The health benefits of passive heating and aerobic exercise: To what extent do the mechanisms overlap?

Cullen, T., Clarke, N. D., Hill, M., Menzies, C., Pugh, C. J. A., Steward, C. J. & Thake, C. D.

Author post-print (accepted) deposited by Coventry University's Repository

Original citation & hyperlink:
Cullen, T, Clarke, ND, Hill, M, Menzies, C, Pugh, CJA, Steward, CJ & Thake, CD 2020, 'The health benefits of passive heating and aerobic exercise: To what extent do the mechanisms overlap?', Journal of Applied Physiology, vol. 129, no. 6, pp. 1304-1309.
https://dx.doi.org/10.1152/japplphysiol.00608.2020

DOI 10.1152/japplphysiol.00608.2020
ISSN 8750-7587
ESSN 1522-1601

Publisher: American Physiological Society

Copyright © and Moral Rights are retained by the author(s) and/ or other copyright owners. A copy can be downloaded for personal non-commercial research or study, without prior permission or charge. This item cannot be reproduced or quoted extensively from without first obtaining permission in writing from the copyright holder(s). The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the copyright holders.

This document is the author's post-print version, incorporating any revisions agreed during the peer-review process. Some differences between the published version and this version may remain and you are advised to consult the published version if you wish to cite from it.

The health benefits of passive heating and aerobic exercise: to what extent do the mechanisms overlap?

Tom Cullen [1*], Neil D. Clarke [1], Matthew Hill[1], Campbell Menzies[1], Christopher J. A. Pugh[2], Charles J. Steward[1], C. Douglas Thake[1]

[1] Centre for Sport Exercise and Life Sciences, Coventry University, Coventry, UK

[2] Cardiff School of Sport & Health Sciences, Cardiff Metropolitan University, Cardiff CF23 6XD, UK

Corresponding author:

Dr Tom Cullen

Centre for Sport, Exercise and Life Sciences

Coventry University

Priory Street, Coventry, UK, CV1 5FB

Email: ad0189@coventry.ac.uk

ABSTRACT

Exercise can induce numerous health benefits that can reduce the risk of chronic diseases and all-cause mortality, yet a significant percentage of the population do not meet minimal physical activity guidelines. Several recent studies have shown that passive heating can induce numerous health benefits, many of which are comparable to exercise, such as improvements to cardiorespiratory fitness, vascular health, glycaemic control and chronic low-grade inflammation. As such, passive heating is emerging as a promising therapy for populations who cannot perform sustained exercise or display poor exercise adherence. There appears to be some overlap between the cellular signalling responses that are regulated by temperature and the mechanisms that underpin beneficial adaptations to exercise, but detailed comparisons have not yet been made. Therefore, the purpose of this mini review is to assess the similarities and distinctions between adaptations to passive heating and exercise. Understanding the potential shared mechanisms of action between passive heating and exercise may help to direct future studies to implement passive heating more effectively and identify differences between passive heating and exercise induced adaptations.

Key words: heat, therapy, exercise, health, adaptation

Introduction

Physical inactivity increases the risk of several chronic diseases, such as cardiovascular disease, type 2 diabetes and obesity (4). In contrast, regular exercise elicits a variety of health benefits and attenuates traditional cardiovascular disease risk factors, including blood pressure and body weight/adiposity, as well as improved blood lipid profiles, insulin sensitivity and cardiorespiratory fitness (43). More recently, this understanding has extended to include non-traditional factors such as antiatherogenic effects propagated by functional and structural adaptations within the vasculature (18) and the anti-inflammatory effects of exercise (48). Despite the overwhelming evidence for its efficacy, exercise is typically not well adhered to, with common self-reported barriers including lack of motivation, time, poor physical fitness, and low self-esteem (53). However older, populations also avoid exercise due to an increased fear of injury and pain (35). As such, alternative or adjunct therapies capable of eliciting similar systemic health benefits have considerable clinical implications and warrant further investigation.

In recent years there has been a resurgence of interest in the potential health benefits of passive heating or 'thermal therapy', with some authors promoting heat therapy as a potential alternative to exercise for populations with physical disabilities and those who find adherence to exercise difficult (7, 26). Thus far, a range of different methods of passive heating have been used such as sauna-bathing, hot water immersion, water-perfused suits or microwave diathermy. Epidemiological studies from Finland, where sauna bathing is common, have demonstrated that regular sauna bathing and a high level of cardiorespiratory fitness (argued to be a surrogate of regular physical activity) independently reduce the risk of death by cardiovascular disease, but this risk is further reduced by a combination of high cardiorespiratory fitness and regular sauna bathing (33). If the protective effects of these therapies are complementary, it raises the question as to *'how'* these protective effects are conferred and to what extent these mechanisms overlap. A growing number of studies have begun to elucidate the mechanisms by which the protective effects of thermal therapy may be conferred, and the reader is directed to reviews on these topics (for example 9, 25, 28). Given that studies of passive heating are still in their relative infancy, understanding the potential shared mechanisms of action with exercise may help to direct future studies and the implementation of passive heating more effectively. In order to focus on the potential overlap of mechanisms this review will primarily draw upon literature from non-diseased populations and will only make reference to other populations where useful to do. The purpose of this mini review is to a) assess the similarity and distinctions between the cardiovascular and metabolic health benefits induced by passive heating and exercise, b) to highlight any areas by which passive heating may lack some of the benefits of exercise and c) to discuss important areas of future study.

Cardiorespiratory Fitness

Cardiorespiratory fitness (typically measured by maximal oxygen uptake, [VO_{2max}]) is a strong predictor of all-cause mortality and death by cardiovascular disease (52), with some authors suggesting that cardiorespiratory fitness is in fact a better predictor of all-cause mortality than established cardiovascular disease risk factors (44). Despite its apparent importance, a limited number of studies have reported the cardiorespiratory fitness responses to thermal therapy, but results thus far are positive, with several studies reporting improvements of ~2-3 mL/kg/min over 6-8 weeks (2, 24, 40).

