Editorial Focus: Acute hot water immersion is protective against impaired vascular function following forearm ischemia-reperfusion in young healthy humans

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Running Title: Editorial Focus

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Ischemia occurs when arterial blood flow is insufficient to meet the metabolic demands of the target tissue, resulting in a series of coordinated molecular, cellular, tissue-specific and systemic events that cause tissue damage. Paradoxically, reperfusion that occurs following ischemia can exacerbate tissue injury and necrosis. The detrimental effects of reperfusion injury were first observed more than 50 years ago, where reperfusion appeared to accelerate the development of necrosis in hearts subjected to coronary ligation (9). More recently, the dramatic effects of ischemia reperfusion (I/R) have been highlighted, suggesting that reperfusion injury can account for up to 50% of myocardial infarct size (17). I/R leads to a cascade of events, resulting in an increase in oxidative and nitrosative stress, inflammation, and endothelial dysfunction. Common settings in which I/R occur include thrombolytic therapy, angioplasty, organ transplant, and major trauma/shock. Consequently, much research has sought to identify therapeutic strategies to minimize this component of tissue injury. Currently, post-ischemic strategies are used, including mild therapeutic hypothermia, which has been reported to benefit patients following cardiac arrest (17). However, novel strategies to prevent and/or mitigate the effects of I/R injury are necessary, as the incidence of ischemic events is increasing.

A growing body of evidence from clinical trials demonstrates the effectiveness of pre-ischemic preventive strategies to blunt the effects of I/R injury. These include, ischemic preconditioning (10), inhibition of sodium-hydrogen-exchange (12) and administration of adenosine (7). Interestingly, a single bout of high-intensity interval exercise was also protective against impaired brachial artery vascular function following I/R (14). Exercise can induce a multitude of systemic effects that may benefit vascular function, including increased shear stress-mediated expression of nitric oxide synthase (NOS) and nitric oxide (NO) production (1, 6).

In this issue of the *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology*, Brunt and colleagues (4) use hot water immersion as a preventive strategy to reduce I/R induced endothelial dysfunction. This approach is counter-intuitive in light of the fact that cold therapy is commonly used during and following ischemia to limit inflammation and oxidative stress.
However, heat stress shares several common physiological effects with exercise, including increases in core body temperature, blood flow and vascular shear stress. In addition to shear stress-mediated NO synthesis, increases in core body temperature can induce expression of heat shock proteins (HSP) which also upregulate NO production (13). Therefore, when used prior to an ischemic event, acute heat stress could theoretically benefit endothelial function, thereby ameliorating impaired vascular function following I/R. Indeed, evidence suggests a benefit of chronic heat therapy on various cardiovascular outcomes in healthy (2, 5) and chronically ill populations (8, 11).

In the current study, Brunt and colleagues (4) exposed healthy, young, recreationally active participants to 60 minutes of passive heat stress (via hot water immersion) or time-matched control (seated rest in a climate-controlled 21-24°C room), followed by 60 minutes of recovery before post-intervention measures. Brachial artery flow mediated dilation (FMD) and reactive hyperemia (RH) were measured as markers of macrovascular and microvascular endothelial function, respectively. The authors found that FMD and RH responses were significantly impaired following I/R in the time-control condition. However, hot water immersion preserved endothelial function following I/R. These results suggest that acute hot water immersion prior to I/R may be protective against endothelial damage and subsequent vascular changes. Therefore, acute heat stress could be used as a preventive therapy in circumstances where it is known that blood flow will be occluded for a period of time, for example in pre-operative patient populations.

Though the current findings of Brunt and colleagues (4) are very interesting, there are a number remaining questions which future research should address. Firstly, the use of a young, healthy and fit population restricts the ability to generalise the current findings to patient populations, in which the safety and efficacy of this approach should be tested. A foreseeable issue is pre-established endothelial dysfunction, where increasing shear rate may not improve endothelial function and NO release following I/R injury. In addition, there are patient populations for which hot water immersion may be contraindicated, such as those with orthostatic intolerance, or unstable cardiovascular and cerebrovascular diseases. Secondly, inferences for the benefit of this intervention to cardiovascular
disease are based on brachial artery function being used as a surrogate for coronary artery function. Indeed, there are benefits to using brachial artery function in this context, as it can be measured non-invasively, and has been shown to correlate with coronary artery function (15, 16). However, it remains to be directly determined whether the benefits of hot water immersion extend to the coronary vasculature. The authors also did not measure biomarkers of endothelial damage such as oxidative stress or inflammatory cytokines, which would provide greater context on the extent of tissue injury following the I/R protocol used. In addition, the role of HSPs in mediating the effects of heating on endothelium function should be further investigated. HSPs, which are increased by a rise core body temperature, have a critical role in activating eNOS. Specifically HSP90 associates with eNOS to increase NO generation (13). It would, therefore, be interesting to determine whether HSPs play a role in the beneficial effects of heat stress on endothelial function in this setting. The independent hydrostatic effects of the head-out water immersion protocol should also be considered, as this would increase lower body pressure and lead to considerable cardiovascular effects such as increased cardiac output, mean arterial pressure and conduit vessel diameter. Previous studies have shown no benefit of thermoneutral water immersion for micro- or macrovascular function in chronic trials (2, 3), although this does not preclude the possibility of acute effects. Finally, if this technique was to be used pre-operatively, its effectiveness should be compared with currently used pharmacological therapies and non-pharmacological techniques such as ischemic preconditioning.

The findings of Brunt and colleagues (4) are important because they reveal a novel, inexpensive and easily accessible preventive method of minimizing the impact of I/R injury, which may help to mitigate associated detrimental vascular changes. The currently available preventive approaches to reducing I/R injury can be uncomfortable, may be contraindicated (e.g. exercise), or require pharmaceutical intervention. Therefore, acute heat stress may be a suitable alternative and warrants further investigation in patient populations.


