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# Cutaneous control of blood pressure

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## Abstract

**Purpose of review—**Textbook theory holds that blood pressure is regulated by the brain, by blood vessels, or by the kidney. Recent evidence suggests that blood pressure could be regulated in the skin.

**Recent findings—**The skin holds a complex capillary counter current system which controls body temperature, skin perfusion, and apparently systemic blood pressure. Epidemiological data suggest that sunlight exposure plays a role in controlling blood pressure. UVA radiation produces vasodilation and a fall in blood pressure. Keratinocytes and immune cells control blood flow in the extensive countercurrent loop system of the skin by producing NO, a key regulator of vascular tone. The balance between HIF-1α and HIF-2α activity in keratinocytes controls skin perfusion, systemic thermoregulation, and systemic blood pressure by NO-dependent mechanisms. Furthermore, the skin accumulates $Na^+$ which generates a barrier to promote immunological host defense. Immune cells control skin $Na^+$ metabolism and the clearance of $Na^+$ via the lymphatic system. Reduced lymphatic clearance increases blood pressure.

**Summary—**Besides the well-known role of the brain, blood vessels, and the kidney, the skin is important for systemic blood pressure control in humans and in experimental animals.

### Keywords

hypertension; skin; keratinocytes; nitric oxide; hypoxia inducible factor; sodium; lymph vessels

The most recent World Health Organisation Global Burden of Disease survey has identified high blood pressure as the world's leading cause of premature death and disease, highlighting the importance of controlling hypertension [1]. However, the

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Conflicts of interest

None.

pathophysiological cause of essential hypertension is still unknown [2]. Hypertension research traditionally focuses on blood vessels, the brain, the heart, and the kidney. Extracellular volume control and blood flow is intimately coupled with long-term blood pressure regulation. Skeletal muscle and skin are the body's major extracellular fluid compartments. The skin holds a complex capillary counter current system which controls body temperature and skin perfusion. Emerging evidence suggests that local regulation of cutaneous blood flow and salt and water metabolism is relevant for systemic blood pressure control. We review recent findings regarding the effects of sunlight exposure, hypoxia-inducible factors, and cutaneous sodium storage on skin vessel function and systemic blood pressure levels.

## Sunlight, skin vessel relaxation, and blood pressure

The process of photo-relaxation was first described by Furchgott half a century ago. Isolated strips of arterial muscle relaxed on exposure to UVA and visible light consistent [3] with photo-reduction of stored nitrogen oxides. The action spectrum of UV induced release of NO from rat aorta matched that of low molecular weight nitrosothiols and nitrite, suggesting that these might be the NO source [4]. Human skin is now shown to contain stores of nitrogen oxides around ten times those present in the circulation [5]. Nitrate ($NO_3$) predominates, but nitrite ($NO_2$) and nitrosothiols are also present in significant quantities. Nitrate has until recently been considered a biologically inert end-product of nitric oxide oxidation, but mammalian nitrate reduction can occur [6], and in the presence of thiols ultraviolet radiation can reduce nitrate [7]. Irradiation of human volunteers with physiologically relevant fluences of UVA radiation produces a fall in blood pressure, greater than that produced by skin heating to the same degree [8, 9], and arterial vasodilatation independent of nitric oxide synthase. UVA does not cause vitamin D synthesis, but contemporaneously with the fall in blood pressure, circulating nitrite levels rose and nitrate levels fell [8]•••, suggesting that UV induced NO mobilisation from the skin to the systemic circulation accounts for sun induced falls in BP. These physiological changes seem analogous to the photo-relaxation described by Furchgott.

## Does sun exposure reduce cardiovascular risk and all-cause mortality?

Epidemiological data suggest that sunlight exposure plays a role in controlling BP. Seasonal variation in blood pressure is well described in individuals living at temperate latitudes[1] and population blood pressure correlates directly with latitude [10]. The synthesis of 1,25 di-hydroxy vitamin D requires irradiation of the skin with ultraviolet B wavelengths. Individuals with measured vitamin D levels in the upper quartile are around half as likely to have hypertension, myocardial infarction, or death from any cause as those in the lowest quartile. Meta-analyses of oral intervention studies show no benefit from supplementary vitamin D on blood pressure [11], heart disease or stroke [12] however. Similarly, genetic determination of lifelong vitamin D levels by the carriage of alleles causing a reduction in synthesis of vitamin D, or substrate availability, is not associated with any increase in cardiovascular disease [13]. Vitamin D levels thus correlate inversely with blood pressure and cardiovascular disease incidence, but are not causative. Vitamin D levels may reflect time spent outside undertaking exercise, which itself reduces BP, but a more parsimonious

explanation which accounts for geographic and Mendelian randomisation data is that sunlight exposure, independently of Vitamin D, is an effective hypotensive agent.