Given that the beneficial health effects of exercise are thought to be due to the diverse physiological adaptations that underpin improved cardiorespiratory fitness, the precise nature of adaptations to both passive heating and exercise should be carefully considered. Even when focussing solely on aerobic exercise, the mechanisms of adaptation are incredibly broad, and span both the cardiovascular and musculoskeletal systems (see Figure 1). Following aerobic training in untrained populations, increases in cardiac output and stroke volume are considered to be amongst the largest contributing adaptations to improvements in cardiorespiratory fitness (50) and these adaptations are thought to be due to increases in left ventricular dimensions, increased myocardial contractility and an increased blood volume (23). There is also a wealth of evidence from the heat acclimation literature that heating induces an expansion of plasma volume (19), which contributes to enhanced cardiorespiratory fitness via subsequent increases in blood volume, cardiac filling and stroke volume (22). Somewhat surprisingly, few studies documenting increased cardiorespiratory fitness following passive heating have assessed haematological or cardiac adaptations and this warrants further consideration. Given the dearth of evidence from longitudinal studies, discussion of the acute physiological responses to passive heating and exercise may help to understand the '*potential*' chronic adaptations.

During maximal aerobic exercise cardiac output can increase by ~18-25 L/min while more modest increases up to ~10 L/min are observed when core temperature is increased ~1.5°C during passive heating using a water perfused suit (16). However, it should be noted that there will be subtle differences in the acute physiological responses dependent upon the method of heating; for example water immersion will cause an increase in hydrostatic pressure and subsequent preload (38). During exercise the increase in cardiac output primarily facilitates an increase in blood flow to the active muscle, while during passive heating a significantly greater proportion of blood is distributed to the skin to facilitate thermoregulation (10). The increase in cardiac output during heating is primarily facilitated by an increased heart rate, which has been shown to increase by ~20-40 beats·min^{-1} depending on the duration and intensity of the heat stimulus, yet this is considerably less than that observed during moderate intensity exercise (15, 54). Furthermore, the increase in heart rate during heating does not coincide with a concomitant increase in stroke volume, as is the case during exercise (11). As such, thermal therapy does induce some cardiac stress, albeit modest in comparison to exercise. Nevertheless, in heart failure patients, the magnitude of stimulus appears sufficient to improve cardiac function and cardiorespiratory fitness. For example, daily sauna bathing (15-20 minutes at 60°C) for 4 weeks has been shown to improve cardiorespiratory fitness in heart failure patients by ~3 mL/kg/min (40). This is similar to what is seen with moderate intensity exercise interventions in heart failure patients, but lower than the reported benefits seen with higher intensity exercise (increase of ~6 mL/kg/min) (58). Perhaps more importantly for this particular cohort, Wisløff et al., only reported beneficial left ventricular remodelling and improved cardiac function in the higher intensity exercise group, suggesting that a relatively increased degree of cardiac stress may be required for subsequent beneficial cardiac adaptations. However, it remains unclear if cardiac adaptations following passive heating extend to populations without severe limitations to their cardiac function and this should be investigated further.

Two recent studies in healthy populations have shown that passive heating, consisting of thrice weekly 30-50-minute sessions for 6-8 weeks, improved cardiorespiratory fitness to a similar extent (~5-8%) as time matched moderate intensity aerobic exercise (2, 24). However, cardiorespiratory fitness was not the primary outcome variable upon which the sample size was calculated in these studies and therefore larger studies are required before it can be firmly concluded that passive heating and exercise induce similar adaptations to aerobic fitness. Interestingly, Hesketh et al., reported adaptations within the skeletal muscle that likely contributed to the observed increase in cardiorespiratory fitness (as described in Figure 1), but there were some differences between the response to exercise and passive heating. Specifically, passive heating enhanced muscle endothelial nitric oxide synthase (eNOS) content and capillary density to a similar extent as exercise, but only exercise enhanced markers of mitochondrial density (24). However, the thermal stimulus employed was relatively low (40-50 min heat chamber exposure at 40°C and ~40% humidity), and in fact core temperature was not elevated by passive heating but was significantly increased by the exercise intervention. The current available evidence suggests that angiogenic adaptations to passive heating require a relatively lower heat stimulus than mitochondrial adaptations, which are not always evident (24, 32) and appear to require a more prolonged increase in intramuscular temperatures which can be achieved more easily with local than whole body heating (20). Taken together, passive heating does appear to improve cardiorespiratory fitness in healthy sedentary and diseased populations, but as with exercise, the exact nature and extent of these adaptations is likely determined by the duration, intensity, mode and location of heating. For a detailed review of the skeletal muscle adaptations to heat therapy the reader is directed to the recent review by Kim et al., (31).

Vascular health

It is widely accepted that most cardiometabolic diseases are characterised by vascular dysfunction, which can include impaired endothelial function, arterial stiffening and increased arterial wall thickness of both peripheral and central arteries. The protective effects of exercise on the vasculature have been extensively reviewed elsewhere (18) and recent evidence suggest that thermal therapy may also elicit a range of vascular benefits (10).

In response to exercise training, it is thought that there is an initial improvement in endothelial function, as measured by brachial artery flow-mediated dilation (FMD), which over time may be superseded by structural adaptations, such as an increased lumen diameter and reduced arterial wall thickness (56). Several studies have shown that passive heating can also enhance brachial artery endothelial function (2, 7, 9), however, it remains unclear whether longer-term heat therapy can elicit any structural remodelling to peripheral vessels.

Brunt et al., have provided the most robust evidence of systemic vascular adaptation following thermal therapy; showing improvements in peripheral artery endothelial function and compliance, alongside reductions in central artery stiffness and wall thickness. Encouragingly, this comprehensive work indicates that the magnitude of peripheral and central artery adaptations following heat therapy are comparable to those typically observed following exercise training. Indeed, Bailey demonstrated that for a similar acute increase in core temperature (0.6-0.8°C) per session, 8 weeks of passive heating elicited the same improvement in brachial artery FMD (1.7%) as continuous moderate intensity exercise training. Nevertheless, it is probable that both the magnitude and time course of adaptation will differ between peripheral and central vessels, and likely be influenced by the magnitude of heat stress. For instance, the considerable vascular adaptations reported by Brunt et al., were in response to a 90 min protocol (aiming to increase core temperature by 1.5°C), while others (2, 9) used a 30 min protocol that increased core temperature by only ~0. 6°C.

