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Regular thermal therapy may promote insulin sensitivity while boosting expression of endothelial nitric oxide synthase – Effects comparable to those of exercise training

Mark F. McCarty [a,b,*], Jorge Barroso-Aranda [b], Francisco Contreras [b]

[a] Natural Alternatives International, 1185 Linda Vista Dr., San Marcos, CA 92078, USA
[b] Oasis of Hope Hospital, Tijuana, Mexico

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SUMMARY

Regular thermal therapy, using saunas or hot baths, has the potential to improve impaired insulin sensitivity and boost endothelial expression of the "constitutive" isoform of nitric oxide synthase – effects, analogous to those of aerobic training that should promote vascular health. Previous clinical reports suggest that hot tubs may be beneficial for diabetic control, and that sauna therapy can decrease blood pressure in essential hypertension and provide symptomatic benefit in congestive heart failure. For those who lack ready access to a sauna or communal hot tub, regular hot baths at home may suffice as practical thermal therapy. Thermal therapy might be viewed as an alternative to exercise training in patients too physically impaired for significant aerobic activity.

Thermal therapy promotes insulin sensitivity via Hsp72 induction

There is recent evidence that thermal induction or overexpression of heat shock protein 72 (hsp72) can counter high fat diet-induced insulin resistance in mice by suppressing activation of N-terminal-Jun kinase (JNK) in skeletal muscle [1]. Indeed, there are numerous reports that hsp72 can function as an inhibitor of JNK [2–5], and fat-mediated activation of JNK, leading to phosphorylation of S307 in IRS-1, is now believed to be a key mediator of fat-induced insulin resistance in skeletal muscle [6–11]. This may rationalize a clinical report that glycemic control improves in diabetic patients (type 2) receiving regular hot tub treatments [12]. Further clinical evaluation of the impact of thermal therapy on insulin resistance in overweight humans is clearly warranted. Intriguingly, skeletal muscle expression of hsp72 mRNA tends to be decreased in patients with type 2 diabetes as compared to healthy age-matched controls [13], and, in a recent Tunisian study, a polymorphism of hsp72 have been linked to increased diabetes risk [14].

Endothelial nitric oxide synthase is heat-inducible

Moreover, several reports conclude that the endothelial isoform of nitric oxide synthase (eNOS) is induced in cultured endothelial cells and cardiomyocytes exposed to mild heat (42 °C) [15,16]. Conversely, inhibition of hsp90 with geldanamycin markedly decreases the transcription of eNOS, without altering the half-life of its mRNA [17]. While these findings suggest that thermal induction of hsp90 mediates the thermally mediated increase in eNOS transcription, a two-fold increase in eNOS protein level was reported in heat-treated bovine endothelial cells in the absence of significant hsp90 induction [16]; thus, whereas hsp90 function appears to be important for basal levels of eNOS transcription, heat treatment may promote eNOS expression through mechanisms independent of hsp90 induction. In any case, eNOS appears to function as a heat shock protein – though there is currently no evidence that the eNOS promoter is activated by heat shock factor-1.

Importantly, endothelial expression of eNOS protein is boosted about 40% *in vivo* in hamsters given daily tolerable heat treatments (15 min of infrared sauna) that raise core temperature by about 1 °C; a marked increase in eNOS mRNA is also observed [18,19]. The authors of these hamster studies suggest that increased blood flow, leading to increased endothelial shear stress, is responsible for this induction; however, as cell culture studies have shown, heat exposure per se may contribute to this inductive effect. It may be feasible to achieve this effect in humans as well – in subjects with cardiovascular risk factors who underwent daily sauna treatment for 2 weeks (15 min of 60 °C infrared sauna followed by 30 min covered with blankets), endothelium-dependent vasodilation was found to increase significantly [20]. This effect has also been observed in patients with congestive heart failure, in whom clinical symptoms also improved and plasma levels of brain natriuretic factor decreased, suggesting improved cardiac function [21]. In genetically cardiomyopathic hamsters, regular sauna therapy improved survival [19].

* Corresponding author. Address: Natural Alternatives International, 1185 Linda Vista Dr., San Marcos, CA 92078, USA.
E-mail address: mccarty@pantox.com (M.F. McCarty).