Dermatological concerns around sun exposure relate to the known carcinogenic effects of UV radiation, particularly on white skinned populations. Remarkably, there are no data showing an increase in all-cause mortality with increased sun exposure. Recently published high quality prospective cohort studies from Scandinavia show a dose dependent fall in all-cause mortality with increased sun exposure [14], in particular cardiovascular mortality [15]. Non-melanoma skin cancer (NMSC) can act as a marker for sun exposure. Case control analysis of the Danish population over the age of 40 shows that a diagnosis of NMSC is associated with a reduced odds ratio of all cause mortality and a greater reduction of myocardial infarction [16]. In summary, experimental data suggest that sun exposure has significant impact on NO-mediated blood flow in the systemic vasculature and thereby lowers blood pressure. This blood-pressure reducing effect of sunlight may reduce cardiovascular risk. The underestimated cardiovascular protection by sunlight may outnumber the well-known carcinogenic effects of UV radiation, and thereby reduce all-cause mortality.

## Keratinocytes control blood flow, thermal adaptation, and systemic blood pressure levels

Keratinocytes and immune cells control blood flow in the extensive countercurrent loop system of the skin. Psoriasis is a keratinocyte-driven autoimmune disease with increased risk of cardiovascular mortality [17]. Interleukin (IL) 17 is an important cytokine to drive auto-inflammation in psoriasis and plays a relevant pathophysiological role in experimental hypertension [18]. Karbach et al. have recently studied the relationship between skin-derived autoinflammation and cardiovascular disease in an experimental psoriasis model with Il-17 overexpression in keratinocytes, and found severe arterial hypertension and premature cardiovascular death in the mice [19]. Systemic inflammation with high systemic Il-17 levels occurred in the mice. The high and rapid cardiovascular mortality in this experimental model may therefore derive from direct pro-inflammatory effects in the systemic vasculature, heart, kidney, and brain; however, the underlying cause of the disease was keratinocyte-driven autoimmune disease.

Cardiac output to the skin in humans can be as little as 1–2% in the cold, and as much as 60% in acute heat stress. Keratinocytes and many other tissues and cell types produce NO, a key regulator of vascular tone [20], via NO synthase 2 (NOS2), in response to inflammatory stimuli as well as hypoxia. NO production via NOS2 is in part under the control of the hypoxia-inducible transcription factors, HIF-1α and HIF-2α. In macrophages, pro-inflammatory M1 polarization induces NOS 2 activity, which is in part promoted by HIF-1α, while HIF-2α helps to drive arginase activity via both the ARG1 and ARG2 loci, and supports alternative M2 polarization with generation of urea osmolyte from L-arginine [21]. Similarly, keratinocytes generate NO in a HIF-1α/NOS2-dependent manner, while HIF-2α promotes keratinocyte arginase expression [22] •••. The balance between HIF-1α and HIF-2α activity in keratinocytes thereby controls skin perfusion, systemic

thermoregulation, and systemic blood pressure [22]. Mice with deletion of HIF-1α in keratinocytes show reduced blood vessel diameter, dissipate less thermal energy through the skin, show increased core temperature after exercise, and have elevated systemic blood pressure. Conversely, deletion of HIF-2α activity in keratinocytes reduces arginase expression, and shifts the balance between NO versus urea production towards NO, resulting in increased skin NO levels, augmented body core temperature loss in the cold, and reduced systemic blood pressure. These findings provide clear mechanistic insights into how systemic blood pressure is regulated in the skin. This keratinocyte-driven NO homeostatic mechanism may also be a factor in the regulation of human arterial pressures: in patients with essential hypertension, increased blood pressure levels are associated with reduced NO levels in the skin, which are paralleled by a reduction of cutaneous HIF-1α protein levels, while HIF-2α protein levels were increased [22].

## Sodium storage in the skin is associated with hypertension

Besides the novel findings on the importance of skin perfusion and temperature regulation, studies also suggest that cutaneous electrolyte metabolism is coupled with systemic blood pressure control. It is a well-documented clinical observation that arterial hypertension occurs with age, and that women have lower blood pressure than men. Quantitative magnetic resonance sodium imaging (23NaMRI) studies have revealed that these characteristics of essential hypertension are closely associated with sodium storage in the skin. Humans increase skin sodium content as they age, and women have lower skin sodium content than men [23]. A recent study suggests that skin sodium storage, besides its “adverse” association with blood pressure increase, may have an unexpected biological advantage: it boosts host defense [24] •••.