Episodic increases in shear stress is an essential stimulus for enhanced endothelial function (18). Indeed, removing shear stress via the use of an inflatable cuff prevents the beneficial effects of both exercise (56) and passive heating (9) on endothelial function. Interestingly, there is evidence that an acute bout of passive heating can induce greater shear stress than dynamic exercise (55), however, this finding is likely dependent upon the individual nature of each stressor (i.e. magnitude and duration of heat stress and intensity of exercise) and direct comparisons should be carefully considered within this specific context. Shear stress is thought to induce a cascade of signalling factors, including eNOS, VEGF, and multiple heat shock proteins (HSPs), which contribute to angiogenesis following exercise (18) and passive heating (10). Recent evidence suggests that nitric oxide appears essential to angiogenic adaptations following passive heating (7, 8), however, the role of other circulating factors including heat shock proteins and VEGF appears less clear and indeed in some cases display distinct responses to exercise and heat (41, 42).

Cardiometabolic health

Regular exercise elicits a range of beneficial effects on cardiometabolic health, with previous research historically focussing on improvements to classic cardiovascular risk factors, such as blood pressure, insulin sensitivity, blood lipid profiles and fat mass (43).

In response to acute exercise (49) and passive heating (39) glucose tolerance is reduced, but once these interventions are repeated for several weeks, glucose tolerance is increased. One of the earliest studies of heat therapy reported daily hot water immersion (38°C – 41°C) for 3 weeks reduced fasting blood glucose and glycated haemoglobin (HbA_{1c}) (28). Several subsequent studies have since reported reductions in fasting glucose and insulin concentration (14, 25, 47), and improved glucose tolerance (for example 13, 23). Some studies have also reported beneficial changes in blood lipid profiles following heat therapy in healthy active (19) and sedentary obese populations (13) that are similar in magnitude to what is reported by large scale meta-analyses of aerobic exercise interventions (30). Relatively large-scale meta-analyses including 54 randomized control trials in normotensive and hypertensive populations have shown that regular aerobic exercise chronically reduces systolic and diastolic blood pressure by 3.8 and 2.6 mmHg respectively (57). In comparison, reductions in blood pressure are also consistently reported following chronic thermal therapy. Importantly, these reductions may indeed be of a larger magnitude than is seen following exercise training, with some studies reporting decreases of systolic and diastolic blood pressure in the region of ~10 and ~5 mmHg respectively (1, 6, 13, 25). Further studies are required to investigate these potential effects in more detail and in conjunction with other complimentary therapies such as dietary and exercise interventions.

Sedentary behaviour or physical inactivity can lead to chronic low-grade inflammation, characterised by 2-4-fold elevations in inflammatory markers, such as C-reactive protein (CRP), TNF-α and IL-6, which are thought to underpin several aspects of metabolic dysfunction including insulin resistance and atherosclerosis (51). For example, TNFa has been shown to directly induce insulin resistance (29), is actively involved in the development of atherosclerotic lesions (5) and also increases the production of reactive oxygen species which are thought to play a role in endothelial dysfunction (37). Exercise can reduce chronic low-grade inflammation via a reduction in visceral fat mass and subsequent reduction in adipokine release from adipocytes and via the transient induction of an anti-inflammatory state with each bout of exercise (17). During exercise, IL-6 is released from the skeletal muscle and is thought to drive the subsequent increase in anti-inflammatory cytokines, such as IL-1Ra, IL-4 and IL-10, and reduce the resting concentration of pro-inflammatory mediators such as CRP and TNF-α (48). Multiple passive heating studies have consistently reported an increase in the circulating concentration of IL-6, while the evidence for acute elevations in other inflammatory mediators such as HSPs is somewhat equivocal (26). However, when exercise and passive heating are matched for the increase in core temperature, the increase in circulating IL-6 is 3-fold greater following exercise (15). This may be important as the modest increases in IL-6 observed during shorter bouts of exercise (30-45 min) may not be sufficient to induce downstream potent anti-inflammatory mediators such as IL-10 and IL-4 (12) which are important for improving insulin sensitivity and glucose metabolism (27). Future studies should attempt to establish an exercise dose response for a wider array of anti-inflammatory mediators.

Despite some convincing epidemiological data supporting the anti-inflammatory effects of thermal therapy (34), there have been few controlled trials assessing chronic inflammatory responses to passive heating and indeed some of these were of only a short duration (~2 weeks) (25). In this regard, longer term studies should be encouraged. Generally, the most beneficial effects have been seen in diseased populations with elevated levels of chronic inflammation (14, 46), which is indeed similar to what is seen with exercise interventions (3). Interestingly, Ely et al., reported no change in body composition or BMI following passive heating, suggesting that the anti-inflammatory effects are more likely due to the transient induction of an anti-inflammatory state rather than a reduction in adipose tissue per se.

In a broader context it is now widely appreciated that improvements in cardiovascular and metabolic health can be seen in the absence of changes in fat mass (21). However, weight loss remains an important goal for many who exercise and often represents a significant barrier to exercise whether this be due to low self-esteem regarding their body image or due to the perceived difficulty of exercising while being overweight (53). From a simplistic perspective, weight loss is dependent on a deficit of energy intake versus energy expenditure and, when matched for the thermal load and duration, exercise results in ~10 times greater energy expenditure than passive heating (15). Indeed, Bailey et al., reported that 8 weeks of moderate intensity exercise reduced body weight while time matched hot water immersion did not (2). Initial evidence also suggests that gut hormone and hunger hormone responses are not altered in response to passive heating, suggesting that as an independent therapy, passive heating is likely to have minimal impact on long-term weight management (36). In populations for whom weight loss is particularly important, it may be beneficial to consider passive heating as a complimentary therapy to existing strategies of exercise and / or diet modification.