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To the extent that thermal therapy also increases endothelial expression of hsp90, this may enhance and improve the activity of eNOS independent of any change in eNOS expression. Thus, by acting as a scaffolding protein linking eNOS to enzymes which target it, hsp90 improves the efficiency with which Akt phosphorylates S1177 of eNOS and calcineurin dephosphorylates T495 – effects which boost eNOS activity [22,23]. Furthermore, association with hsp90 appears to reduce the propensity of eNOS to generate superoxide – improving the quality of its activity [24]. Perhaps this effect plays a role in the observation that a systemic marker of oxidative stress (urinary 8-epi-prostaglandin F-2alpha) declines following regular sauna therapy in patients with high baseline levels of oxidant stress [25].

Benefits analogous to aerobic training

Two of the most important benefits of aerobic training are an increase in muscle insulin sensitivity (primarily in the exercised muscles) and an increase in endothelial expression of eNOS. The improvement in insulin sensitivity is mediated in large part by increased expression of GLUT4, PI3 kinase, and certain other signaling intermediates activated by insulin [26–28] – an effect quite different, but likely complementary to, the impact of thermal treatment on fat-induced insulin resistance. The effect of exercise on eNOS expression is mediated by a temporary increase in endothelial shear stress, which enhances the half-life and translatability of the eNOS mRNA via increased 3' polyadenylation [29,30]; whether heat stress influences this polyadenylation is unknown, although hsp90 activity does not appear to. In any case, it seems likely that aerobic training and regular thermal therapy could exert complementary effects on both insulin sensitivity and eNOS expression – key determinants of vascular health. Sauna also resembles exercise training in that it induces a temporary increase in cardiac output and workload [31]. Increased heart rate variability has been reported after both regular sauna treatment and aerobic training [32,33].

In individuals too physically impaired to achieve effective aerobic training, the possibility that regular thermal therapy might represent a feasible alternative, providing somewhat similar benefits for vascular health, merits consideration, as suggested by Tei and colleagues [34]. Granted, there is little reason to suspect that thermal therapy would provide the weight control benefits associated with aerobic training. Surprisingly, however, Tei reports that obese subjects tend to lose body fat during several weeks of daily sauna treatment [34]; whether this observation can be replicated in well controlled trials remains to be seen.

Thermal therapy for hypertension

Since insulin resistance and impaired activity of eNOS both play a role in the pathogenesis of essential hypertension, one would anticipate that regular thermal therapy could lower blood pressure in overweight insulin-resistant hypertensives. The utility of exercise training in this regard is well known [35]. Indeed, in a series of investigations with moderately hypertensive patients, Winterfeld and colleagues have reported that twice-weekly sauna bathing for 3 months was associated with significant reductions in resting systolic and resting diastolic pressure, averaging 20–23 mmHg and 14–18 mmHg, respectively [36–38]; these results were at least as large as those seen in control groups asked to run twice weekly. Significant reductions in blood pressure – both systolic and diastolic – have also been reported in hamsters given daily sauna treatments [18].

Other measures with potential for increasing eNOS expression include supplemental fish oil (more specifically, DHA) [39,40] and statin therapy [41–43] – both of which can lower elevated blood pressure [44,45]. The health-protective utility of newly-induced eNOS may be promoted by supplementation with high-dose folic acid, which helps to insure that eNOS generates nitric oxide rather than superoxide when tetrahydrobiopterin availability is suboptimal [46–48].

Practical implementation and contraindications

Since many people do not have ready access to a sauna or communal hot tub, a reasonable alternative may simply be the hot bath. In most tubs, it is feasible to submerge all of the body except the head and knees; 15 min of a hot bath, followed by about half an hour under a warm blanket (as suggested by Tei following sauna [34]), would likely constitute a useful thermal therapy. Hot baths are somewhat enervating, so they are best taken in the evening prior to bedtime. Care should be taken to arise only gradually after a hot bath, so as to avoid orthostatic hypotension.

Much like aerobic exercise, thermal therapy imposes a physiological stress that is not appropriate for all subjects. Nguyen et al. list the following contraindications for sauna: unstable angina, recent myocardial infarction, decompensated heart failure, cardiac arrhythmias, uncontrolled hypertension, and severe aortic stenosis [49].

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