Fever. *Pediatrics* 1980;66:720-4.
5 Hirayama E, Atagi H, Hiraki A, et al. Heat shock protein 70 is related to thermal inhibition of nuclear export of the influenza virus ribonucleoprotein complex. *J Virol* 2004;78:1263-70.
6 Li G, Zhang J, Tong X, et al. Heat shock protein 70 inhibits the activity of Influenza A virus ribonucleoprotein and blocks the replication of virus in vitro and in vivo. *PLoS One* 2011;6:e16546.
7 Conti C, De Marco A, Mastromarino P, et al. Antiviral effect of hyperthermic treatment in rhinovirus infection. *Antimicrob Agents Chemother* 1999;43:822-9.
8 Ryan M, Levy MM. Clinical review: fever in intensive care unit patients. *Crit Care* 2003;7:221-5.
9 Earn DJ, Andrews PW, Bolker BM. Population-level effects of suppressing fever. *Proc Biol Sci* 2014;281:20132570.
10 Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg Infect (Larchmt)* 2005;6:369-75.
11 Axelrod YK, Diringer MN. Temperature management in acute neurologic disorders. *Crit Care Clin* 2006;22:767-85; abstract x.
12 Hartmann A. [Asiatic flu in 1957; sauna baths as prophylactic measure]. *Hippokrates* 1958;29:153-4.
13 Kunutsor SK, Laukkanen T, Laukkanen JA. Sauna bathing reduces the risk of respiratory diseases: a long-term prospective cohort study. *Eur J Epidemiol* 2017;32:1107-11.
14 Kunutsor SK, Laukkanen T, Laukkanen JA. Frequent sauna bathing may reduce the risk of pneumonia in middle-aged Caucasian men: The KIHD prospective cohort study. *Respir Med* 2017;132:161-3.
15 Brenke R. [Not Available]. *Forschende Komplementarmedizin (2006)* 2015;22:320-5.
16 Laurent H. Control of typhus fever in Finland during World War II. *Vesalius* 2009;15:71-9.
17 Ernst E, Pecho E, Wirz P, et al. Regular sauna bathing and the incidence of common colds. *Ann Med* 1990;22:225-7.
18 Xue J, Fan X, Yu J, et al. Short-Term Heat Shock Affects Host-Virus Interaction in Mice Infected with Highly Pathogenic Avian Influenza Virus H5N1. *Frontiers in microbiology* 2016;7:924.
19 Wojda I, Taszlow P. Heat shock affects host-pathogen interaction in Galleria mellonella infected with Bacillus thuringiensis. *J Insect Physiol* 2013;59:894-905.
20 Taszlow P, Wojda I. Changes in the hemolymph protein profiles in Galleria mellonella infected with Bacillus thuringiensis involve apolipophorin III. The effect of heat shock. *Arch Insect Biochem Physiol* 2015;88:123-43.

21 Chang CC, Wu JM. Modulation of antiviral activity of interferon and 2',5'-oligoadenylate synthetase gene expression by mild hyperthermia (39.5 degrees C) in cultured human cells. *J Biol Chem* 1991;266:4605-12.
22 Payne J, Nair MP, Ambrus JL, et al. Mild hyperthermia modulates biological activities of interferons. *Int J Hyperthermia* 2000;16:492-507.
23 Pilch W, Pokora I, Szygula Z, et al. Effect of a single finnish sauna session on white blood cell profile and cortisol levels in athletes and non-athletes. *Journal of human kinetics* 2013;39:127-35.
24 Zhu LL, Gao XH, Qi R, et al. Local hyperthermia could induce antiviral activity by endogenous interferon-dependent pathway in condyloma acuminata. *Antiviral Res* 2010;88:187-92.
25 Weber F, Mirazimi A. Interferon and cytokine responses to Crimean Congo hemorrhagic fever virus; an emerging and neglected viral zonoosis. *Cytokine Growth Factor Rev* 2008;19:395-404.
26 McCarty MF, DiNicolantonio JJ. Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. *Prog Cardiovasc Dis* 2020.
27 Akerstrom S, Mousavi-Jazi M, Klingstrom J, et al. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. *J Virol* 2005;79:1966-9.
28 Akerstrom S, Gunalan V, Keng CT, et al. Dual effect of nitric oxide on SARS-CoV replication: viral RNA production and palmitoylation of the S protein are affected. *Virology* 2009;395:1-9.
29 Chen L, Liu P, Gao H, et al. Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing. *Clin Infect Dis* 2004;39:1531-5.
30 Gryka D, Pilch WB, Czerwinska-Ledwig OM, et al. The influence of Finnish sauna treatments on the concentrations of nitric oxide, 3-nitrotyrosine and selected markers of oxidative status in training and non-training men. *Int J Occup Med Environ Health* 2020;33:173-85.
31 Huang PH, Chen JW, Lin CP, et al. Far infra-red therapy promotes ischemia-induced angiogenesis in diabetic mice and restores high glucose-suppressed endothelial progenitor cell functions. *Cardiovasc Diabetol* 2012;11:99.
32 Ikeda Y, Biro S, Kamogawa Y, et al. Repeated sauna therapy increases arterial endothelial nitric oxide synthase expression and nitric oxide production in cardiomyopathic hamsters. *Circ J* 2005;69:722-9.
33 Lin CC, Liu XM, Peyton K, et al. Far infrared therapy inhibits vascular endothelial inflammation via the induction of heme oxygenase-1. *Arterioscler Thromb Vasc Biol* 2008;28:739-45.
34 Brunt VE, Eymann TM, Francisco MA, et al. Passive heat therapy improves cutaneous microvascular function in sedentary humans via improved nitric oxide-dependent dilation. *Journal of applied physiology (Bethesda, Md : 1985)* 2016;121:716-23.
35 Wu F, Szczepaniak WS, Shiva S, et al. Nox2-dependent glutathionylation of endothelial NOS leads to uncoupled superoxide production and endothelial barrier dysfunction in acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2014;307:L987-97.

36 Pach D, Knochel B, Ludtke R, et al. Visiting a sauna: does inhaling hot dry air reduce common cold symptoms? A randomised controlled trial. *Med J Aust* 2010;193:730-4.
37 Tyrrell D, Barrow I, Arthur J. Local hyperthermia benefits natural and experimental common colds. *BMJ* 1989;298:1280-3.
38 First data on stability and resistance of SARS coronavirus compiled by members of WHO laboratory network. https://www.who.int/csr/sars/survival_2003_05_04/en/. Accessed March, 21, 2020.