Conclusion and future directions

There is considerable overlap between the protective effect of passive heating and exercise, with beneficial adaptations reported in cardiorespiratory fitness, vascular function and metabolism. Yet, heating does not appear to confer all the important benefits of exercise and potentially not to the same degree in all cases (see Figure 2 for a summary). It is important to consider that our understanding of the health benefits of exercise has developed over several decades, providing considerable detail and nuance to how different populations respond to different forms of exercise, while the study of passive heating is still in its relative infancy. In this regard exercise should be considered as the primary route for maintaining and improving health. Having said this, the health benefits of passive heating have been observed in healthy sedentary and some diseased populations, supporting the supposition that passive heating may be a promising therapy in those who display poor exercise adherence. In this regard, research should continue to focus on those specific populations who may benefit most, and a wide range of populations remain unstudied. It will be hugely important to investigate the risks and potential adverse outcomes associated with passive heating. These remain relatively unexplored, but include potential heat illness, orthostatic intolerance and an increased risk of falling, especially in older individuals (28, 45). Similarly, the physiological basis of these events and any subsequent mitigating strategies should be developed as they have been with exercise.

A limitation of the current comparison between passive heating and exercise is that passive heating interventions are often designed to induce the largest tolerable dose of heating and then subsequently compared to a bout of exercise. Although often similar in terms of the time required, significantly larger volumes of exercise could be tolerated (motivation and time availability notwithstanding). Future studies should also consider the perceptual stress and enjoyment of different interventions with a view to better understanding the potential impact on long-term adherence. If passive heating is to be promoted as an alternative to exercise, future studies should take a systematic approach to understanding the optimal method and dose responses for different health related adaptations. These studies should carefully consider different durations, frequencies, intensities, mode of heating (i.e. sauna vs. water immersion) and degree of body exposure (i.e. whole-body vs. peripheral), as each factor may well impact subsequent chronic adaptations. Finally, it remains to be seen whether passive heating may be used in conjunction with exercise, either before or after, to enhance or supplement the subsequent health benefits of either intervention when performed in isolation.

DISCLOSURES

The authors have no conflicts of interest, financial or otherwise to declare.

REFERENCES

1. **Akerman AP**, **Thomas KN**, **van Rij AM**, **Body ED**, **Alfadhel M**, **Cotter JD**. Heat therapy vs. Supervised exercise therapy for peripheral arterial disease: A 12-wk randomized, controlled trial. *Am J Physiol - Hear Circ Physiol* 316: H1495–H1506, 2019. doi: 10.1152/ajpheart.00151.2019.
2. **Bailey TG**, **Cable NT**, **Miller GD**, **Sprung VS**, **Low DA**, **Jones H**. Repeated Warm Water Immersion Induces Similar Cerebrovascular Adaptations to 8 Weeks of Moderate-Intensity Exercise Training in Females. *Int J Sports Med* 37: 757–765, 2016. doi: 10.1055/s-0042-106899.
3. **Beavers KM**, **Brinkley TE**, **Nicklas BJ**. Effect of exercise training on chronic inflammation. *Clin. Chim. Acta* 411 NIH Public Access: 785–793, 2010.
4. **Booth FW**, **Roberts CK**, **Laye MJ**. Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2: 1143–1211, 2012. doi: 10.1002/cphy.c110025.
5. **Brånén L**, **Hovgaard L**, **Nitulescu M**, **Bengtsson E**, **Nilsson J**, **Jovinge S**. Inhibition of tumor necrosis factor-α reduces atherosclerosis in apolipoprotein E knockout mice. *Arterioscler Thromb Vasc Biol* 24: 2137–2142, 2004. doi: 10.1161/01.ATV.0000143933.20616.1b.
6. **Brunt VE**, **Eymann TM**, **Francisco MA**, **Howard MJ**, **Minson CT**. Passive heat therapy improves cutaneous microvascular function in sedentary humans via improved nitric oxide-dependent dilation. *J Appl Physiol* 121: 716–723, 2016. doi: 10.1152/japplphysiol.00424.2016.
7. **Brunt VE**, **Howard MJ**, **Francisco MA**, **Ely BR**, **Minson CT**. Passive heat therapy improves endothelial function, arterial stiffness and blood pressure in sedentary humans. *J Physiol* 594: 5329–5342, 2016. doi: 10.1113/JP272453.
8. **Brunt VE**, **Weidenfeld-Needham KM**, **Comrada LN**, **Francisco MA**, **Eymann TM**, **Minson CT**. Serum from young, sedentary adults who underwent passive heat therapy improves endothelial cell angiogenesis via improved nitric oxide bioavailability. *Temperature* 6: 169–178, 2019. doi: 10.1080/23328940.2019.1614851.