Sodium accumulates at the site of skin infections and triggers pro-inflammatory activation of macrophages. This NOS2-dependent M1 polarization improves the cells’ antimicrobial capacity. Local salt deposition apparently serves as an ancient mechanism to aid in immune-mediated pathogen removal. This ancient pattern might become activated with age when biological barrier function against microbial invaders declines, yet at the price of arterial hypertension. Salt metabolism thus is not just a renal affair [25–27], but instead a homeostatic process that is regulated locally at the tissue level in response to inflammatory stimuli. Similarly, high-salt conditions reduce the ability of non-inflammatory macrophages to suppress CD8+ and CD4+ T cells.[28] Comparable salt-driven “*M(Na)*” macrophage polarization is not restricted to the skin, but also found in lung macrophages [29].

The pathophysiological mechanisms by which sodium storage in the skin may elevate systemic blood pressure are currently unknown. One hypothesis is that salt storage induces a pro-inflammatory *“host defense-like”* immune response, which leads to local reactive oxygen species generation with vasoconstriction and elevated blood pressure [24]. In line with this idea, cutaneous blood vessels show increased contractility when salt storage is induced in the skin [30]. An alternative approach towards the role of immune cell action in the salt-rich microenvironment of the skin is the concept that immune cells act as physiological regulators of local tissue sodium content by controlling a kidney-like functional vascular countercurrent/lymphatic clearance system hidden in the skin [31].

## Macrophages control lymphatic skin electrolyte clearance and blood pressure

Ultra high-field 23NaMRI studies with higher resolution have revealed that the age-dependent $Na^+$ accumulation in humans takes place inside or directly under the skin keratinocyte layer [32]. Analysis of the microanatomy of cutaneous $Na^+$ distribution suggests energy-dependent electrolyte concentration processes in the basal layer of the skin, with high salt concentrations in the dermal papillae directly under the keratinocyte layer [33]. It is unclear how these kidney-like electrolyte gradients are generated. Epithelial sodium channel activity in keratinocytes might play an important major role in the concentration process [34]. Arterioles ascend through the dermis and perfuse a capillary countercurrent loop system that extends upward into the dermal papillae just beneath the epidermis. Lymph vessels drain interstitial fluid from these blood vascular counter current loops. Similarly to renal control of sodium excretion, this local cutaneous lymphatic clearance process is intimately coupled with systemic blood pressure control. In rodents, skin macrophages exposed to high salt concentrations exert physiological-regulatory activity [35], induce increased lymph capillary pumping [36, 37] and improve lymphatic clearance of cutaneous sodium reservoirs by a vascular endothelial growth factor C (VEGF-C)-dependent mechanism. Blockade of this lymphatic clearance mechanism leads to sodium accumulation in the skin and blood pressure increase [35, 38–40]. Clinical studies indicate that humans with age-dependent blood pressure increase and skin sodium accumulation show reduced levels of pro-lymphangiogenic VEGF-C [41]. These findings suggest that local, tissue specific control of skin electrolyte homeostasis is relevant for systemic blood pressure control.

## Summary

Systemic blood vessels dilate when skin NO levels are elevated. Keratinocytes elevate skin NO levels and lower blood pressure when the skin is exposed to sunlight, and when HIF1-α levels are increased. In reverse, constriction of cutaneous blood vessels elevates systemic blood pressure. Such increases in vascular contractility are triggered by keratinocytes by HIF 2-α/arginase-driven competition for L-arginine as a substrate for urea generation, by pro-inflammatory cytokine release from keratinocytes and skin immune cells, and by $Na^+$ storage in the “kidney-like” cutaneous vascular counter current system. Blood pressure regulation in humans and in experimental animals may thus be only skin deep.

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**Key points**

- The skin hold a complex capillary counter current system which controls body temperature, skin perfusion, and apparently systemic blood pressure.
- UVA irradiation modulates NO release and export from cutaneous stores and reduces blood pressure, which could explain seasonal variation of blood pressure.
- Keratinocytes control skin blood flow via a balance between hypoxia inducible factor (HIF) 1α and HIF 2α.
- Sodium is stored in the skin and its clearance through cutaneous lymph vessels is controlled by homeostatic immune cells, which thereby control systemic blood pressure.