9. **Carter HH**, **Spence AL**, **Atkinson CL**, **Pugh CJA**, **Naylor LH**, **Green DJ**. Repeated core temperature elevation induces conduit artery adaptation in humans. *Eur J Appl Physiol* 114: 859–865, 2014. doi: 10.1007/s00421-013-2817-2.
10. **Cheng JL**, **MacDonald MJ**. Effect of heat stress on vascular outcomes in humans. *J. Appl. Physiol.* 126 American Physiological Society: 771–781, 2018.
11. **Crandall CG**, **Wilson TE**. Human cardiovascular responses to passive heat stress. *Compr Physiol* 5: 17–43, 2015. doi: 10.1002/cphy.c140015.
12. **Cullen T**, **Thomas AW**, **Webb R**, **Hughes MG**. Interleukin-6 and associated cytokine responses to an acute bout of high-intensity interval exercise: the effect of exercise intensity and volume. *Appl Physiol Nutr Metab* 41: 803–808, 2016. doi: 10.1139/apnm-2015-0640.
13. **Ely BR**, **Francisco MA**, **Halliwill JR**, **Bryan SD**, **Comrada LN**, **Larson EA**, **Brunt VE**, **Minson CT**. Heat therapy reduces sympathetic activity and improves cardiovascular risk profile in women who are obese with polycystic ovary syndrome. *Am J Physiol - Regul Integr Comp Physiol* 317: R630–R640, 2019. doi: 10.1152/ajpregu.00078.2019.
14. **Ely XBR**, **Clayton ZS**, **McCurdy XCE**, **Pfeiffer J**, **Needham KW**, **Comrada LN**, **Minson CT**. Heat therapy improves glucose tolerance and adipose tissue insulin signaling in polycystic ovary syndrome. *Am J Physiol - Endocrinol Metab* 317: E172–E182, 2019. doi: 10.1152/ajpendo.00549.2018.
15. **Faulkner SH**, **Jackson S**, **Fatania G**, **Leicht CA**. The effect of passive heating on heat shock protein 70 and interleukin-6: A possible treatment tool for metabolic diseases? *Temperature* 4: 292–304, 2017. doi: 10.1080/23328940.2017.1288688.
16. **Gagnon D**, **Romero SA**, **Ngo H**, **Sarma S**, **Cornwell WK**, **Poh PYS**, **Stoller D**, **Levine BD**, **Crandall CG**. Healthy aging does not compromise the augmentation of cardiac function during heat stress. *J Appl Physiol* 121: 885–892, 2016. doi: 10.1152/japplphysiol.00643.2016.
17. **Gleeson M**, **Bishop NC**, **Stensel DJ**, **Lindley MR**, **Mastana SS**, **Nimmo MA**. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 11: 607–615, 2011. doi: 10.1038/nri3041; 10.1038/nri3041.
18. **Green DJ**, **Hopman MTE**, **Padilla J**, **Laughlin MH**, **Thijssen DHJ**. Vascular adaptation to exercise in humans: Role of hemodynamic stimuli. *Physiol Rev* 97: 495–528, 2017. doi: 10.1152/physrev.00014.2016.
19. **Gryka D**, **Pilch W**, **Szarek M**, **Szygula Z**, **Tota Ł**. The effect of sauna bathing on lipid profile in young, physically active, male subjects. *Int J Occup Med Environ Health* 27: 608–618, 2014. doi: 10.2478/s13382-014-0281-9.
20. **Hafen PS**, **Preece CN**, **Sorensen JR**, **Hancock CR**, **Hyldahl RD**. Repeated exposure to heat stress induces mitochondrial adaptation in human skeletal muscle. *J Appl Physiol* 125: 1447–1455, 2018. doi: 10.1152/japplphysiol.00383.2018.
21. **Hainer V**, **Toplak H**, **Stich V**. Fat or fit: what is more important? *Diabetes Care* 32 Suppl 2 American Diabetes Association: S392, 2009.
22. **Heathcote SL**, **Hassmén P**, **Zhou S**, **Stevens CJ**. Passive Heating: Reviewing Practical Heat Acclimation Strategies for Endurance Athletes. *Front Physiol* 9: 1851, 2018. doi: 10.3389/fphys.2018.01851.
23. **Hellsten Y**, **Nyberg M**. Cardiovascular adaptations to exercise training. *Compr Physiol* 6: 1–32, 2016. doi: 10.1002/cphy.c140080.
24. **Hesketh K**, **Shepherd SO**, **Strauss JA**, **Low DA**, **Cooper RJ**, **Wagenmakers AJM**, **Cocks M**. Passive heat therapy in sedentary humans increases skeletal muscle capillarization and enos content but not mitochondrial density or glut4 content. *Am J*

Physiol - Hear Circ Physiol 317: H114–H123, 2019. doi: 10.1152/ajpheart.00816.2018.

25. **Hoekstra SP**, **Bishop NC**, **Faulkner SH**, **Bailey SJ**, **Leicht CA**. Acute and chronic effects of hot water immersion on inflammation and metabolism in sedentary, overweight adults. *J Appl Physiol* 125: 2008–2018, 2018. doi: 10.1152/japplphysiol.00407.2018.
26. **Hoekstra SP**, **Bishop NC**, **Leicht CA**. Elevating body termperature to reduce low-grade inflammation: a welcome strategy for those unable to exercise? [Online]. *Exerc. Immunol. Rev.* 26 NLM (Medline): 42–55, 2020. https://europepmc.org/article/med/32139348 [1 Jul. 2020].
27. **Hong EG**, **Hwi JK**, **Cho YR**, **Kim HJ**, **Ma Z**, **Yu TY**, **Friedline RH**, **Kurt-Jones E**, **Finberg R**, **Fischer MA**, **Granger EL**, **Norbury CC**, **Hauschka SD**, **Philbrick WM**, **Lee CG**, **Elias JA**, **Kim JK**. Interleukin-10 prevents diet-induced insulin resistance by attenuating macrophage and cytokine response in skeletal muscle. *Diabetes* 58: 2525–2535, 2009. doi: 10.2337/db08-1261.
28. **Hooper PL**. Hot-tub therapy for type 2 diabetes mellitus [5]. *N. Engl. J. Med.* 341 Massachussetts Medical Society: 924–925, 1999.
29. **Hotamisligil GS**, **Shargill NS**, **Spiegelman BM**. Adipose expression of tumor necrosis factor-α: Direct role in obesity-linked insulin resistance. *Science (80-)* 259: 87–91, 1993. doi: 10.1126/science.7678183.
30. **Kelley GA**, **Kelley KS**, **Vu Tran Z**. Aerobic exercise, lipids and lipoproteins in overweight and obese adults: A meta-analysis of randomized controlled trials. *Int. J. Obes.* 29 Int J Obes (Lond): 881–893, 2005.
31. **Kim K**, **Monroe JC**, **Gavin TP**, **Roseguini BT**. Skeletal muscle adaptations to heat therapy. *J Appl Physiol* 128: 1635–1642, 2020. doi: 10.1152/japplphysiol.00061.2020.
32. **Kim K**, **Reid BA**, **Casey CA**, **Bender BE**, **Ro B**, **Song Q**, **Trewin AJ**, **Petersen AC**, **Kuang S**, **Gavin TP**, **Roseguini BT**. Effects of repeated local heat therapy on skeletal muscle structure and function in humans. *J Appl Physiol* 128: 483–492, 2020. doi: 10.1152/japplphysiol.00701.2019.
33. **Kunutsor SK**, **Khan H**, **Laukkanen T**, **Laukkanen JA**. Joint associations of sauna bathing and cardiorespiratory fitness on cardiovascular and all-cause mortality risk: a long-term prospective cohort study. *Ann Med* 50: 139–146, 2018. doi: 10.1080/07853890.2017.1387927.
34. **Kunutsor SK**, **Laukkanen T**, **Laukkanen JA**. Longitudinal associations of sauna bathing with inflammation and oxidative stress: the KIHD prospective cohort study. *Ann Med* 50: 437–442, 2018. doi: 10.1080/07853890.2018.1489143.
35. **Lees FD**, **Clark PG**, **Nigg CR**, **Newman P**. Barriers to exercise behavior among older adults: A focus-group study. In: *Journal of Aging and Physical Activity*. Human Kinetics Publishers Inc., p. 23–33.
36. **Leicht CA**, **James LJ**, **Briscoe JHB**, **Hoekstra SP**. Hot water immersion acutely increases postprandial glucose concentrations. *Physiol Rep* 7: e14223, 2019. doi: 10.14814/phy2.14223.
37. **Libby P**, **Ridker PM**, **Hansson GK**. Inflammation in Atherosclerosis From Pathophysiology to Practice. *JAC* 54: 2129–2138, 2009. doi: 10.1016/j.jacc.2009.09.009.
38. **Löllgen H**, **v. Nieding G**, **Koppenhagen K**, **Kersting F**, **Just H**. Hemodynamic response to graded water immersion. *Klin Wochenschr* 59: 623–628, 1981. doi: 10.1007/BF02593853.
39. **Maley MJ**, **Hunt AP**, **Stewart IB**, **Faulkner SH**, **Minett GM**. Passive heating and glycaemic control in non-diabetic and diabetic individuals: A systematic review and

meta-analysis. *PLoS One* 14 Public Library of Science: 2019.
40. **Miyamoto H**, **Kai H**, **Nakaura H**, **Osada K**, **Mizuta Y**, **Matsumoto A**, **Imaizumi T**. Safety and efficacy of repeated sauna bathing in patients with chronic systolic heart failure: A preliminary report. *J Card Fail* 11: 432–436, 2005. doi: 10.1016/j.cardfail.2005.03.004.
41. **Morton JP**, **MacLaren DPM**, **Cable NT**, **Bongers T**, **Griffiths RD**, **Campbell IT**, **Evans L**, **Kayani A**, **McArdle A**, **Drust B**. Time course and differential responses of the major heat shock protein families in human skeletal muscle following acute nondamaging treadmill exercise. *J Appl Physiol* 101: 176–182, 2006. doi: 10.1152/japplphysiol.00046.2006.
42. **Morton JP**, **MacLaren DPM**, **Cable NT**, **Campbell IT**, **Evans L**, **Bongers T**, **Griffiths RD**, **Kayani AC**, **McArdle A**, **Drust B**. Elevated core and muscle temperature to levels comparable to exercise do not increase heat shock protein content of skeletal muscle of physically active men. *Acta Physiol* 190: 319–327, 2007. doi: 10.1111/j.1748-1716.2007.01711.x.
43. **Myers J**. Exercise and Cardiovascular Health. *Circulation* 107: 1–4, 2003. doi: 10.1161/01.CIR.0000048890.59383.8D.
44. **Myers J**, **Prakash M**, **Froelicher V**, **Do D**, **Partington S**, **Edwin Atwood J**. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346: 793–801, 2002. doi: 10.1056/NEJMoa011858.
45. **Nagasawa Y**, **Komori S**, **Sato M**, **Tsuboi Y**, **Umetani K**, **Watanabe Y**, **Tamura K**. Effects of hot bath immersion on autonomic activity and hemodynamics: Comparison of the elderly patient and the healthy young. *Jpn Circ J* 65: 587–592, 2001. doi: 10.1253/jcj.65.587.
46. **Oyama JI**, **Kudo Y**, **Maeda T**, **Node K**, **Makino N**. Hyperthermia by bathing in a hot spring improves cardiovascular functions and reduces the production of inflammatory cytokines in patients with chronic heart failure. *Heart Vessels* 28: 173–178, 2013. doi: 10.1007/s00380-011-0220-7.
47. **Pallubinsky H**, **Phielix E**, **Dautzenberg B**, **Schaart G**, **Connell NJ**, **Wit-Verheggen V**, **Havekes B**, **Baak MA**, **Schrauwen P**, **Marken Lichtenbelt WD**, **de Wit-Verheggen V**, **Havekes B**, **van Baak MA**, **Schrauwen P**, **van Marken Lichtenbelt WD**. Passive exposure to heat improves glucose metabolism in overweight humans. *Acta Physiol* 229, 2020. doi: 10.1111/apha.13488.
48. **Petersen AMW**, **Pedersen BK**. The anti-inflammatory effect of exercise. *J Appl Physiol* 98: 1154–1162, 2005. doi: 10.1152/japplphysiol.00164.2004.
49. **Rose AJ**, **Howlett K**, **King DS**, **Hargreaves M**. Effect of prior exercise on glucose metabolism in trained men. *Am J Physiol - Endocrinol Metab* 281, 2001. doi: 10.1152/ajpendo.2001.281.4.e766.
50. **Saltin B**, **Calbet JAL**, **Wagner PD**. Point: In health and in a normoxic environment, V̇O2max is limited primarily by cardiac output and locomotor muscle blood flow. *J. Appl. Physiol.* 100 American Physiological Society: 744–748, 2006.
51. **Shoelson SE**, **Lee J**, **Goldfine AB**. Inflammation and insulin resistance. *J. Clin. Invest.* 116 American Society for Clinical Investigation: 1793–1801, 2006.
52. **Steell L**, **Ho FK**, **Sillars A**, **Petermann-Rocha F**, **Li H**, **Lyall DM**, **Iliodromiti S**, **Welsh P**, **Anderson J**, **MacKay DF**, **Pell JP**, **Sattar N**, **Gill JMR**, **Gray SR**, **Celis-Morales CA**. Dose-response associations of cardiorespiratory fitness with all-cause mortality and incidence and mortality of cancer and cardiovascular and respiratory diseases: The UK Biobank cohort study. *Br J Sports Med* 53: 1371–1378, 2019. doi: 10.1136/bjsports-2018-099093.
53. **Stutts WC**. Physical activity determinants in adults. Perceived benefits, barriers, and

self efficacy. *AAOHN J* 50: 499–507, 2002. doi: 10.1177/216507990205001106.

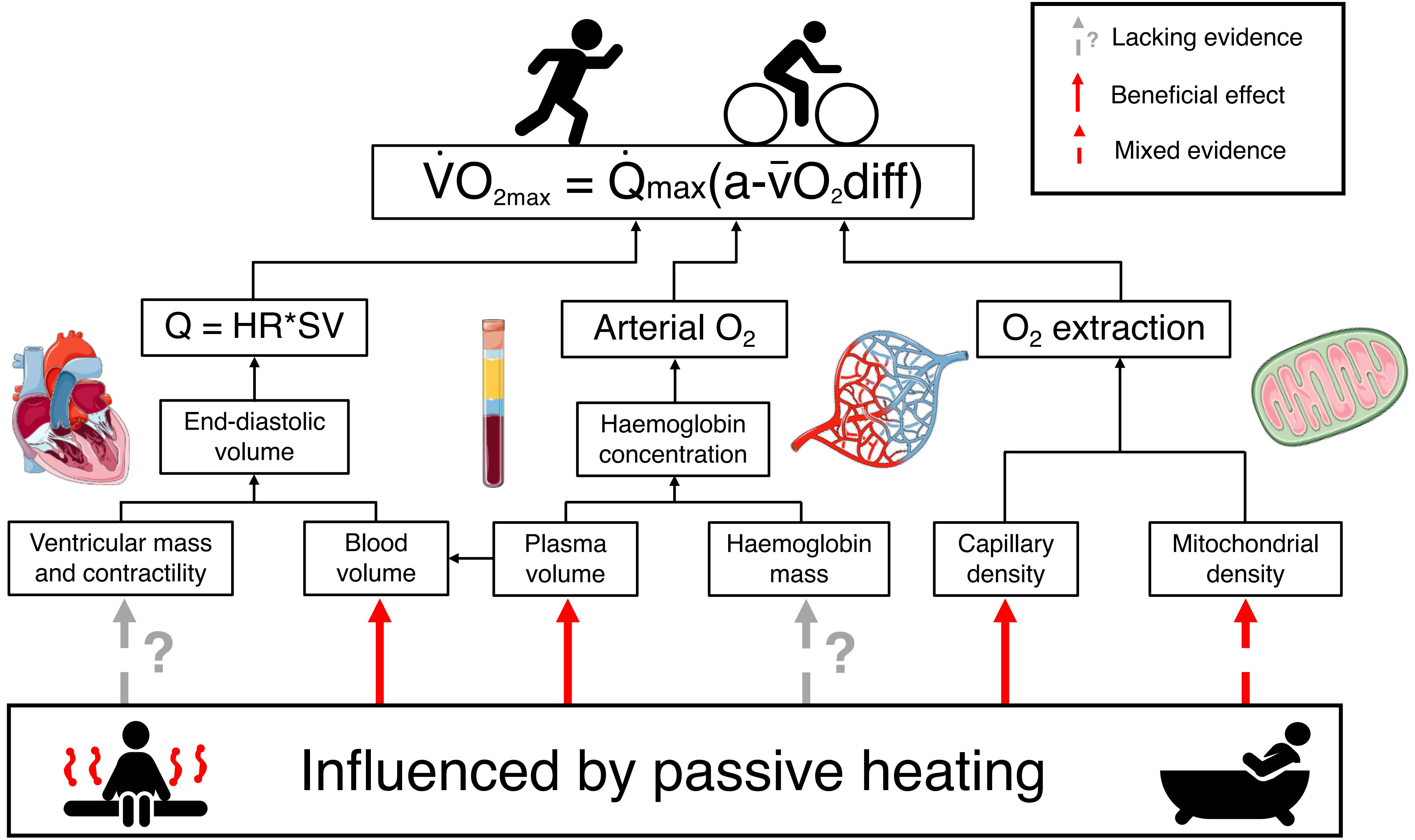
54. **Thomas KN**, **van Rij AM**, **Lucas SJE**, **Cotter JD**. Lower-limb hot-water immersion acutely induces beneficial hemodynamic and cardiovascular responses in peripheral arterial disease and healthy, elderly controls. *Am J Physiol - Regul Integr Comp Physiol* 312: R281–R291, 2017. doi: 10.1152/ajpregu.00404.2016.
55. **Thomas KN**, **van Rij AM**, **Lucas SJE**, **Gray AR**, **Cotter JD**. Substantive hemodynamic and thermal strain upon completing lower-limb hot-water immersion; comparisons with treadmill running. *Temperature* 3: 286–297, 2016. doi: 10.1080/23328940.2016.1156215.
56. **Tinken TM**, **Thijssen DHJ**, **Black MA**, **Cable NT**, **Green DJ**. Time course of change in vasodilator function and capacity in response to exercise training in humans. *J Physiol* 586: 5003–5012, 2008. doi: 10.1113/jphysiol.2008.158014.
57. **Whelton SP**, **Chin A**, **Xin X**, **He J**. Effect of aerobic exercise on blood pressure: A meta-analysis of randomized, controlled trials. *Ann Intern Med* 136: 493–503, 2002. doi: 10.7326/0003-4819-136-7-200204020-00006.
58. **Wisløff U**, **Støylen A**, **Loennechen JP**, **Bruvold M**, **Rognmo Ø**, **Haram PM**, **Tjønna AE**, **Helgerud J**, **Slørdahl SA**, **Lee SJ**, **Videm V**, **Bye A**, **Smith GL**, **Najjar SM**, **Ellingsen Ø**, **Skjærpe T**. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation* 115: 3086–3094, 2007. doi: 10.1161/CIRCULATIONAHA.106.675041.

Figure Legends

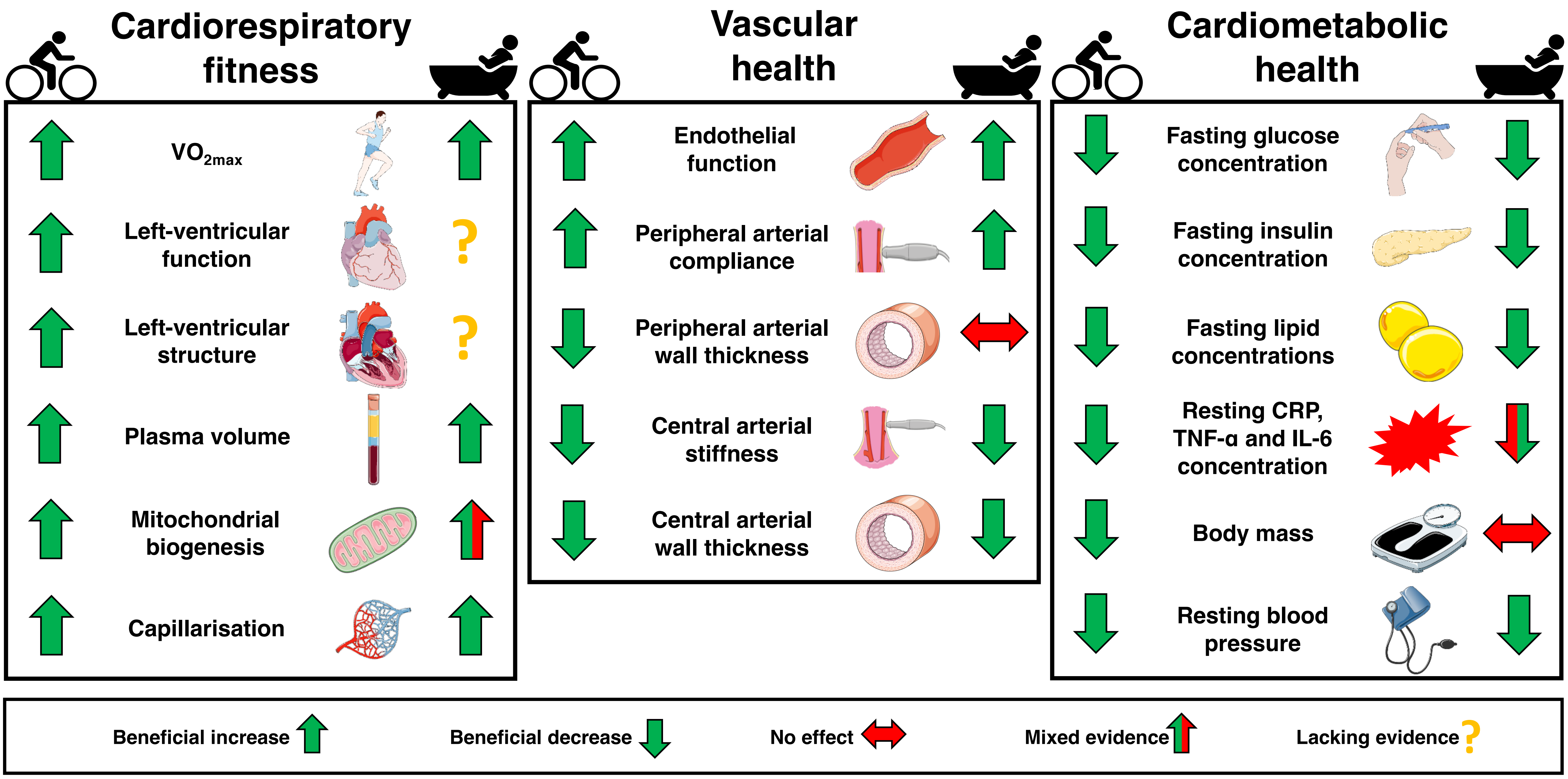
Figure 1. Summary of the determinants cardiorespiratory fitness measured by of VO_{2max} and the *'potential'* influence of passive heating on those determinants. a-vO_2diff is the difference in oxygen content between a –arterial blood and v –venous blood.

Scientific illustrations produced by Servier Medical Art.

Figure 2. Summary of chronic adaptations to exercise and passive heating. Where evidence is indicted as 'mixed' this may be due different results observed dependent upon the population studied or the nature of the heating stimulus. Scientific illustrations produced by Servier Medical Art.



Lacking evidence
Beneficial effect
Mixed evidence
$\dot{V}O_{2max} = \dot{Q}max(a\text{-}\bar{v}O_2diff)$
Q = HR*SV
Arterial O_2
O_2 extraction
End-diastolic volume
Haemoglobin concentration
Ventricular mass and contractility
Blood volume
Plasma volume
Haemoglobin mass
Capillary density
Mitochondrial density
?
?
Influenced by passive heating



Cardiorespiratory fitness
VO_{2max}
Left-ventricular function
Left-ventricular structure
Plasma volume
Mitochondrial biogenesis
Capillarisation
Vascular health
Endothelial function
Peripheral arterial compliance
Peripheral arterial wall thickness
Central arterial stiffness
Central arterial wall thickness
Cardiometabolic health
Fasting glucose concentration
Fasting insulin concentration
Fasting lipid concentrations
Resting CRP, TNF-α and IL-6 concentration
Body mass
Resting blood pressure
Beneficial increase
Beneficial decrease
No effect
Mixed evidence
Lacking evidence